

Making evidence, making legitimacy:
The introduction of HPV (Human Papillomavirus) vaccines in
Colombia

Oscar Javier Maldonado Castañeda
B.A. Sociology; M.Sc. Sociology

Submitted in fulfilment of the requirements for the degree of Doctor of Philosophy
May 2015

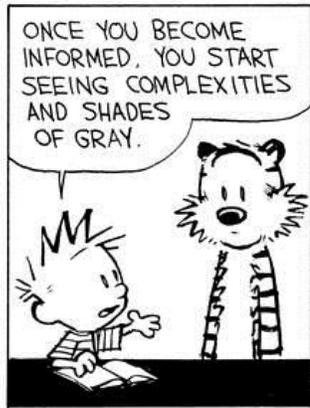
Department of Sociology
Lancaster University

DECLARATION

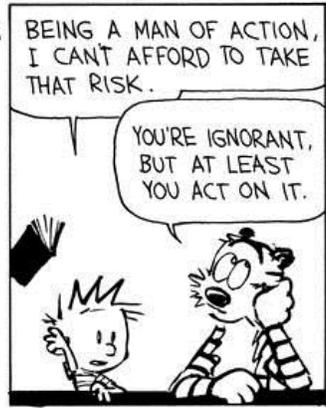
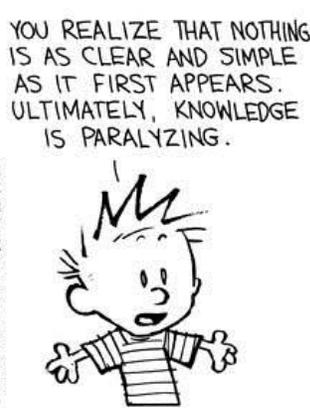
I declare that this thesis is my own work and that it has not been submitted in any form for the award of a higher degree elsewhere.

Oscar Javier Maldonado Castañeda

13th May 2015



© 1993 Watterson/Distributed by Universal Uclick



Calvin and Hobbes, 1985-1995

Abstract

Cervical cancer is strongly associated with the persistent and untreated infection with specific types of Human Papillomavirus (HPV). There are currently two vaccines which protect against the HPV types associated with 70% of cervical cancers. In 2013 the Colombian government introduced Gardasil® (Merck's HPV vaccine) into the Colombian Expanded Programme of Immunisation. Since that year, three million girls have received the vaccine in Colombia. This thesis offers an empirical analysis of the configurations of evidence, efficiency and anticipation that this intervention entails.

Based on diverse sources including policy documents, scientific literature, memoranda, minutes and interviews with experts, consultants and members of the National Committee of Immunisation Practices, I show how evidence and efficiency are the result of different calculation practices. They constitute modes of ordering heterogeneous sets of objects, data and people. These orderings perform different values, including trust, efficiency, legitimacy, accountability and objectivity. I argue that evidence and efficiency are performed in health policy by means of calculation devices such systematic reviews, cost-effective analysis, statistical modelling and pharmaco-economics, and that these practices are not isolated from the political and cultural practices and discourses that constitute a policy. On the contrary, these elements constantly reshape calculation practices by configuring affective economies in relation to policy objects. Drawing on material semiotics of numbers, valuation studies and political sociology of science, I undertake a detailed analysis of the calculation and the transformation of data, figures and numbers in their movements between documents, technical committees, regulations and media. This exploration shows the contingency and the complexity in any claim regarding evidence and their role in contemporary policy legitimisation. A central concern of this thesis is to ask: why do numbers and quantified expressions matter in healthcare policy?

This thesis contributes to science and technology studies and sociology by devising methods to research the relationships between policy and calculation. These conceptual and methodological tools allow the practices of producing figures and numbers and their public use and political consequences to be traced and followed. This thesis extends social studies of evidence in healthcare by exploring the Colombian experience in the reception and adaptation of evidence based medicine in vaccination policy. Moreover, it contributes to the social science literature about HPV vaccines by analysing the process of selection and decision making undertaken in technical committees and the role of calculations in constituting the HPV vaccines as a matter of public interest.

Table of contents

Introduction.....	14
Evidence, policy and anticipation regimes	20
Thesis summary	23
Chapter One	
Cervical cancer, HPV vaccines and contemporary healthcare in Colombia. In search of a context for the production of evidence	27
Introduction	27
Introducing HPV vaccines in Colombia: a matter of evidence and efficiency	28
Landscape of the disease: Cervical cancer: development, difference and sexuality	32
<i>Cancer epidemiology and sexuality</i>	<i>33</i>
<i>HPV, sexuality and opening the edge to vaccines</i>	<i>34</i>
<i>Locating difference: the cancer of underdevelopment</i>	<i>36</i>
<i>Geographical enactments: tracing imaginaries in cervical cancer policy</i>	<i>39</i>
Landscape of the cure: Cervical screening programmes and vaccines.....	42
<i>From the complexity of cervical screening to the “simplicity” of vaccination</i>	<i>43</i>
<i>The world and body meet in a needle: risk, anxiety and geopolitics</i>	<i>45</i>
<i>Moral calculation: Free riders, informed decisions and responsibility</i>	<i>48</i>
Geopolitical landscape: living in the middle and healthcare in Colombia	50
<i>Healthcare (market) reforms and the politics of evidence in Colombia.....</i>	<i>53</i>
<i>Replicating global difference at national scale.....</i>	<i>57</i>
Conclusion: providing a context for the production of evidence.....	60
Chapter Two	
Textuality, calculation and value. Tools to study policy, quantification and governance in HPV vaccines introduction	62
Introduction	62
Studying policy.....	63
<i>Policy as documents, telling stories through documents: an institutional cartography</i>	<i>63</i>
<i>Textual analysis, intertextuality and genres in policymaking</i>	<i>67</i>
<i>Policy actors: committees, experts and decision makers</i>	<i>69</i>
Studying calculation and quantification in policymaking: numbers and words	72
<i>Looking at devices</i>	<i>74</i>
<i>Performativity and calculation.....</i>	<i>76</i>

<i>Material semiotics of numbers: indexes, symbols and icons</i>	77
<i>Thinking a strategy of ordering</i>	80
Studying value as enacted in policy.....	82
<i>Pragmatist and axiological approaches to value</i>	83
<i>To value is a question of method</i>	85
Conclusion: policy, modes of calculation and modes of ordering.....	86

Chapter Three

Making HPV vaccines evident. Evidence, systematic review and other technologies of legitimation..... 88

Introduction	88
Health policy based on evidence: promises for a system in crisis.....	90
Systematic literature reviews: calculating inside the HPV textual laboratory.....	96
Systematic reviews outside the textual laboratory: the political and legal entanglements of the National Committee of Immunisations	104
Technologies of legitimation, technical committees and consensus rhetorics.....	105
<i>New calculative spaces, minutes as literary technologies</i>	107
Evidence in controversy, extending calculation accounts and confronting valuation strategies	109
Conclusion.....	113

Chapter Four

Making HPV vaccines efficient. Cost-effectiveness analysis, health currencies and the economic assemblage of healthcare..... 116

Introduction	116
Cost-effectiveness: Efficiency and rationalisation of public decision making.....	118
Measuring life, the development of human health metrics.....	122
Qualifying human life through quantification: risk, rationality and the consequences of calculability.....	125
Burden of disease, development and economisation, DALY as calculation device	128
Locating metrics, the search for the right measure unit for Colombia	132
Cost-effectiveness studies, HPV vaccines and the economical assemblage of public health concerns.....	137
Genital Warts and DALYS, assembling matters of concern through economic valuation	143
Iconic cost-effectiveness and closing black boxes in health decision making	147
Conclusion.....	149

Chapter Five

Making the right target for vaccination. Markov chain simulation, HPV vaccines and the enactment of a Colombian female population..... 151

Introduction	151
--------------------	-----

Temporality and causalities: the ontology of cervical cancer	153
Markov chain simulation, probability and the tame of uncertainty	163
Markov chain modelling of cervical cancer: virtual trials and the taming of clinical complexity	165
Enacting the women of the nation: Statistical reflexivity and homogenization	172
Exclusion: disentangling difference in calculation, re-enacting difference in the policy arena	178
Conclusion	182
Chapter Six	
Finding the right price for prevention. The price of pricelessness, HPV vaccines as commodities and gifts in Colombia	185
Introduction	185
Prices, valorimeters, calculation and the constitution of markets.....	188
Market, exchange and the constitution of agencies	191
Pricing and calculation strategies: Pharmaco-economics and value based pricing	194
<i>Reference price and commensurability</i>	196
<i>Price fairness</i>	200
<i>Price segmentation and the enactment of market geopolitics</i>	202
Price and value, re-entangling money in calculation.....	205
<i>Price, gift and the priceless</i>	207
<i>The Right, the Gift and the price of State paternalism</i>	211
Conclusions	214
Conclusion	216
Numbers that matter:	216
Evidence, responsibility and caring with numbers	216
Summing up.....	216
Thinking HPV vaccines in the South and other contributions.....	221
Evidence, humility and caring with numbers: in defence of evidence based medicine	223
References.....	228
Official documents and Policies	249
Appendix I	254
Appendix II.....	260
Appendix III	262

LIST OF IMAGES

Image 1 Carmen de Bolívar's Public demonstration against HPV vaccination	16
Image 2 Stills from the promotional video ‘Vaccine campaign against cervical cancer Vaccine to prevent cervical cancer- It is effective, it is safe.	18
Image 3 Launch of Bogotá's Pilot HPV vaccination programme	38
Image 4 Cochrane Collaboration logo	94
Image 5 HPV-mediated progression to cervical cancer.....	155
Image 6 Webpage Merck’s informative campaign “Haría lo que fuera” in Colombia.....	210
Image 7 Promotional poster HPV vaccine (Bogotá, Colombia 2012).....	211
Image 8 Screenshot from, political video from MIRA, about the Act 1626 of 2013	213

LIST OF MAPS

Map 1 Estimated Cervical Cancer Incidence Worldwide in 2008	40
Map 2 Cervical cancer, mortality standardised ratio by town 2000-2006	59
Map 3 Members of the International Network of Agencies for Health Technology Assessment (INAHTA).....	92
Map 4 Global Burden of disease, DALY rates, 2004.....	130
Map 5 GAVI Alliance, International Price negotiations	205

LIST OF TABLES

Table 1 Verran’s Signs typology based on Peirce	79
Table 2 Hierarchy of evidence.	93
Table 3 Systematic review terminology. Informe No 24 ETES.....	98
Table 4 HTA Summary. Informe No 24 ETES	98
Table 5 Checklist for health technology assessment reports (Health Technology Assessment). 100	
Table 6 Systematic review terminology.....	101
Table 7 Articles selected to complete reading.....	102
Table 8 Technical description of HPV vaccines	108
Table 9 Steps in Cost-Effectiveness and Cost-Benefit Analysis.....	120
Table 10 Burden of disease metrics and QALY definition	124
Table 11 Example of recent NICE technology appraisals	136
Table 12 Vaccine prices for year 2013 (Prices PAHO and CDC). Expanded programme of immunization	139
Table 13 Cost-effectiveness analysis HPV vaccines in Colombia.....	141
Table 14 Basic scenario comparison the four strategies	143
Table 15 Incremental cost-effectiveness HPV vaccination in Colombian women, taking into account genital Warts. Base case.	145
Table 16 Incremental cost-effectiveness HPV vaccination in Colombian women, taking into	

account genital Warts. Competitive analysis	145
Table 17 Disability weightings associated with cervical cancer.....	146
Table 18 Criteria to determinate causality	160

LIST OF FIGURES

Figure 1 Timeline HPV vaccination programme in Colombia	30
Figure 2 <i>A consensus phylogenetic tree of 117 HPV L1 sequences.</i>	35
Figure 3 Documentary and institutional cartography of the introduction of HPV vaccines in Colombia.....	65
Figure 4 Composition National Committee of Immunisation Practices.	70
Figure 5 Devices of calculation and decision making in the introduction of HPV vaccines in Colombia.....	82
Figure 6 Values and Methods of valuation.....	85
Figure 7 Evidence Pyramid.....	95
Figure 8 Institutional pathways in the introduction of HPV vaccines into Extended Programme of Immunisation	105
Figure 9 Graphic representation of DALY and QALY in relation to time and health	126
Figure 10 Age-weighting DALY.....	132
Figure 11 Journal articles about vaccines cost-effectiveness.....	137
Figure 12 Memorandum 201221102384491. Technical concept from Ministry of Health to Colombian Congress about Bill 260 of 2012.....	148
Figure 13 Evolution of epidemiological research on HPV and cervical cancer 1980-2000.....	157
Figure 14 Epidemiological considerations important for causal inference	158
Figure 15 Selected examples of the strength of the associations (RR/OR) between risk factors and human cancer.....	161
Figure 16 Example of a two-state Markov Chain.....	164
Figure 17 Acceptability curves and Monte Carlo PSA for the evaluation of HPV vaccines' cost-effectiveness to prevent cervical cancer in Colombia.....	170
Figure 18 Scatter plotter Monte Carlo PSA for the evaluation of HPV vaccines' cost-effectiveness to prevent cervical cancer in Colombia. Source (UNAL, 2011: 19).....	171
Figure 19 Markov chains model for the evaluation of HPV vaccines' cost-effectiveness to prevent cervical cancer in Colombia.....	173
Figure 20 Infections by HPV type and region	177
Figure 21 A hypothetical cash-flow curve for a pharmaceutical product	199

ACRONYMS

ANT	Actor Network Theory
CEA	Cost-effectiveness analysis
CIN	Cervical intraepithelial neoplasia
COP	Colombian Pesos
CRES	Comisión Reguladora de Salud
DALY	Disability Adjusted Life Years
DANE	Departamento Nacional de Estadística
EBM	Evidence Based Medicine
EPI	Expanded programme of immunisations
FDA	Food and Drug Administration
FUTURE	Females United to Unilaterally Reduce Endo/Ectocervical Disease (Trial).
GAVI	GAVI Alliance
GBP	British Pound
GDP	Gross Domestic Product
GSK	Glaxo Smith Kline
HPV	Human Papillomavirus
HSV	Herpes Simplex Virus
HTA	Health Technology Assessment
IADB	Interamerican Development Bank
IARC	International Agency for research on Cancer
ICER	Incremental cost-effectiveness ratio
IETS	Instituto para la evaluación de tecnologías en salud
INAHTA	International Association of Health Technology Assessment
INC	Instituto Nacional de Cancerología
INS	Instituto Nacional de Salud
INVIMA	Instituto Nacional de Vigilancia de Medicamentos y Alimentos
MMR	Mumps, Measles and Rubella
MPS	Ministerio de Protección Social
NCIP	National Committee of Immunisation Practices
NICE	National Institute for Clinical Excellence
PAHO	Panamerican Health Organisation
PAI	Programa ampliado de inmunizaciones
PATRICIA	PApilloma TRIal against Cancer In young Adults

PSA	Probabilistic sensitivity analysis
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled trials
UNAL	Universidad Nacional de Colombia
USD	United States Dollar
WHO	World Health Organisation
YLL	Year Life Lost

Acknowledgements

It is thought that a Ph.D. thesis should be primarily an expression of individual and original work. However in practice such an achievement is just possible because of the support and care of many others. Firstly and foremost I would like to express my sincere gratitude to my supervisors Maggie Mort and Celia Roberts. They have been incredibly generous with their time and knowledge during my Ph.D. Their support, continuous reading and even through caring corrections always helping me to improve my writing. But most importantly they constantly encouraged me to keep thinking, writing and working on the ideas I present in this thesis. Muchas gracias por todo Celia y Maggie. I also have had the fortune and the privilege of studying in an outstanding and creative sociology department. I am very grateful to Vicky Singleton, Maureen McNeil and Lucy Suchman for their comments and advice.

Many ideas developed in this thesis were written during my visit to TEMA Institute at Linköping University in Sweden. I learnt lots from the seminars and the comments I received there. I want to thank Ericka Johnson, C.F. Helgesson and Lotta Björklund Larsen and to the participants of P6 and ValueS seminars.

During these years I have had the luck of finding friends that are working precisely on HPV vaccines. A special thanks to Ali Hanbury and Lisa Linden. We have had lots of coffee and good conversations around feminist technoscience, HPV and vaccines. Also I would like to mention and thank my writing group friends: Joann Wilkinson, Mette Furbo, Emils Kilis and Felipe Raglianti. We had the nice opportunity of sharing ideas, biscuits, tea... sometimes coffee and beer, always supporting each other. As I would like to thank Tabby Middleton for her kindness and help, reading my texts and showing me ways to improve my academic writing.

I want to specially thank to the researchers of the Cervical Cancer Research Group at the Colombian National Institute of Cancer, to the staff of the Expanded Programme of Immunisation (Ministry of Health) and to the members of the National committee of immunisation practices for their time and generosity with this research.

Moreover I want to thank my teachers and colleagues in Universidad Nacional de Colombia, Olga Restrepo Forero, Malcolm Ashmore, Alexis De Greiff and Yuri Jack Gómez. They introduced me into science and technology studies and kindly encouraged me to pursue my Ph.D.

I want also thank my parents Marina and Javier for teaching me the love of study. Despite they barely had completed high school. Their trust in education has been an inspiration for keeping working and learning. Thinking that sociology and critical thinking can make a difference in the world.

Finally I want to thank my life partner, Derly Sánchez Vargas. Words are not enough to express how important she is, how her love, care and patience have been the fuel of my life. Derly thanks for always being there, in the happy and in the hard times. Thanks for encouraging me when I was down and for being critical when I was excessively comfortable with my work.

This research was sponsored with public funds from *Generacion del Bicentenario Scholarship* of Colciencias. Therefore I am really grateful to the people of my country. I have had the privilege of studying abroad and I really hope to contribute as scholar, social researcher and not to disappoint my future students.

Introduction

September 2014 was a month full of news about HPV (Human Papilloma virus) vaccines in Colombia. This subject, which had previously barely attracted the attention of journalists, suddenly became the centre of an enormous controversy. The trigger was a strange outbreak of adverse vaccine-related effects in a small town of the Colombian Caribbean coast, Carmen de Bolívar. During the month of August, days after the vaccination campaign, hundreds of girls were hospitalised. These girls had symptoms ranging from fainting to numbness in the hands and headaches. Although some cases of adverse effects had been reported before, the Carmen de Bolívar outbreak concentrated the attention of media, politicians and governmental institutions because of the number of girls affected and the mobilisation of their parents demanding State action.

In Colombia, as in other Latin American countries, journalists and politicians have widely praised HPV vaccines as public health intervention against cervical cancer since 2009. The launches of the vaccination campaigns have been public events with the presence of the President and Health Ministers. Such enthusiasm amongst politicians and healthcare authorities has been connected to the burden of cervical cancer in the region and a generalised perception of vaccines as public goods.

Cervical cancer is the second most frequent cancer in women in the world and the third most common cause of death from cancer in women. The World Health Organisation estimates more than 85% of the 270.000 deaths from cervical cancer every year occur in developing countries (WHO, 2013). Global health authorities and specialists argue that cervical screening programmes in developed countries have significantly reduced the impact of this cancer. In developing countries, in contrast, limited access to effective screening and poor treatment has meant a higher rate of death from cervical cancer. In Colombia, the National Cancer Institute estimates that 7.000 cases of cervical cancer are diagnosed every year, one of 25 women will have cervical cancer at some point of their lives and 2.300 women will die of this malady. Cervical cancer is the first cause of female mortality by cancer in the country.

Cervical cancer is strongly associated with the persistent and untreated infection with specific types of HPV (most frequently types 16 and 18). There are currently two vaccines that protect against both HPV 16 and 18, which are associated with 70% of cervical cancers (WHO, 2013). Gardasil® produced by Merck and Cervarix®, by Glaxo SmithKline¹. As I will show later, this relationship is more complex than this statement suggests. However, this context —produced by means of epidemiological data about the burden of cervical cancer in the country and in the world— in 2012 justified the introduction of HPV vaccines in the Colombian expanded programme of immunisation. According to the Ministry of Health, since that year three million girls have received the vaccine in Colombia, whilst 120 million doses have been delivered worldwide.

During this period only a couple of cases of adverse effects associated with the vaccines were made public in Colombia. Most journalists' and public accounts of the vaccine focused on its benefits in terms of cancer prevention and extension of healthcare to vulnerable populations. The Carmen de Bolívar crisis has in many ways changed the public perception of HPV vaccines in Colombia, rendering visible a set of tensions in the relationships between trust, risk, sexuality, anticipation and evidence. The Carmen de Bolívar adverse effects' outbreak demanded the public mobilization of a set of narratives and technical repertoires about evidence production that often remain invisible.

This outbreak has also made manifest the growing division between political parties in relation to conceptions and governance of human life. The conservative groups that have traditionally opposed the voluntary termination of pregnancy have gradually directed their attention against HPV vaccines. Political movements such as “Catholic vote Colombia” have argued that the HPV vaccine does not protect but rather hurts the young by promoting promiscuity. At the same time actors who identify themselves as politically and culturally liberal (some journalists, women's movements, public health experts) have supported HPV vaccination and the scientific evidence that legitimise their use. Journalists as Hector Abad Faciolince have denounced the Colombian General Prosecutor —an important Catholic right-wing politician— for encouraging parents, often from Catholic schools, to denounce serious effects that the HPV vaccine could be causing.

In this context, the definition and attribution of evidence has become a critical matter and zone of dispute. In cases where the vaccine has been criticised for its possible adverse effects or its lack of efficacy, the government and the health authorities have reacted by affirming that evidence is on their side. This was

¹ Gardasil protects against four types (tetraivalent) of HPV: HPV 6 and 11 associated with Genital Warts and HPV 16 and 18 associated with Cervical Cancer. Cervarix protects against two types (Bivalent) of HPV: HPV 16 and 18.

the initial reaction of the Colombian government when the Carmen de Bolívar outbreak reached the national and international media. The government called the reported adverse effects a manifestations of “collective hysteria” (Semana, 30th August 2014). The local community received such declarations angrily and started a protest that ended in riots and clashes with the police. After this, the Ministry of Health called a committee of experts (comprising almost all the members of the National Committee of Immunisation) to assess the situation. Toxicologists were sent to Carmen de Bolívar and the health authorities changed their language, medicalising the social tensions generated by the vaccination. The description of this phenomenon changed from “collective hysteria” to a “psycho-social disease” (Caracol Radio, 24th September 2014).



Image 1 Carmen de Bolívar's Public demonstration against HPV vaccination

In the girls' signs, from left to right: 1. We want an answer. 2. Vaccines that kill and organised crime. Big Pharma corrupt the Health System. 3. We want healthy girls, without adverse effects of HPV vaccination. 4. Breaking news: Mass hysteria in the Ministry of Health. 400 girls victims of HPV vaccine. Carmen de Bolívar, Colombia 2014.

Source: RCN T.V.

National health and toxicology experts travelled to the town to collect blood samples and investigate possible environmental hazards. Their conclusion was that there is no evidence that the vaccine was the cause of the girls' symptoms. They argued these results verify the “extensive international testing and regulation globally” that recognize the safety of the vaccine. However, these conclusions had little impact in calming parents' and community concerns (see Image 1). A blog published in the local newspaper *El*

Heraldo describes the people's disillusionment with the government and the expert evidence. The column echoes a traditional song (a cumbia) that sings the beauty of Carmen de Bolívar's women. The author modifies the song's lyrics to tell the drama of the outbreak:

Dear Carmen, lovely land, there are shadows and nightmares under your sky. It is useless that you hide amongst the María's Mountains. There is a voice about what is happening, here in the intimacy of your streets garnished with virgins. Your virgins of flesh are decaying. With the pieces of pain and tears of 439 girls vaccinated against a sexual transmitted virus. Your people are solving a puzzle and blame the government. Because after months of faintings and the dance of psychological explanations and the laboratory analysis just a diagnosis is clear: No one knows the truth about what is happening, but everyone knows it stinks².

This outbreak has highlighted serious problems in the delivery of vaccines beyond their possible adverse effects. In many cases, parental consent had been taken for granted, whilst other families have reported they were told by nurses at schools that if their daughters did not get the vaccine, they could lose social benefit payments (El Heraldó, 28th September 2014). This happens whilst the government presents HPV vaccination as a social intervention that will benefit the poorest populations in the country, those at higher risk of developing cervical cancer.

Politicians have promoted vaccines as a tool for women's empowerment, a health equity intervention and prevention for cancer. These narratives are embedded into the multicultural repertoire that has shaped the political rhetoric and Colombian social and health policy during the last 20 years. This point is illustrated in the campaign material developed by the Ministry of Health. The campaign "Que vivan las mujeres" (Viva women!) explicitly avoids any reference to either sexuality or HPV. Instead it promotes the vaccine as a cure for cervical cancer that protects the lives of Colombian girls regardless their region, class or race.

² "Carmen querido, tierra de amores, hay sombras y pesadillas bajo tu cielo. De nada sirve que te escondas entre las faldas verdes de los Montes de María. Se corre la voz de lo que está pasando aquí abajo, en la intimidad de tus calles adornadas con estatuas de vírgenes. Tus vírgenes de carne y hueso se desmoronan. Con los pedacitos de llanto y dolor que van dejando regados 439 niñas recién vacunadas contra un virus de transmisión sexual, tu gente arma un rompecabezas que acusa al Gobierno. Porque los meses de desmayos y la danza de explicaciones psicológicas y análisis de laboratorio solo dejan un diagnóstico claro. Nadie sabe de verdad qué pasa, pero todos saben que apesta".



Image 2 Stills from the promotional video 'Vaccine campaign against cervical cancer'³ Vaccine to prevent cervical cancer- It is effective, it is safe. Colombia, Ministry of Health, 2012

The case of Carmen de Bolívar has motivated an important debate about vaccine's safety and effectiveness. The government and scientific experts point out that they have weighed the scientific evidence, and argue that HPV critics have based their position on opinion and moral prejudice (La W Radio, 26th September 2014). In this public debate, evidence has meant having data, numbers, expert and institutional support. The Colombian writer Héctor Abad Faciolince summarises such evidence in a column that backs HPV vaccination:

There are rigorous studies around the world about the possible adverse effects of the vaccine. From 67 million of doses, 25.000 adverse effects have been reported. From these 25.000, 92% were not serious effects (fever as in my daughter, skin redness). The rest, 2000 cases were serious effects, that is 0.003% of the cases, a bit higher than the placebos. The World Health Organisation WHO is right when they affirm that the HPV vaccine is safe. The same is said by one of the few Colombians who deserves a Nobel prize in medicine: Dr. Nubia Muñoz (El Espectador, 5th October 2014).

Indeed Nubia Muñoz has embodied the voice of science and evidence in this debate. This Colombian epidemiologist was head of the Department of Cancer Epidemiology of the International Agency for Research on Cancer (IARC) of the WHO. She directed an important part of the epidemiological studies that allowed the identification of the causal link between HPV and cervical cancer. Muñoz was special guest at the vaccination launch and has been often interviewed by international and national media. In one

³ <https://www.youtube.com/watch?v=V3viICe-FnY>

of her most recent interviews (5th October 2014), she passionately defended the evidence regarding the safety and effectiveness of HPV vaccines. She declares that international agencies such as WHO, PAHO, FDA and EMA have recognised that HPV vaccine is safe and that there is no evidence showing that HPV vaccine generates autoimmune diseases (Guillán-Barré, multiple sclerosis,). However, her answer to a question about the opinion of a toxicologist who found a relation between the HPV vaccine and the development of Transverse myelitis, offers a way of understanding evidence and how it is different from scientific knowledge:

Journalist: In Cali a girl became paralysed by transverse myelitis, according to a toxicologist because of the aluminum in the vaccine...

NM: I don't believe you... show me the data and we will see. I have not seen the study, but it is impossible that just a doctor, who can be outstanding, with just one case can say this against the opinion of committees of experts that have reviewed the evidence in thousands of cases (El Pais -Cali Colombia- 5th October 2014).

As she notes, the production of evidence has to do with the practice of reviewing, the methodical selection of “thousands of cases” and their discussion and legitimation by a technical committee, a particular group of experts with authority on that matter. These technical committees have a monopoly in the definition of evidence. By means of practices of calculation, they divide and select technical information that acquires a higher status as evidence. The production of evidence is an effort to organize a diverse, contradictory and messy universe of technical information in order to enact a unique and clear voice for science. These practices have had an important impact in the shaping of contemporary healthcare governance by means of the promise of clear and reliable decision making. At the same time, the use of these methods of analysis and organisation has raised concerns amongst medical and patient communities about the limitations that the very concept of evidence imposes on scientific knowledge⁴.

The importance of evidence production in the governance of contemporary healthcare has been recognised by patients' organisations and some of them have critically appropriated this framework to enhance their own claims. As Madeleine Akrich and colleagues have noted, the use of evidence in healthcare decision making implies a disjunctive between experiential and formalised knowledge (Akrich

⁴ Sometimes the clash between these different conceptions can constitute acts of violence on patients and their families. For instance, when the suffering of girls and parents is denied or considered ‘hysterical’ because its accounting does not correspond with the reduced kinds of knowledge that are considered as legitimate sources of evidence. The doctoral research of Ali Hanbury at Lancaster University provides an analysis of adverse effects of HPV vaccines in the UK and the problem associated with the credibility of girls' accounts of suffering.

et al., 2014: 129). Whilst policymakers have adopted a formalistic approach to evidence; patients' organisation and some medical communities have used the concept evidence to express the authority of their experiential knowledge (Rabeharisoa et al., 2014: 112; Akrich et al., 2014: 129). In the case of patients' activism "knowledge and evidence play a pivotal role in creating an interface for engagements between users and professionals" (Akrich et al., 2014: 129).

The governance of healthcare technologies such as HPV vaccines is shaped not only by commitments to evidence but also to efficiency and anticipation. Behind any decision about the inclusion of health technologies and procedures, there is a set of calculations and considerations about the best use of scarce economic resources. On the other hand, these calculations situate healthcare in a temporal horizon in which the future determines the choices and experiences of the present. The production of evidence in the case of HPV vaccines has been closely related to their cost-effectiveness and the estimation of future economic scenarios. In this context, decisions about healthcare are expressed in terms of numbers, prices, money and data. These simultaneously have a life in the future as estimations and imagined entities, and in the present as calculated objects. The debate about HPV vaccines in Colombia shows the increasing power of evidence in the governance of life and healthcare. This debate raises key questions about the production of evidence and its relation with health governance. Who has the authority to define what is or is not evidence? How is such authority granted? Where does evidence come from and reside? How is evidence assembled and through what objects and practices?

This thesis explores the role of narratives and calculation practices used in evidence-based medicine for the management of the tensions, risks and uncertainties that HPV vaccines entail. My research shows how evidence is the result of different calculation practices, which constitute modes of ordering heterogeneous sets of objects, data and people. These orderings perform different values, including trust, efficiency, legitimacy, accountability and objectivity. Such enactments are always partial and contingent, they are constantly re-enacted and their persistence relies on their multi-sited and constant replication. Taking the Colombian experience as a case study I explore the ways in which evidence is constituted and used to manage these uncertainties and to produce legitimacy in this particular context.

Evidence, policy and anticipation regimes

Existing work on HPV vaccines explore contemporary transformations in healthcare such as its biomedicalization (Connell and Hunt, 2010), pharmaceuticalization (Mamo and Epstein, 2014) and the rise of anticipation regimes (Adam et al., 2009; Carpenter and Casper, 2009; 2010). Connell and Hunt (2010) have noted HPV vaccine campaigns show the intertwining of "regulatory discourses of moralization and medicalization in an era of biopolitics" (Connell and Hunt, 2010: 66). Expert discourses

and self-regulation converge in HPV vaccination narratives in contexts of neoliberal governance of healthcare (Connell and Hunt, 2010: 66).

Adams, Murphy and Clarke have proposed the concept ‘regime of anticipation’ to describe a contemporary mode of techno-political governance characterised by its obsession with the future and the reshaping of the present through anticipation (Adams et al., 2009: 260). These regimes imply a change from regimes of truth to orderings in which anticipation is constituted through modes of prediction and instrumentality. These regimes have affective dimensions, in which the subjects are engaged in affective economies of fear, hope, salvation and precariousness “oriented temporally toward futures already made ‘real’ in the present” (Adams et al., 2009: 260). Different authors (Adams et al., 2009; Carpenter and Casper, 2009; 2010; Mihra and Graham, 2012) have noted that HPV vaccines are a good case to trace the ways in which these regimes are constituted and how they operate in healthcare. Firstly, HPV vaccines are distinctive from other vaccines. Mihra and Graham (2012), for example, analyse the production of risk and gender in the case of HPV vaccination programmes of girls in Canada. They use a Foucauldian approach to link power, knowledge and discipline, paying special attention to the role of gender in the projects of control. Whilst conventional vaccines rely on politics of contagion and containment, HPV vaccines have been framed as an anticipated intervention into cancer (Carpenter and Casper, 2009). Advertising and campaigns have emphasised the role of HPV vaccines in the prevention of cervical cancer rather than in the control of a sexually transmitted disease. Secondly, Carpenter and Casper (2010) have noted Gardasil –the commercial name of tetravalent HPV vaccine- is a new gendered technology built from the ambiguous relationship between cervical cancer and HPV. This vaccine has generated an epistemological and practical confusion of the relation between cervical cancer and HPV that has contributed to sexualize and to gender political debates: “Because the HPV vaccine’s target is sexually transmitted, it provokes longstanding controversies swirling around sex, gender, and women’s bodies in the US” (Carpenter and Casper, 2010: 896).

HPV vaccines also constitute an interesting case to trace the ways in which pharmaceuticals interact and transform their political and cultural landscape “(re)shaping the pharmaceutical’s life course in turn” (Carpenter and Casper, 2010: 896). As Mishra and Graham (2012) have noted, the reception of new vaccines is the result of “a complex interplay of science, marketing, healthcare policies and practices, media representations and social perceptions” (Mishra and Graham, 2012: 64).

Most social science research about the reception of HPV vaccines has privileged the analysis of marketing, campaigns, media and political discourse to trace tensions that these pharmaceuticals entail

(Carpenter and Casper, 2009, 2010; Mihra and Graham, 2012; Colgrove et al., 2010; Epstein, 2010; Aronowitz, 2010; Mamo et al., 2010, Ramogola-Masire, 2010; Livingstone et al, 2010; Linden, 2013). For instance, the book *Three shots at prevention* edited by Keith Wailoo, Julie Livingston, Steven Epstein and Robert Aronowitz (2010) provides a collection of works about the impact of HPV vaccines, mainly in North America and Europe. Two chapters analyse the introduction of these vaccines in Africa in the context of global health international cooperation (Ramogola-Masire, 2010; Livingstone et al, 2010). Little work has critically examined how these tensions are enacted in the process of selection and decision making undertaken in technical committees and the role of calculations in constituting the HPV vaccine as a matter of public interest. Moreover, few works have discussed the impact of HPV vaccines in the “Global South”, particularly in the so-called middle income countries.

In this thesis I extend the analysis of the constitution of regimes of anticipation by examining the role of calculation and quantification in their configuration. The regimes of anticipation depicted by Adams and colleagues (2009) is materialised in the realm of health policy by the rise of evidence based medicine techniques such as cost-effectiveness analysis and systematic reviews. The practices of calculation, quantification and monetisation that they entail enact the reality in relation to simulated and estimated futures. The analysis of practices and devices of calculation is the best way of tracing some features of anticipation regimes such as the relation between modes of prediction and instrumentality, affective economies and the reshaping of knowledge (Adam et al., 2009: 260). In the following chapters I offer an analysis of the role of different devices of calculation in the enacting of anticipation regimes of cervical cancer and HPV vaccines.

Devices such as systematic reviews, cost-effective analysis and modelling are extensively used to find evidence regardless of the “nature” of the healthcare technology or procedure that is assessed. These devices are highly standardised and the space for local adaptation in principle is narrow. However, these practices of calculation are not isolated from the political and cultural practices and discourses that constitute a policy. On the contrary, as I will present, these elements constantly reshape calculation practices. They configure affective economies in policy design and implementation. These practices and devices are locally situated. This thesis analyses what is specific about the production of evidence in relation to HPV vaccines and what is particular and specific about making calculations in and for Colombia.

This study offers an empirical analysis of the configurations of evidence and anticipation in Colombia through the study of the introduction of HPV vaccines. It contributes to science and technology studies

and to sociology by devising methods to research the relationships between policy and calculation, providing a detailed analysis of calculation and the transformation of data, figures and numbers in their movements between documents, technical committees, regulations and media. This exploration shows the contingency and the complexity in any claim of evidence and their role in contemporary practices of policy legitimisation. Finally, it opens up a discussion of why numbers matter and of the political and ethical importance of tracing the practices of producing figures and numbers and following their public use.

This thesis makes an empirical contribution to the study of the relationship between knowledge practices and governance in contemporary healthcare policies. It details the ways in which normative claims of evidence and efficiency are materialised in methods of valuation and devices of calculation providing a detailed analysis of the ‘reception’ of evidence-based policy repertoires in Colombia and their use by policymakers and pharmaceutical companies in the introduction of HPV vaccines. This is a project about a technology and a policy in the making: the noted events have unfolded as I have been thinking and writing about them.

Thesis summary

The first chapter presents the research question: how is evidence produced the introduction of HPV vaccines in Colombia? I make a brief overview of the contemporary perceptions on cervical cancer and vaccines, emphasising the ways in which the South is depicted in global narratives about cure and disease. I describe the tensions that render vaccines a contested technology and cervical cancer a marginal disease associated with poverty and sexual stigma. I discuss the persistence of these narratives in contemporary policies and practices around cervical cancer and the role of HPV vaccines in establishing socio-material connections between the worlds of cervical cancer and vaccines. These technologies not only gather such tensions, but also make visible new problems such as the co-production of gender, technology and disease, and the development of ‘anticipated’ cure.

This chapter also presents how HPV vaccines and cervical cancer have been framed as objects of knowledge and political interventions geopolitically situated. Global Health methods have enacted local and national problems as objects located on a global landscape. Data and policies that are used to introduce cervical cancer and HPV vaccines as matters of public concern are the result of extended infrastructures that segment global health into geopolitical categories. In the case of ‘middle income countries’ such as Colombia, healthcare governance and calculations have been shaped by commitments of development, efficiency and modernisation.

These ‘principles’ have framed the introduction of HPV vaccines in Colombia and have highlighted the importance of methods of valuation such as cost-effectiveness analysis in the techno-political justification of healthcare technologies and their incorporation in Public Health programmes. Through this analysis I reflexively provide a context (Asdal and Moser, 2012) that situates the analysis developed in this thesis. The introduction of HPV vaccines constitutes one of the earliest attempts to use the repertoires of policies based on evidence in the governing of healthcare technologies in Colombia, thus it offers a unique opportunity to think about the transformation of contemporary healthcare in the South.

The second chapter explores how these objects can be studied, presenting a set of methodological and conceptual tools to analyse policy and calculation. Firstly, I discuss the role of documents in the assemblage of policies and institutions, and the ways in which they can be analysed in order to understand policies in action. My research is principally based on documental sources such as policy papers, regulations, websites, scientific papers, software, news, committee minutes, conferences reports, forms, budgets, statistical reports among others. Secondly, a methodological proposal is drawn for the analysis of calculation practices through technical documents and the role of learning practices. Dealing with technical literature, statistics and simulations has involved engaging with some calculation processes and technologies. This chapter presents conceptual and methodological tools to undertake the analysis developed in the following chapters, presenting in detail the framework that shapes the selection of problems and its study. This framework offers a strategy to understand the relationships between calculation and governance, taking a material-semiotic approach to numbers and a pragmatist understanding and approach to the production of value. These problems emphasise multiple and different aspect of the relations between knowledge and legitimacy.

In the chapters 3, 4, 5 and 6, readers will find an analysis of the ways in which evidence and value are enacted through different strategies of calculation. These devices of calculating involve different ways of ordering and quantifying a quite heterogeneous set of objects to produce justifications for policymaking based on evidence and efficiency. I argue that the analytical description of these configurations provides a way of understanding the ways in which some of the big features of contemporary healthcare regimes such as its increasing marketisation (Moreira, 2012b) and its pharmaceuticalisation (Mamo and Epstein, 2014) are produced in practice. The devices of calculation that I analyse in the introduction of HPV vaccines in Colombia are systematic reviews, cost-effectiveness analysis, Markov chain simulation and pharmaco-economic pricing.

Chapter Three analyses the role of systematic review in producing evidence through the selection of “relevant” scientific articles for policy. I analyse systematic review as a practice or a device of calculation, in which entities such as papers, tables and data are detached from their original context, classified, and ordered within a single space (new tables, Health Technology Assessment HTA forms). These entities are compared, manipulated, and transformed according to particular rules, in this case through searching syntax, the hierarchy of evidence, HTA Guidelines, grading methodologies and evidence checklists. Finally, results such as rankings are produced both to summarize and to represent the entities in the calculative space. In the case of systematic review, the result is evidence enacted as a selection of “pertinent” papers which became iconic and a set of ‘trustworthy’ data.

In Chapter Four I analyse a second device of calculation (cost-effectiveness analysis) and the ways in which efficiency is enacted in the introduction of HPV vaccines. Cost-effectiveness analysis (CEA) is a strategy of calculation whose main objective is to compare and make decisions about the best, the most efficient solution (costs vs. benefits) to a particular problem. In particular, the use of CEA in healthcare has focused on comparing technologies and procedures with the aim of reducing costs through rationalising care. To compare is never an easy task. It involves taming objects, reducing them to analytical features, and establishing standards and measurements units. I argue here that cost-effectiveness analysis not only provides a framework to compare healthcare interventions which in practice seem incommensurable; it also performs a set of assumptions regarding the nature of healthcare and the behaviour of individuals, such assumptions are embedded into narratives and ontologies based on market and rational choice theory. This chapter presents the role of CEA analysis in the transformation of healthcare policies toward market-based decisions and in particular its role in the introduction of vaccines. I describe how health currencies are calculated and the consequence of the use of Disability-adjusted Life years (DALY) as a unit of measurement of burden of disease and cost-effectiveness in Colombia; analysing how these results are interpreted in the technical reports and in other arenas such as the NCIP committee, the Colombian Congress and the Council of State.

Chapter Five describes the different elements that constitute Markov chain modelling as a device, the entities that are disentangled, the creation of calculative spaces, its rules of calculation and the ways in which results and the natural history of disease are enacted. This strategy of modelling has meaningful consequences in the production of new entanglements between individual and social histories of the disease. In principle, the natural history of cervical cancer describes the development of this malady through different stages in a “typical” individual; these are changes that happen within an individual body. However, through epidemiological modelling this dynamic is extended to populations through the

use of cohorts. Markov chain simulation based on cohorts produces material and semiotic connections between individual bodies and the social body. Such connections interfere with the particular narratives about risk, future and anxiety that are targeted towards populations and particular individuals.

Chapter Six explores the performativity of prices and pricing practices. It analyses the nature of pricing as a practice of calculation, the entanglements that this entails and its role in the configuration of particular socio-technical relations around vaccines and healthcare. I present an analysis of this process in Colombia through following the constitution of HPV vaccines as a good. If in the previous chapters I have presented a set of practices of calculation in which the calculative is the Colombian State, a multiple and heterogeneous actor, this chapter is an attempt to constitute pharmaceutical companies as agents. I analyse the ways in which pharmaceutical companies have enacted relations between price and value in the case of HPV vaccines in Colombia. I present the use of pharmaco-economics in the calculation of pharmaceutical prices and explore the role of price in enacting the value of HPV vaccines. Although price is primarily used as a measurement of economic value, HPV vaccines' price becomes a measurement of other values beyond economic valuation. It becomes a comparison unit to estimate the compromise and engagement of parents with their daughters and of the State with its female citizens.

The final chapter offers a conclusive reflection about the relationship between responsibility, accountability and calculation. This thesis is an effort to present the contingency in policymakers' attributions of evidence and causality. Such contingency is denied by experts and governments in public arenas, whilst it is recognised as an attribute of the "lay" attributions done in people's reports of adverse effects. It is not my intention to underestimate the value of EBM in the production of better policies in terms of social justice and human dignity. However I argue that such potential can also be fulfilled through the modest recognition of contingency and the transformations that calculation and quantification entail.

Chapter One

Cervical cancer, HPV vaccines and contemporary healthcare in Colombia

In search of a context for the production of evidence

Introduction

This chapter presents a brief history of the introduction of HPV vaccines in Colombia, locating the production of evidence in this process. I introduce a set of contexts that are relevant to addressing particularities involved in the making of evidence for HPV vaccines as a tool for cervical cancer prevention. I have identified at least three contexts that show the complexity and the messiness (Law, 2004) of the objects and the practices involved in the production of evidence about HPV vaccines in the country. These contexts are the different landscapes-sets of historical configurations in which the production of evidence can be located.⁵

The production of evidence in the introduction of HPV vaccines in Colombia invokes different landscapes in which is possible to situate this process and to trace its complexity. I want briefly to develop three stories about these landscapes I consider most interesting and important to understand this process. These are configurations around cervical cancer as disease, vaccines as cure and Colombia as geopolitical setting.

These configurations are deeply intertwined. Their presentation as fragmented horizons is a narrative resource that I have used to tell a relatively coherent and tidy story about the introduction of HPV vaccines in Colombia. However, these landscapes constantly intersect each other. Stories about cervical cancer and vaccines are shaped by geopolitical segmentations, in particular by the material, representational and political orderings of social and economic development.

⁵ Configuration as Lucy Suchman notes is a “device for studying technologies with particular attention to the imaginaries and materialities that they join together” (Suchman, 2012: 49). Devices are things that do things. Configuration as device is a tool to produce narratives about the complexities of material-semiotic arrangements. A detailed discussion about devices is developed in next chapter.

Introducing HPV vaccines in Colombia: a matter of evidence and efficiency

The process of introducing a vaccine into publicly funded programmes encompasses the debate, study and decision making about its pertinence, cost-effectiveness and safety. This is a fragmented but relatively linear process that involves a diverse set of agents, most of them part of the Colombian State (Ministry of Health, Council of State, National Cancer Institute, Colombian Food and Drugs Administration – INVIMA- and Colombian Congress) but also international agencies (WHO, PAHO, FDA) and pharmaceutical companies.

This process starts after the vaccine obtains a commercial license. During licensing the safety and the effectiveness of the vaccine are tested and endorsed by technical agencies such as the FDA in the U.S or INVIMA in Colombia. Licensing implies the assessment of trial results by committees of independent experts and technical bureaucrats. Such endorsement allows pharmaceuticals to enter the market. After this the key discussion, for public health professionals and authorities, focuses on the vaccine's inclusion into government funded programmes based on their epidemiological pertinence and cost-effectiveness (Munira and Fritzen, 2007).

In 2006 the FDA approved Gardasil (HPV quadrivalent vaccine produced by Merck) and two year later, Cervarix (bivalent vaccine) produced by Glaxo SmithKline (GSK). In 2009 INVIMA, the Colombian food and drugs authority, approved Gardasil and one year later Cervarix obtained registration. After that, private clinics and medical insurance companies began to promote the vaccination of their female patients. The cost of the vaccine, approximately 150 USD per dose, limited access to the urban middle classes.

Since 2010, different local authorities started a discussion about the importance of organising public, free vaccination programmes. Bogotá, the capital of the country, and Casanare, a wealthy oil-producing state, were the first regions to approve and start pilot vaccination programmes. At the same time, the Expanded Programme of Immunisation (Programa Ampliado de Immunización, PAI in Spanish) on behalf of the national government made an agreement with Universidad Nacional de Colombia to develop a technical study about cost-effectiveness of HPV vaccines. This study considered the effectiveness of a national screening programme and the international cost of vaccines in the market (Gardasil and Cervarix), concluding that at the international prices of that time (2009), a national HPV vaccination programme was not cost-effective (UNAL, 2009: 60).

Many voices within the medical community expressed disappointment with the conclusions of that study.

However, a legal class action was the event that forced reconsideration of the study results by the government. In December 2010, Mrs María Teresa Tovar Rojas brought a class action against the Ministry of Health to protect the rights to public health and security that were breached because of the non-inclusion of HPV vaccines into Mandatory Healthcare Plan (POS). As result of this class action, the Court recognized that the Right to Public Health was breached by omission, establishing a deadline of 3 months after the ruling to complete new cost-effectiveness studies. Finally, the Court ruled that if the HPV vaccine was found to be cost-effective, the Ministry had one month to include it in the Mandatory Healthcare Plan. The Ministry of Health and the Health Regulatory Commission appealed this ruling and the case was transferred to Council of State. In parallel to this legal process, in 2011 the congressman Luis Enrique Salas Moisés proposed a Bill in the Colombian Congress in order to guarantee free and mandatory HPV vaccination.

At the end of that year, the Ministry of Health asked Universidad Nacional for a second technical study. This second study included an analysis of the burden of genital warts and concluded that at the international prices of that time (2011), a HPV vaccination programme using Gardasil was cost-effective. Accordingly, the National Committee of Immunisation Practices on behalf of the Ministry of Health approved the introduction of Gardasil into the expanded programme of immunisation. Officially the national vaccination programme against HPV started in August of 2012. President of Colombia Juan Manuel Santos presided over the campaign launch.

In 2013, the Colombian Congress approved Act 1626 (2013) to guarantee an item from the national budget to support long-term HPV vaccination programmes. In the same year the first cases of adverse effects were made public in the national media. Despite these cases, the programme was widely praised by politicians, medical communities and journalists. As I noted earlier, the programme became heavily questioned in 2014 after the Carmen de Bolívar crisis in which hundreds girls were hospitalised after being vaccinated against HPV. This generated a huge controversy in the media and sprawled local protests. Since then, through bodies of experts, the Colombian government has defended the vaccination programme and argued that the evidence supports the safety and effectiveness of the vaccine.

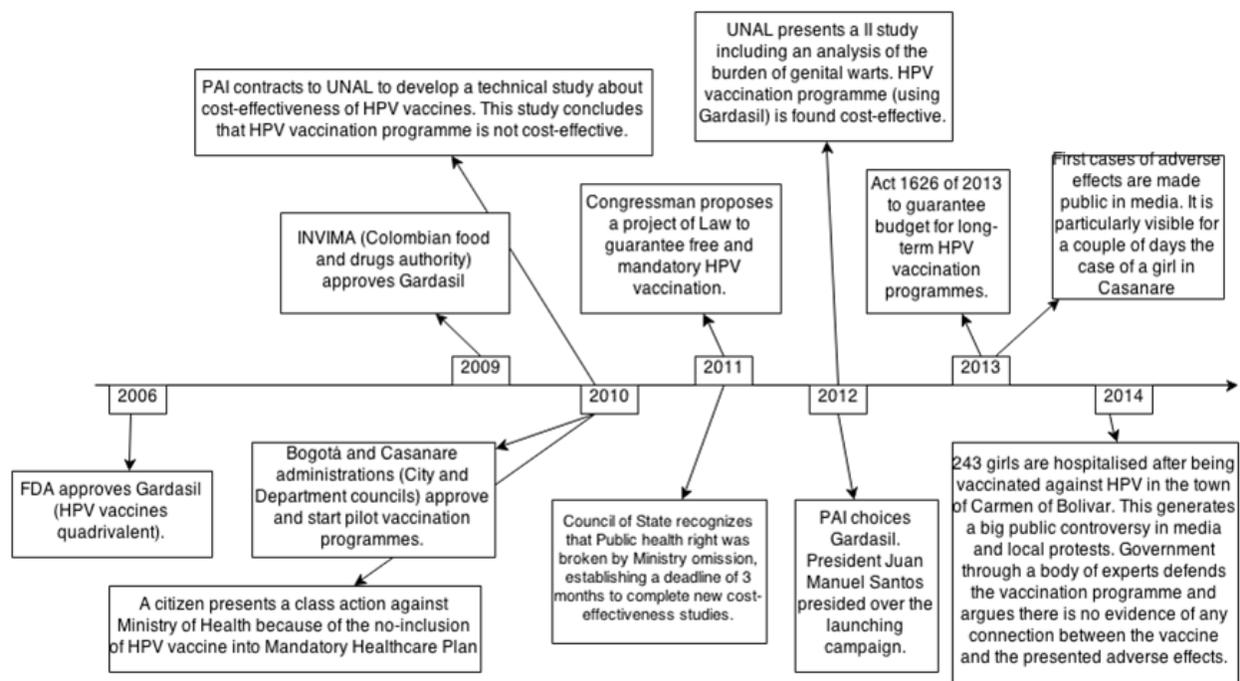


Figure 1 Timeline HPV vaccination programme in Colombia

This set of dates provides an overview of the development of the HPV vaccine's programme and the main issues that have surged in a particularly short period of four years, in parallel with my Ph.D. studentship.

This brief story constitutes the empirical ground of this thesis and is summarized in Fig. 1. In this thesis I analyse the ways in which evidence, and later efficiency, are constituted in the process of introduction of HPV vaccines, tracing the movements of data and numbers between papers, technical committees and decision making arenas. As I will show, the production of evidence in this particular case has been framed by the technical repertoire of Evidence Based Medicine (EBM). EBM is a movement that has extensively promoted the use of techniques such as systematic review, cost-effective analysis and modelling to find evidence, regardless of the nature of the healthcare technology or procedure that is assessed.

In Colombia, evidence and efficiency have been claimed as principles for the healthcare system since its “modernisation” in the 1990s (Act 100 [1998], Agreement 117 [1998] and Agreement 232 [2002]). This regulative framework has presented an ideal of policy based on efficiency, evidence and the proper management of information. Accordingly a good policy is the result of the right data and the right calculation tools. Despite this normative approach, the first attempts to create an institution devoted to the collection and definition of evidence for healthcare policymaking did not happen until 2007 with the establishment of the CRES (Health Regulatory Commission). This institution disappeared in 2012 after a debate about its technical competence and was replaced by the IETS (Institute of Health Technologies Assessment) a public-private organisation based on the model of NICE (National Institute for Health and

Care Excellence) in the United Kingdom. Moreover, in practice, just a small number of procedures and technologies have been evaluated following EBM standards in Colombia. However, amongst these, vaccines have had an important place. PAI has regularly used cost-effectiveness analysis and systematic reviews for the decision about the introduction of new vaccines in the country.

Vaccines provide an interesting case to illustrate the transformation of healthcare governance from international to global health. In 1974 the WHO enacted its 27th Resolution, which fights contagious diseases in children by means of global vaccination programmes. The result of this policy was the creation of extended programmes of immunisation around the world, with particular emphasis on the developing world. “Such effort considered immunisation as the beginning of the extension of healthcare service coverage” (MPS, 2010: 44). In Colombia the Expanded Program of Immunisation (PAI in Spanish) was established in 1974. PAI has had the responsibility of eradicating and controlling contagious diseases through immunisation, particularly in the population under five. However, in the last few years such targets have been extended to other populations, such as 9 year old girls for the HPV vaccine and older people for flu.

In Colombia during the 1990s the programme experienced a reduction of resources that meant a serious reduction in vaccination coverage. The PAI was moved from the Ministry of Health to the Colombian Health Institute (INS in Spanish). The programme was reformed in 2005 with the support of the Inter-American Development Bank (IADB). Bank resources were used for improving the technical capacity of the programme by means of extending PAI technical staff, promoting information systems and developing new guidelines for the introduction of vaccines. The PAI currently covers the following vaccines: Tuberculosis MTB, Polio, Diphtheria, Tetanus, Pertussis, and Meningitis by *Haemophilus influenzae* type B, Hepatitis B, Measles, Mumps, Rubella, Yellow Fever and HPV.

The reformed PAI have adopted EBM tools and in particular cost-effectiveness analysis to decide which new vaccines to introduce. According to current PAI guidelines, any new vaccine must be evaluated to ascertain its technical quality and financial sustainability. The introduction of a new vaccine is made on the basis of the ‘public health character’ of the disease that it immunizes against. In other words, the impact of a vaccine should be expressed in terms of population wellbeing and protection rather than individuals’ health. These considerations coincide with the World Health Organization (WHO) guidelines to assist decision-making on new vaccines⁶. These considerations are presented by WHO as a strategy for

⁶ WHO “has developed a framework that poses a series of questions in the form of a checklist, helping to provide answers to the following considerations: whether the disease is a public health burden; whether immunization is

providing decision makers with rational and convincing arguments to support vaccination (Mayor et al., 2010: 44).

This thesis analyses the role of the EBM repertoire in the managing of the tensions that HPV vaccines entail. Such tensions are related with the historical configuration of vaccines as public health tools, and HPV and cervical cancer as diseases. Techniques such as systematic review, cost-effectiveness analysis and cohort modelling are highly standardised and the space for local adaptation in principle seems narrow. However, as STS has shown, any universal claim is deeply local; the result of situated interactions. In this particular case, such locality is multiple. It is configured by the intersection of different landscapes that intersect and shape each other.

In what follows I will present a brief description of these landscapes. Each one provides a context to address the introduction of HPV vaccines in Colombia and to depict what is specific about the production of evidence and efficiency in this particular case. These landscapes summarise different contributions from medical sociology and STS about the historic configurations of cervical cancer and vaccines. Moreover, this exercise provides an introduction to Colombia as a geopolitical entity in which these elements acquire a particular configuration.

Landscape of the disease: Cervical cancer: development, difference and sexuality

In her book *A Woman's Disease: The history of cervical cancer*, Ilana Löwy notes that “cervical cancer no longer occupies an important place on the list of diseases dreaded by Western women. Breast cancer is everywhere, but cervical cancer is barely visible” (Löwy, 2011: 17). Nowadays cervical cancer is considered a highly preventable disease. However, whilst prevention strategies have been effective in terms of public health in the “North”, cervical cancer has become a disease of the developing world.

Cervical cancer historically has been characterised as a malady that embodies inequity, gender differences and power asymmetries (Löwy, 2011). Epidemiological and medical research on cervical cancer attributed this disease to social groups and women in situations of marginality. Cervical cancer during the last 150 years has been connected with sexuality, race, poverty and nowadays underdevelopment (Löwy, 2011). These categories have shaped epidemiological research, data and policy. As Steven Epstein has noted in *Impure Science*, “epidemiology is inevitably a ‘normalizing’ science, employing—and

the best control strategy; if the existing immunization programme is working well enough to add a new vaccine; estimate the net impact of the vaccine; whether it is a good investment in terms of cost effectiveness; how the vaccine will be funded and how the addition of the vaccine will be implemented” (Piñeros et al, 2007: 901).

reinforcing—unexamined notions of normality to measure and classify deviation from the norm” (Epstein, 1996: 49). Epidemiologic versions of class, race and gender have played an important role in the identification of particular groups as sources of risk and pollution.

Cancer epidemiology and sexuality

One of the first epidemiological portrayals of cervical cancer was made by the Italian physician Domenico Righi-Stern (1842). He found a statistical relation between sexual behaviour and the development of cervical and uterine cancer (Scotto and Bailar, 1969). Such relationship had been reported before by different physicians who observed that cervical lesions were less frequent in nuns than among married women and prostitutes. In contrast, breast tumours were more frequent amongst nuns (Löwy, 2011: 130). During the late 19th century a set of risk factors for the disease were gradually developed. Frederick Hoffman (1896) in his study *Race traits and tendency of the American Negro*, highlighted the relation between “exacerbated sexual behaviour”, “multiple pregnancies” and cervical cancer and features were associated with Black populations (Löwy, 2011: 130). These narratives produced an image of cervical cancer as a consequence of immoral behaviour.

During the first half of the 20th century, class as category of classification becomes important in defining cervical cancer epidemiology. Löwy notes that, for instance, British educational films up to the 1960s presented cervical cancer as a scourge that disproportionately and unfairly affected working-class mothers rather than a direct consequence of immoral behaviour (Löwy, 2011: 134).

Cervical cancer epidemiology has integrated categories such as sexuality, race and class throughout its history. Such classifications appear iteratively in the medical discourses about this disease during the twentieth century. Poverty, sexual behaviour and race are part of the repertoire of risk factors that characterise a disease in which is impossible to distinguish a proper cause. However, within this multi-causal narrative it is also widely recognised that poor women are also affected by frequent pregnancies, inadequate medical care, and harsh life conditions that make them vulnerable to cancer (Löwy, 2011: 134).

Nevertheless, women’s and men’s sexual behaviour took an important role, again, in the understanding of cervical cancer in the 1970s. For the first time a number of large epidemiological studies around the world determined the role of sexually transmitted infections in the development of cervical lesions. These studies were supported by the WHO and its research institute IARC (Interview with Muñoz, 2012). This time the Herpes Simplex (HSV), Cytomegalovirus and the Human Papillomavirus (HPV) were

considered as possible agents (Muñoz et al., 2003). These studies constituted the basis for the molecular biological research into a possible connection between an infectious agent and cervical cancer. In 1982 Harald Zur Hausen demonstrated a causal connection between infection by two types of HPV (16-18) and the development of cervical lesions and neoplasia.

HPV, sexuality and opening the edge to vaccines

Although HPV is depicted as a singular and a stable entity in public and policy arenas, it denotes a family of viruses, more than 100 types of HPV have been identified and approximately half of them infect the genital tract (see figure 2). Approximately thirty percent of these have been associated with the developing of cervical cancer. HPV then, are classified as high and low risk ‘types’.

Pharmaceutical companies have presented HPV 16 and 18 as the main high risk types for cervical cancer, selecting these types as the targets of their vaccines. However, there are other 15 high risk types that have been identified as potential agents of cervical cancer: (HPV 51, 69, 82, 18, 39, 45, 59, 68, 70, 16, 31, 33, 35, 52, 58, 67) (IARC, 2007: 53). As a matter of fact, in some regions these types have a greater incidence than HPV 16 and 18. For instance, in the Sub-Saharan Africa where HPV 42 is the most prevalent, current HPV vaccines could be less effective in reducing cervical cancer. These types have been also found in anogenital and oropharyngeal and epithelial cancers (IARC, 2007: 56). However, in terms of health policy, this link has remained invisible. Scholars such as Epstein (2012) have noted that such marginality is related with their perception as “gay” cancers.

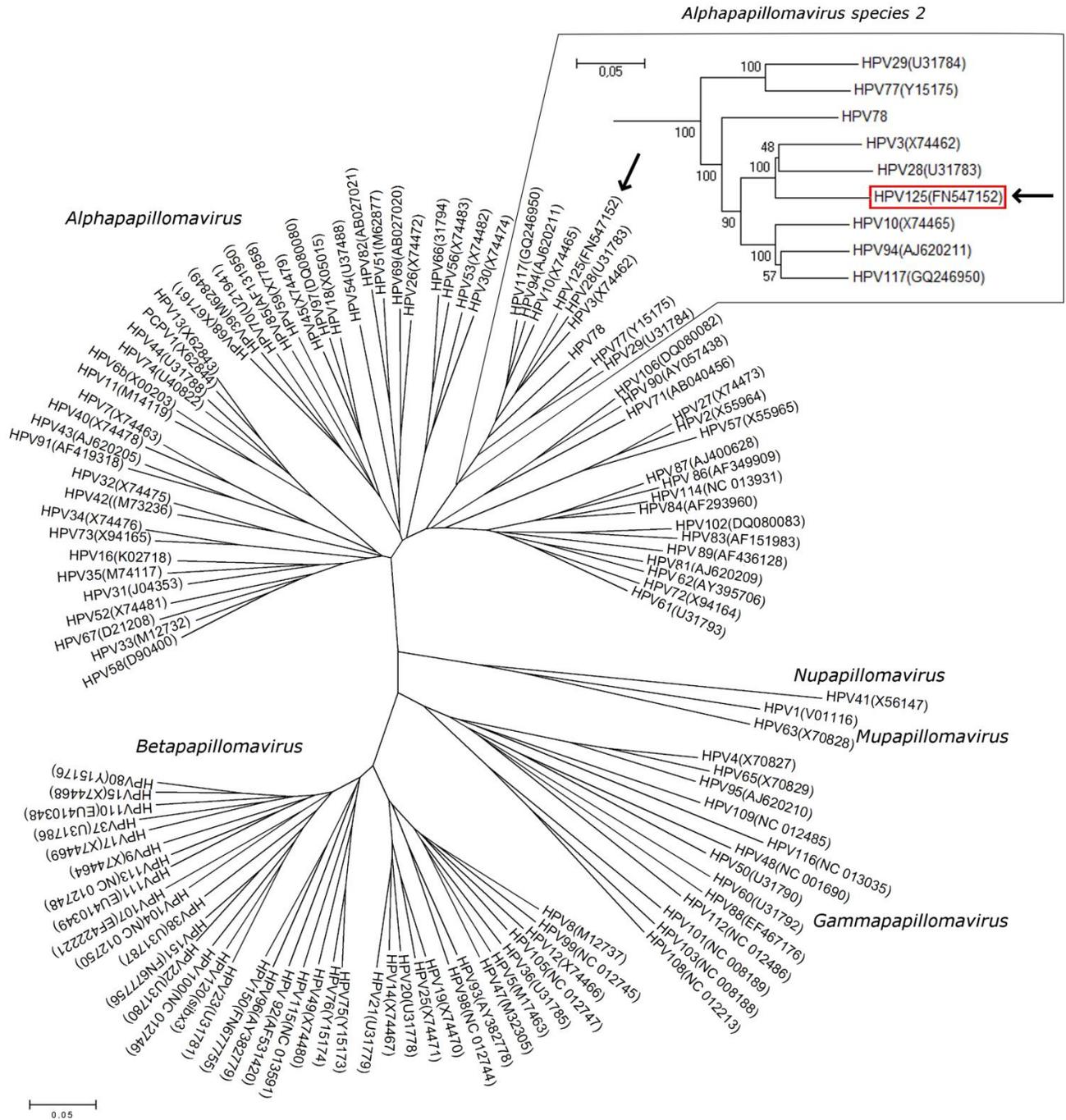


Figure 2 A consensus phylogenetic tree of 117 HPV L1 sequences (Kovanda et al., 2011⁷).

This tree shows the diversity of Human Papilloma viruses (HPV). Most of Alphapapillomavirus (superior branch) has been related to the development of cervical neoplasia, amongst them HPV 16 and 18.

HPV has reshaped understanding of cervical cancer, figuring sexuality once more as the key element in the disease. Although since the beginnings of epidemiological research sexual contagion was considered

⁷ Characterization of a Novel Cutaneous Human Papillomavirus Genotype HPV-125 Kovanda A, Kocjan BJ, Potočnik M, Poljak M - PLoS ONE (2011)

as a possible transmission route for cervical cancer (Rigoni-Stern, 1842) and genital related agents, such as Herpes Simplex virus (HSV), HPV and human sperm were considered possible causes of cervical cancer. It was not until 1980s that the technology to trace molecular DNA allowed a “complete” model to be assembled of the natural history of cervical cancer based on the understanding of HPV proteins’ role in causing cervical mutations.

Such reconfiguration was the basis of the development of a pharmaceutical solution to cervical cancer prevention. At the same time, HPV has been transformed in this process, changing from a relative innocuous agent—HPV is the commonest infection worldwide and in the 99% of cases body develops natural immune response—to a carcinogenic menace and a public health concern (IARC, 2007). Once cervical cancer was redefined as a sexually transmitted disease, now associated with HPV, “the links between social class and cervical cancer were attributed—again—to differences in sexual mores” in men and women (Lowy, 2011: 141). Cervical cancer nowadays is understood basically as the result of a sexually transmitted disease (HPV infection): other factors have been rendered invisible.

Locating difference: the cancer of underdevelopment

These contemporary imaginaries about the disease were developed in a context in which cervical cancer mortality was strongly reduced in developed countries whilst increasing in developing countries. The contemporary cartography of cervical cancer is defined by the gap between the developed and the developing world in relation to its incidence and mortality. Amongst public health specialists cervical cancer became known as the cancer of underdevelopment (PAHO-INC, 1994).

This difference has meant a change of policy priority and public health concerns for international agencies and local healthcare authorities. In developing countries the policy question has not been how to improve health services providing the maximal level of protection, but how to reduce dramatic levels of mortality from this disease. These alternatives of health policy have been expressed in terms of the dilemmas between horizontal and vertical health interventions⁸. In developing countries cervical cancer has been tackled by means of horizontal health interventions. More vertical intervention has been perceived as expensive and a privilege of those who have access to a complete supply of health services.

The contemporary portrayal of cervical cancer in the global south has been framed by policymakers and health authorities (WHO, PAHO, local Ministry of Health) as a matter of economic and social

⁸ A horizontal intervention in Healthcare policy is related to the improvement of population cover, whilst a vertical intervention is related with the improvement in the quality and complexity of healthcare services.

development. From a technocratic perspective an implicit conclusion is that the improvement of the technical infrastructure of screening programmes will make them as efficient as those in industrialized countries (Piñeros et al., 2007; Löwy. 2011: 166). However, such technical infrastructures have faced the social, cultural and political features of the contexts in which they are assembled. Many of these problems are related with serious issues of gender equity. Women have to bear the material and embodied consequences of asymmetric and unfair social, political, economic and affective relations (Gregg, 2011; Livingstone, 2012).

Cervical cancer is a heavily stigmatised disease because of its relation with sexuality. Cancer is presented in public health campaigns in Colombia as a consequence of an uncontrolled sexuality and women as victims of men's promiscuity. These narratives are particularly strong in developing countries in which gender and social inequality are deeply related. Such narratives have been widely reproduced in campaigns and information materials. In countries such as Colombia, public health strategies for the control of cervical cancer have been focused on "populations at risk", those groups whose ways of living correspond with the risk factors defined by epidemiological research. These factors have mainly highlighted the relation between socio-economic marginality and sexual behaviour, in a guide for the attention of cervical cancer developed by PAHO in 1994 for Colombia, for example, it is noted:

Regarding the risk of cervical cancer it is necessary to highlight the wider cultural acceptance of polygyny, temporal unions and the definition of masculinity in relation to the quantity of sexual relations with different women. PAHO-INC (1994: 3)

Despite cervical cancer and HPV contagion being present in the whole population, cervical cancer is defined as a problem of particular segments of society by attributing risk factors. Many of the so-called risk factors describe behaviour that is common to many people regardless of their social and economic resources. However, to extent that some marginalised groups are stigmatised, these factors are only recognized in them.

In Colombia campaigns to promote national cervical screening programme have reinforced these imaginaries. In 2008 the Colombian National Cancer Institute (NCI) developed a campaign to communicate risk factors of cervical cancer and to promote periodic screening as the best strategy of prevention. One of the key elements of this campaign was a graphic soap opera (Fotonovela) about a "working class" couple who faced at the same time husband's infidelity and wife's abnormal Pap test results. This story gathers together many of the narratives that I have described above in which women

are victims of uncontrolled male sexuality, cervical cancer dwells in poor settings, and the disease entails stigma.

HPV vaccines were introduced in this context. The first pilot programmes in Colombia focused on populations at risk. Bogotá's earliest campaign of vaccination was directed at girls from working class neighbourhoods and was extensively promoted as a health equity intervention (Image 3). However, the most extreme case was the vaccination programme of Casanare—a Colombian region—in which the targets were daughters of sex workers. Casanare's Health authorities perceived that these girls were at higher risk of having cancer because of their mothers' work. Nevertheless, once the programme aimed to reach a general and wider population, these strategies and their associated narratives changed toward a more general and desexualised account of risk. Such narrative change has emphasised this technology as vaccine against cancer rather than as strategy of prevention of sexually transmitted disease infection.



Image 3 Launch of Bogotá's Pilot HPV vaccination programme

In the picture, Mayor of Bogotá, Clara López Obregón, nurse from the Health Department and girls from Engativá. Bogotá, Colombia, Department of Health (2011)

Geographical enactments: tracing imaginaries in cervical cancer policy

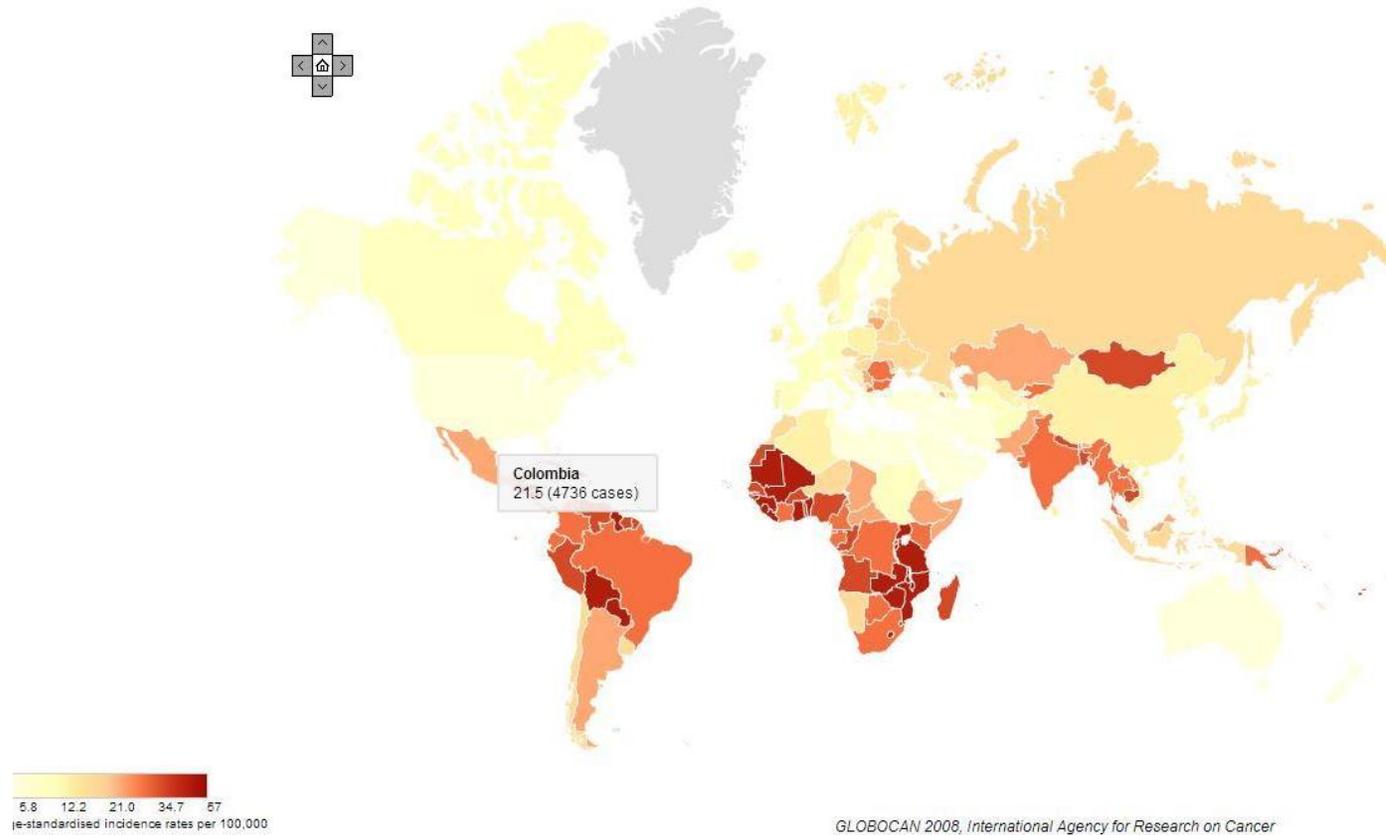
Narratives of cancer and underdevelopment are constantly recreated in the documents that promote HPV vaccines as strategy for the control of cervical cancer in the developing world (WHO, 2007; 2008; 2009; IAVI-PATH, 2007). The contemporary portrayal of cervical cancer in the global south has been framed by policymakers and health authorities as a matter of economic and social development. Such a claim is visually enacted by maps such as the one produced by Globocan (e.g. Map 1). This map reproduces these narratives situating them in a geopolitical scenario.

This map presents a visual representation of the “estimated cervical cancer incidence worldwide in 2008”, which has been produced using the cancer database Globocan Project⁹. Globocan was created by the International Agency for Research in Cancer (IARC) to provide estimates of the incidence, mortality, prevalence and disability-adjusted life years (DALYs) for different cancers at national level. Currently, Globocan provides data for 184 countries of the world. This database is a tool to make and render visible comparisons between cancers and between countries.

Although this information should be collected routinely by cancer registries; in practice many countries do not have the infrastructure to produce these data. Some countries have to rely on data from a few locations to produce a complete and national portrayal by using complex estimation techniques and models. The methods of estimation used by Globocan are country specific and the quality of the modelling and the estimations depends on the information available and its quality. For instance the estimation of the incidence of cervical cancer in Colombia is created by modelling, using data recorded from four Colombian cancer registries covering only 8% of the population for the period 2003-2007 (Cali, Bucaramanga, Manizales and Pasto). These contingencies are rendered invisible in the public presentation of these data. Once the map is produced, it constitutes a rhetorical device to situate cervical cancer in a segmented international context.

⁹ <http://globocan.iarc.fr/>

Estimated Cervical Cancer Incidence Worldwide in 2008



Map 1 Estimated Cervical Cancer Incidence Worldwide in 2008
Source: <http://globocan.iarc.fr/factsheets/cancers/cervix.asp>

Using colour, the map literally renders some countries invisible (those with rates below 12.1) whilst directing our gaze towards a cluster of countries and regions in which the incidence of cancer is high, namely Latin America, Africa and Southeast Asia. This visual representation is often accompanied by texts that emphasise the gap between regions in terms of healthcare infrastructure and impact of the disease. For instance, the following text from a Position Paper of the WHO about HPV vaccines notes such connection:

In 2005, there were about 500.000 cases of cervical cancer and 260.000 related deaths worldwide. Cervical cancer incidence rates vary from 1–50 per 100.000 females; rates are highest in Latin America and the Caribbean, sub-Saharan Africa, Melanesia, and south-central and South-East Asia. Most cases of cervical cancer are diagnosed in women aged >40 years. Countries with well-organized programmes to detect and treat precancerous abnormalities and early stage cervical cancer can prevent up to 80% of these cancers. However, effective screening programmes and follow-up of women with abnormal screening tests have been difficult to implement in low-resource and middle-resource settings. Mortality rates from cervical cancer are therefore much higher in the developing world (WHO, 2009: 119).

These position papers are the official voice of WHO in relation to the safety and importance of health technologies. These documents are extensively used to enact WHO's authority in health policy making. In relation to cervical cancer, this position paper unfolds a geographical imaginary showing an overlap between those countries where rates are purported to be highest and those where surveillance is traditionally worst. Maps provide a rhetorical tool to associate phenomena that seem related but whose causal connection is unknown. In particular the Globocan map renders visible a set of estimations about cervical cancer incidence and mortality which are framed by the interpretative context provided by the geopolitical and symbolic division between North and South.

These kinds of maps and their descriptions are used to produce a landscape in the local (national) policy documents. These devices are used to construct an international scenario in which is possible to locate Colombia. The country is located in the developing world specifically in Latin America, a region in which cervical cancer is rendered a public health concern through the description of its average incidence: 21.4 per 100.000, (i.e 4736 cases detected per year). This map presents countries such as Colombia as

geopolitical spaces in which cervical cancer has a particular shape and specificity. These specifics make sense when contextualised through the comparison with data from other locations¹⁰.

This map highlights the geopolitical nature of the incidence levels of cervical cancer and produces a visual classification between regions. Latin American countries such as Colombia are represented as entities that dwell in ‘the middle’ in relation to the different axes that shape this scenario. Such a link between cancer and development is constantly replicated in global health specialists’ discourse about cervical cancer impact and HPV vaccines (Kane et al., 2006; ACCP, 2004; Parikh et al., 2003). Global health consultants not only argue there is a relation between cervical cancer and development, but also represent HPV vaccines in this context as a matter of technological transfer. For them, these vaccines should be firstly introduced in the North to promote its massive production in order to be transferred to the South at affordable prices. For instance, in a paper published in *Vaccine* in 2006, Kane and colleagues point out:

Human papillomavirus (HPV)-related morbidity and mortality from cervical cancer primarily occurs in the developing world, where, unfortunately, access to vaccines in general and expensive newer vaccines in particular, is often more limited than in the industrialized world. In addition, secondary prevention methods such as HPV screening, Pap testing, or visual inspection are uncommon in the developing world. The HPV vaccine will be first introduced into the industrialized countries and it will then, over the course of time, become used in the developing countries (Kane et al. 2006).

Social and economic development has framed not only cervical cancer as disease but also, as I will argue, vaccines as a medical technology.

Landscape of the cure: Cervical screening programmes and vaccines

Vaccines and cervical cancer have a recent history together. This relation started in the 1980s with the identification of the process by which some types of HPV caused pre-cancerous lesions in epithelial cervix tissue (IARC, 2007: 35). Since 1990 for 15 years different laboratories (National Cancer Institute, University of Rochester, Georgetown University and Queensland University) worked towards the development of a “prophylactic” vaccine against some types of the virus (HPV 16-18 mainly). Finally, in 2006 Gardasil (commercial name of tetravalent vaccine of Merck) and one year later Cervarix (bivalent

¹⁰ For example, a rate of 21.4 (Colombia) is of serious concern when compared with lower rates in the region (Chile: 14.4, Argentina: 16.5) or in the World (U.S.: 5.7, U.K.: 7.2). Nevertheless, Colombia’s rate does not seem so serious when compared with Bolivia (36.4), Nicaragua (39.9) or Guinea (56.3).

vaccine¹¹ of GSK) entered the market. In 2009 the WHO published a position paper recognising the safety and efficiency of these vaccines and recommending their introduction into national vaccination programmes based on affordability and cost-effectiveness. Before this socio-technical arrangement, vaccines and cervical cancer had their own separate worlds of actors, institutions, things and narratives. The prevention of cervical cancer had been based primarily on the development of strong national screening programmes directed at adult women.

From the complexity of cervical screening to the “simplicity” of vaccination

Cervical screening programmes are complex and diverse infrastructures that encompass hospital pathology laboratories, local health authorities, systems of transport, doctors, lay women, health visitors, nurses, local clinics and tests. Although, public health literature (WHO, 2009) often attributes to cervical screening programmes reduced of the incidence of cervical cancer in developed countries, in practice such ‘success’ has been quite contested. The diagnosis of cervical cancer relies on the expertise of highly trained clinicians that visually identify ambiguous anomalies found in Pap tests (Casper and Clarke, 1998: 266). The possibility of mistakes is high and there are many stories about false positives and patients’ overtreatment in cervical screening programmes.

The complexity of the screening systems has attracted the attention of different STS scholars.¹² They have noted the contrast between cervical screening’s contingency and instability, and the narratives about its success in beating cancer. However, as Singleton (1998: 86) notes, such instability has an important role in the performance of the system and particularly in the position that laboratories and scientists have in the programme and within national healthcare systems.

Cervical screening programmes are extended artefacts that demand considerable economic and political resources in order to be able to operate. Since the 1980s the WHO and other health authorities such as PAHO have strongly promoted the development and improvement of cervical screening programmes in developing countries. For instance, Teixeira and Löwy (2011) have described the attempts to create a Brazilian National Program for the Control of Cancer (PNCC) since the 1970s and the difficulties of assembling an effective infrastructure around Pap tests. In Brazil such failure encouraged the use of alternatives to Pap test such as colposcopy as a technology of diagnosis. Colposcopy allowed the doctors

¹¹ The tetravalent vaccine immunises against 4 types of virus (HPV 3, HPV 11, HPV 16, HPV 18), the bivalent vaccines against two (HPV 16, HPV 18). HPV 16 and 18 can cause precancerous lesions in the cervix (cervical cancer) and HPV 5 and HPV 11 are associated with the development of genital warts.

¹² E.g. UK-NHS programme: Singleton, 1998; U.S. Screening programme: Casper and Clarke, 1998; Colposcopy in Brazil: Teixeira and Löwy, 2011.

to deliver a diagnosis in situ without having to wait for results from a central laboratory as in the case of Pap tests (Teixeira and Löwy, 2011: 3).

The organisation of cervical screening programmes in the South has been a difficult task; in part because of the set of institutions and resources they demand which are not available in many countries. Even in the cases in which the infrastructures have been built, decision makers lack of support for programmes and the difficulty in delivering diagnosis to women who have taken the tests are major concerns. Such is the case in Colombia. Despite the different attempts to create cervical screening programmes since the 1970s, a national programme was only established in 1990 (Murillo, 2008: 1). However, this programme lost political support quite early because of its costs and the lack of funding from the central government. With the reform of the healthcare system of 1993, the programme lost vertical and centralised control. Although the regulation included mandatory Pap tests; the treatment of positives was not mandatory for patients without employment insurance (Murillo, 2008: 3). Currently in Colombia only big cities such as Bogota and Medellin have well organised cervical screening with a significant coverage of their female population.

In this context HPV vaccines have been presented as an efficient and simple solution. Although vaccine delivery requires a complex infrastructure of campaigns, storage, cold chain transportation, amongst other, this infrastructure is rendered invisible in public narratives. HPV vaccines are presented as an effective intervention, just three shots to prevent cervical cancer by health authorities. This image heavily contrasts with the complexities and explicit contingencies of screening. Whilst the attention of cervical screening has been focused on the extended network beyond the test; in the case of HPV vaccines such infrastructure is ignored by vaccination policymakers. HPV vaccines have introduced immunisation into the strategies of cervical cancer prevention, broadening cervical cancer prevention from adult women to teenagers and children.

HPV vaccines are thought to be an antidote for cervical cancer's cause: HPV. HPV has transformed the causality of this disease from a multi-caused malady associated with different risk factors to one whose development relies on sexual transmitted viral contagion.¹³ Pharmaceutical companies have been an important actor in this transformation. They have actively promoted a renewed awareness about cervical

¹³ This relation is very complex in the sense that although some HPV types are recognised as causes of lesions in cervical tissue, between the development of such lesions and the occurrence of cervical cancer there are many stages and alternatives. On the other hand, not all the cases of cervical cancer are caused by HPV infection, there are some cases associated with the use of Diethylstilbestrol. <http://www.cancer.gov/cancertopics/factsheet/Risk/DES>.

cancer around the world. In Colombia, for instance, despite the efforts of PAHO and local medical communities to raise cervical cancer as public concern, particularly amongst politicians and decision makers, it was not considered a priority of public health for decades (Wiesner, et al., 2009: 4). However, once HPV vaccines entered the market, this situation changed. Cervical cancer became a public concern, different governors have discussed the development of local vaccination programmes and politicians started the discussion of a law in the congress to regulate cervical cancer prevention and to promote HPV vaccines.

This interest has reshaped narratives about cervical cancer in relation to risk, stigmatisation and inequality. Some of these narratives have had a global reach because they have been produced through international research and global policy. However such narratives and representations are locally enacted in relation to particular material and discursive contexts. To the same extent that HPV vaccination policy has appropriated and reconfigured narratives and materialities from cervical cancer, it has inherited a set of problems from vaccines' history. As I will explain such history is marked by different tensions: between vaccines' global infrastructure and the personal and embodied experience of immunisation, their promise of anticipated protection and their actual risks, and their altruistic social contract and the consequences of individual choice.

The world and body meet in a needle: risk, anxiety and geopolitics

Vaccines are a medical technology with a history full of tensions and contradictions. They are considered the most effective tool of public health and the cause of medicine's most significant triumphs: the eradication of smallpox and the fight against the polio. "Vaccination – and especially mass childhood immunization – is acclaimed as the most successful and effective form of public health intervention that there has ever been" (Leach and Fairhead, 2007: 6). However, they have also been the target of criticism and distrust. The anti-vaccines movement has been one of the clearest manifestations of patients' resistance to promises of medical science¹⁴.

From a Global Health perspective, vaccines have been perceived as a "basic good", important as water and food. As Leach and Fairhead (2007) have noted, wars have been suspended for vaccination. For instance, during the 1990s war in Sierra Leone, vaccines crossed front lines that food convoys did not (2007: 6). Vaccines have had significant political support, in particular when they are dealing with

¹⁴ Anti-vaccine reactions have been heterogeneous. In Europe and North America, it can be characterised as a middle-class movement. In other locations it has sometimes resulted in violent protests such as in the case of the Taliban's opposition to Polio vaccination programmes in Pakistan (Financial Times, 7th June 2013).

pandemics and tropical diseases. Vaccines have been considered tools to reduce mortality mainly in developing countries and to provide long-term healthcare through population immunisation by international organisations.

In 1974 the WHO launched the Expanded Program on Immunization (EPI), from then until 1990s vaccine coverage in developing countries increased dramatically (Mahoney et al, 2007: 4005). For instance, the Colombian Expanded Programme on Immunisation (PAI in Spanish) was established in 1974, being very successful in eradicating smallpox and polio. Such victory has meant important support from government, politicians and media. Despite the success of vaccination in the Americas, The Expanded Programmes of Immunisation have had serious difficulties in Africa and Southeast Asia. In response to the difficulties of maintaining the coverage of current vaccines, as well as the additional difficulties and cost of introducing new ones, the Global Alliance for Vaccines and Immunization (GAVI) was created in 2001 (Mahoney et al, 2007: 4005).

Such dynamics of international cooperation and partnerships are not entirely altruistic. In a world of mobile people and microbes, eradicating infectious diseases is increasingly a global public good. The rich can catch the diseases of the poor. “An agenda of mutual north–south self-interest has undoubtedly played a role in pushing immunization up international political agendas” (Leach and Fairhead, 2007:7). As Roalkvam and Sandberg (2010) note a global system of policies, institutions, economic resources and narratives has been developed around vaccines. Such infrastructure has been created at global scale with a clear segmentation between “North” as designer and funder and “South” as beneficiary and target of intervention (Roalkvam and Sandberg, 2010: 293).

The devices that enable the mobility of the vaccines among national regulation and geographic locations are an important element in the study of co-production of local-global dynamics and medical technologies. Roalkvan and Sandberg point out that vaccines not only move from the global to the local in a physical sense, but also that they pass through multiple decision-making arenas. Such arenas entail the interaction of actors located at different levels (Blume and Zanders, 2006; Blume and Tump, 2010). Similarly, the WHO has a network of technical assistance offices around the world connected with Geneva. “When national authorities make decisions on the composition of their immunization programme, their advisory groups often have international members. Finally, local health facilities are connected with the national health system through the exchange of information and national policies” (Roalkvam and Sandberg, 2010: 296).

Vaccines as a health technology act through an extended network of actors and institutions beyond the vaccines themselves (Blume, 2009, Oudshoorn, 2003). They involve a socio-technical arrangement that encompasses things such as needles, syringes and oral droppers; other technical systems including refrigeration, transport and technologies of population registration and record-keeping; and institutional and governance regimes and institutions (Leach and Fairhead, 2007: 8). Such socio-technical networks produce connections between global arrangements and the most personal and embodied experiences. Vaccines are produced, distributed and monitored within a globalized system. Such systems at the same time are very personal. Vaccination registers, for example, are designed for following and identifying each child who gets the vaccine.

The power of vaccines in contemporary societies relies on these transits between global and local, however, the same blurriness of such boundaries is a source of risk and mistrust. Vaccine programmes have been attacked in different parts of the world because they have been perceived as control strategies of international powers. Leach and Fairhead have described how different governments in Africa have rejected vaccines and international aid programmes related with immunisation because they have been perceived as biological weapons and strategies of forced sterilisation. In Colombia, for example, PAI health workers have pointed out that during the 1980's in some villages and small towns, they were attacked because local priests condemned the vaccination programme, pointing out that it was an imperialistic effort of mass sterilisation (Mayor et al., 2011). Gardasil have been seen by right and left wing groups in Europe and U.S. as an expression of corporate capitalism, of its hunger for profit and its lack of interest in the rights of families or the health of girls (Forbes, 23rd March 2012).

Health inequities and the heterogeneous geographical distribution of diseases interfere with the shaping of vaccines as technology and with their politics. Vaccines in the poorest countries have been framed in global health policy as a good for achieving the Millennium Development Goals and to reduce childhood mortality. Vaccines are presented as a direct action against diseases whose effects (death and suffering) are evident. In contrast in the regions where vaccines have been successful in the reduction of transmittable diseases, the vaccines' scenario has substantially changed. Vaccines are envisaged as solutions to the excesses of over-consumption: important resources have been invested in the development of promising vaccines against obesity, drug addiction and cancer (Leach and Fairhead, 2007: 6).

However, at the same time the legitimacy of traditional vaccination has been eroding by its own success. The reduction of mortality by means of vaccination has made some diseases invisible while vaccines'

risks have reached a wider attention. Death and epidemics associated with contagious diseases seem part of a distant past in developed countries, while information about adverse effects and risk are available on the internet for public consultation. This image contrasts with the situation of poor countries where transmittable diseases are still one of the main causes of mortality. For developed countries contagious diseases are a matter of concern to the extent viruses and diseases are perceived as highly mobile, breaching their national boundaries; (The Ebola outbreak is a current example).

Moral calculation: Free riders, informed decisions and responsibility

This trade-off between benefits and risks has highlighted the moral character of vaccines. Vaccination programmes as public health interventions assume a social contract in which individuals take individual risks in favour of a collective good: community immunity by herd effect. The rejection of vaccines has been considered by vaccines' promoters as a breach of this tacit agreement. Some analysts have described this behaviour in terms of the Prisoner's Dilemma, or the Tragedy of the Commons, in which is rational to avoid the vaccine once herd effect is sufficiently strong. "As vaccine-derived herd immunity builds, the probability of being infected declines and eventually goes to zero" (Bauch et al. 2010: 1).

Beyond these interpretations of individualistic behaviour and rational choice, the perceptions of risk have been a key factor in the rejection of vaccines and in the shaping of anti-vaccine movements. Once the visible effects of contagious disease are controlled, probability, risk and causality of vaccine and disease become a visible matter of concern. Vaccines are prophylactic technologies, they are administered to healthy individuals to prevent a disease. The value of a vaccine depends on the calculation of the probability of occurrence of the disease and the weight of the risks associated to immunisation. Any pharmaceutical drug entails some risk and regulatory authorities are aware of potential adverse effects. Vaccines in that regard constitute a special kind of drug because they are given to healthy individuals to prevent a disease to which may be never be exposed (Tomljenovic, 2011: 1).

The origins of contemporary resistance to vaccines can be traced in the 1970s when different cases of adverse effects questioned their reliability and safety.¹⁵ In 1976 the swine-flu vaccine distributed in the United States was associated with Guillain-Barré syndrome, a paralytic disorder that is often treatable but can cause long-term disability or death (Kwok, 2011: 438). However, one of the biggest recent controversies took place in the United Kingdom in the late 1990s. A group of parents—that had perceived

¹⁵ For a history of the early opposition to vaccination in England see: Bodily Matters: Durbach, Nadja. 2006. *The Anti-Vaccination Movement in England, 1853–1907*. Durham: Durham University Press. In Colombia, see: Obregón, Diana. 2014. *La vacuna o la política de las cosas*. Bogotá: Ensamblado en Colombia.

adverse effects of MMR vaccination in their children—began to come into contact with medical specialists who might take their experiences seriously. “Key among these was Dr Andrew Wakefield of London’s Royal Free hospital, whose work was already suggesting possible links between measles virus and the development of inflammatory bowel disease” (Leach, 2005: 7). In 1998 Wakefield and his colleagues published a paper in *The Lancet* (Wakefield et al. 1998), detailing how 12 children of previously normal development had suddenly lost their language and social skills, and had developed a new type of bowel disease (ileocolonic lymphoid nodular hyperplasia). Although they conceded that this condition could have happened by chance, they suggested that they had found a particular disease: autistic enterocolitis. The paper did not claim that this disease was caused by MMR vaccine, but it mentioned that some children’s parents believed that MMR had been a trigger. “This and then a subsequent paper reviewing the literature on the MMR vaccine and suggesting that its original safety studies had been inadequate were reported dramatically in the media, sparking what became a high-profile controversy”(Leach, 2005: 8).¹⁶

The claims about a possible relationship between MMR and autism were strongly discredited by international health authorities. Different studies conducted by the National Health Institute (US), National Health Service (NHS) and the Center for Disease Control (US) found no links between this vaccine and autism or bowel disease. Finally, Wakefield was accused of fraud by manipulation of data and in 2010 *The Lancet* retracted Wakefield (1998) paper. In spite of the discrediting of the MMR-autism relationship, other studies have found that adverse effects are greater when the vaccine is administered with other vaccines in a single shot. In 2007, researchers at Kaiser Permanente Vaccine Study Center in Oakland, California found that children aged between 12 and 23 months who had been immunized with a combined vaccine for measles, mumps, rubella and varicella (MMRV) had more febrile convulsions 7–10 days after vaccination than those receiving separate MMR and varicella vaccines. “The finding prompted a US immunization advisory committee to withdraw its preference for the MMRV vaccine. A subsequent study suggested that the combined vaccine resulted in one more febrile convulsion per 2,300 doses than the MMR and varicella vaccines given separately” (Kwok, 2011: 438).

HPV vaccines’ introduction has been followed by complaints of adverse effects from chronic fatigue syndrome to death. However, health authorities around the world have systematically dismissed those claims arguing lack of evidence about the cause of such adverse effects. They argue clinical trials have extensively demonstrated the safety of these vaccines (WHO, 2009). HPV vaccines offer an empirical

¹⁶ In the UK recently this debate have resurged in media because the measles outbreak in Wales and a sense that there is now a generation of young people who are not sufficiently protected by vaccines.

case to understand the ways in which these medical technologies are governed through socio-material assemblages and the impact of the narratives that circulate through them in the enactment of different subjectivities confronted by risk, anxiety and anticipation. Narratives and debates about safety and risk are shaped by calculation practices and devices of production of “legitimate” evidence.

This tension between vaccines’ promises and the risk they entail has been described by Leach and Fairhead (2007) in terms of anxiety. The notion of anxiety is central in contemporary debates about immunisation, particularly in relation to the experience of parents. According to Leach and Fairhead, anxiety is a double-edged word. “Used in a negative sense, anxiety implies a state of unease, worry or concern. Yet it also has a positive meaning, implying an earnest, focused desire for something, or to do something” (Leach and Fairhead, 2007: 3). Anxiety can be understood as an affective effect of the calculation of risks and their consequences. In the case of HPV vaccines, the anxiety is experienced not only by parents but also young people. These vaccines have been promoted by means of discursive repertoires that emphasise self-care and responsibility.

HPV vaccines are changing the traditional focus of vaccines on population health and they are becoming drugs against individual risk (Aronowitz, 2010). This strengthens the disjuncture between civic responsibility and consumer choice that is framed into the health policy notion of efficacy as risk reduction and control of the disease. To the extent that vaccines are promoted by pharmaceutical companies on a global scale, these processes can be perceived in different locations around the world, in developing and developed countries (Carpenter and Casper, 2009, 2010; Mihra and Graham, 2012; Colgrove, 2010; Epstein, 2010; Aronowitz, 2010; Mamo et al., 2010; Ramogola-Masire, 2010; Livingstone et al, 2010). Authors such as Aronowitz have pointed out “it is possible that when the vaccines are co-constructed as proprietary drugs against individual risks, they are in danger of losing their appeal as public goods” (Aronowitz, 2010: 32). As I will present in this thesis, in Colombia, as is happening in other places, HPV vaccines are simultaneously promoted and perceived as drugs for individual risk when they are distributed through the market and as public goods within government vaccination programmes. However, these alternatives are not mutually exclusive; on the contrary these narratives depend on each other to communicate their value.

Geopolitical landscape: living in the middle and healthcare in Colombia

The configurations of cervical cancer and vaccines have been shaped by geopolitical classifications and narratives about the degree of social and economic development of the locations in which disease and cure are enacted. In this last section I elaborate some features of Colombia as a geopolitical location in

which cervical cancer, vaccines and the production of evidence reach a particular configuration. Within the scenario produced by data, policies and global health narratives, Colombia is defined as a middle income country whose cervical cancer mortality and incidence corresponds to its level of development. The implicit assumption is that middle levels of development are deeply related with “half-table” positions regarding the burden of particular diseases. In this framework, cervical cancer is related with undevelopment and this with poverty. The higher the inequity of a society, the heavier the burden of preventable diseases such as cervical cancer.

At the same time being a middle income country implies the recognition of financial and technical capacities that confer an increasing autonomy in the governance of healthcare. The cooperation of international organisations (WHO, PAHO, IADB and the World Bank) is nowadays focused on technical assistance. In that regard, cost-effectiveness analysis and the use of tools for the production of evidence has been strongly promoted by these actors. On the other hand, countries such as Colombia are perceived as new markets for the pharmaceutical industry. Middle income countries are presented as nations that have made “important” progress in terms of economic growth and social development (WHO-ICO, 2010). However, they are far from being a developed country yet.

Policies and technical documents about cervical cancer and HPV vaccines present data for establishing classifications between countries and suggesting correlations between disease and other socio-material conditions. The Globocan project, for instance, in the presentation of the burden of cervical cancer, uses the Human Development Index (HDI¹⁷). These classifications have important outcomes in relation to economic and political resource distribution and the shaping of health policy governance. The WHO has established a classification in different regions for promoting the introduction of vaccination programmes. These regions are: The Americas (Latin America and Caribbean), Africa and South-East Asia. WHO’s support is to provide technical assistance. Furthermore a set of countries has been defined through the GAVI Alliance¹⁸ for priority attention. “GAVI aims to focus its support on the world's poorest countries¹⁹”.

¹⁷ <http://hdr.undp.org/en/statistics/indices/>. There are many indexes of development which materialise different ideas about development. HDI is a composite index of four indicators that reflect “major dimensions” of human development: longevity, knowledge and access to resources (Noorbakhsh, 1998). These dimensions are derived from Amartya Sen’s human capabilities notion. HDI is an attempt to deal with the complexity of socio-economic realities whilst avoiding the extreme reduction of other classifications based on income such as GDP. However, the calculation of international HDI shares the material limitations that affect the production of data about cancer incidence: disparities in data infrastructure. Nevertheless, HDI renders visible a classification of countries beyond the dichotomy between developed and developing countries.

¹⁸ GAVI is a public-private partnership focused on promoting access to immunisation in poor countries.

¹⁹ Eligibility is therefore determined by national income with all countries with a Gross National Income (GNI) per capita below or equal to US\$ 1,520 (according to World Bank data for the latest available year) qualifying for support. There are currently 57 GAVI-eligible countries. However, not all of these countries qualify for every type

Alternatives to the dichotomy developed-developing such as HDI and income per capita have shaped the idea of middle-income countries. These classifications are political acts. Institutions such as the WHO and the World Bank by means of classification “exercise the specifically symbolic power to impose the principles of construction of reality, which is an important dimension of political power” (Fourcade, 2013: 265). Country classifications and denominations such as ‘middle-income countries’ attempt a more detailed ordering of the differences between countries in terms of development.

The idea of middle-income countries has been received positively by global health experts and policy makers in Latin America. Some of them, such as Frenk and colleagues (1989) have noted that is simplistic to classify world health in bipolar terms, such as East vs West, or North vs South. For them, the classification done by the World Bank based on national income per capita addresses the particularity of Latin America health scenarios. Such scenarios are better depicted by the concept ‘middle-income countries’ than by developing countries (Frenk et al., 1989: 30).

These representations have reproduced narratives about the nature of Colombian society that have shaped the regulations and the policies that constitute the national healthcare system. In Colombia since the 1990s the healthcare structure has been transformed following the insurance-based system and the managed-care model of the United States (Dezalay and Garth, 2002; Florez, 2009; Escobar, 2010). These reforms meant the end of the previous “subsidies to supply” approach (direct money transfers to public hospitals) and the beginning of “subsidies to demand” (governments buy managed-care insurance for the poor from competing insurance companies) (Abadia and Oviedo, 2009). Colombia was pioneer of these reforms in Latin America adopting a model called ‘structured pluralism’²⁰.

In the paper “Structured pluralism: towards an innovative model for health system reform in Latin America” published in 1998 in the journal *Health Policy*, Juan Luis Londoño and Julio Frenk make a detailed presentation of this model. This paper is interesting for several reasons. Its authors are representatives of the Latin American technocracy and were protagonists of healthcare reforms²¹ in

of support because GAVI sets conditions for each type of support” (GAVI, 2014). GAVI has approved the support for HPV vaccines; the plan is introduce the vaccine into the GAVI funding schema for 2020. Colombia as a middle-income country is excluded from such schema.

²⁰ This model is defined “as an organizing structure with explicit rules and functions for the interactions of a choice exerting population, a modulating state, a financing social security network of institutions and an increased pool of service providers” (Abadia and Oviedo, 2009: 1153).

²¹ Juan Luis Londoño, Ph.D. in Economics (Harvard) was twice Minister of Health of Colombia (1990-1992; 2002-2003) and Julio Frenk, physician and Ph.D. in Sociology (Michigan) was Minister of Health in Mexico (2000-2006). Both were consultants of international organisations such as WHO, PAHO, World Bank and IADB

Colombia and Mexico. But most importantly, the paper makes explicit many assumptions about the “nature” of Latin American societies and its relationship with healthcare reforms. In particular, I would like to highlight the characterisation of Latin America and Colombia as a transition region and the role of inequalities. These are the same narratives that have framed the reading of geographical images such as Map 2.

According to Londoño and Frenk the main challenge for healthcare systems in Latin America is to deal with the deep social inequalities and the diversity of problems that such conditions entail.

Health systems in this region have to face a dual challenge: on the one hand, they must deal with a backlog of accumulated problems characteristic of underdeveloped societies; on the other hand, they are already facing a set of emerging problems characteristic of industrialized countries (Londoño and Frenk, 1997: 1).

Inequality produces a context where some people have the same living standards as those in developed countries, whilst simultaneously an enormous population lives in extreme poverty:

The combination of rapid and unequal change in many Latin American countries has brought them face to face with a series of new problems—characteristic of the more developed societies—without having totally solved the old problems typical of poorer societies (Londoño and Frenk, 1997: 3).

Such characterisation of health and disease in Latin America shares many features with the geographies that are rendered visible in international policies and their cartographies. Some conditions and diseases are presented as endemic to regions and living conditions, while other health problems are recognised as global (or that links global populations that share common characteristics – i.e. the poor, slum dwellers, women etc). Global health narratives and technical resources have addressed contagious and non-contagious diseases as matters of global action, even if the strategies are locally and nationally limited (Roalkvam and Sandberg, 2010). The answer proposed by “structured pluralism” to these global-local challenges is to shape healthcare as a market, where patients, as customers, can choose the best option available (Act 100 [1993]). Healthcare providers in this scenario are in constant competition. The role of the state changes from direct delivery of services to the funding and surveillance of these services.

Healthcare (market) reforms and the politics of evidence in Colombia

Social security systems were the main targets of market reforms (Escobar, 2010) in which healthcare provision and pension systems underwent deep changes. In Latin America this transformation started in the 1990s, as an enterprise promoted by national technocracies and multilateral organisations (Dezalay

and Garth, 2002; Escobar, 2010, Dargent, 2015). Insurance-based healthcare reforms were promoted by national governments and multilateral organisations (IADB, World Bank, PAHO) following the Managed-Care model of the United States.

Market reforms in healthcare have involved a change in the delivery of healthcare services from public institutions to insurance and health companies and the transformation of the state into a market regulator. For the state this new role has involved the development of institutions, regulation and calculation devices. States have to assure the quality of goods and services, as well as define strategies for a sustainable distribution of subsidies by means of cost-effectiveness analysis of health interventions. In Latin America, the healthcare reforms affected by the ‘Washington Consensus’ were not monolithic, uniform, or unidirectional. For instance, in Colombia, the market reforms were developed in a context of democratic renewal expressed in the 1991 Colombian Constitution (Atun et al., 2015). As result the 1990s reform of the healthcare system is shaped by narratives of solidarity, distributive justice, efficiency and marketised choice.

In Colombia healthcare reform was materialized in the Act 100 [1993], which defines the institutional and regulatory architecture of Colombian healthcare system. This “structure” has been considered as the first large-scale experiment with managed competition in the developing world (Guerrero et al. 2011; Abadia and Oviedo, 2009, Ewig and Bello, 2009). Colombia has been a ‘laboratory’ for the implementation of a system of regulatory commissions, health care insurance companies, service provider institutions and patients. In this setting, patients are portrayed as consumers who would exert power by choosing the best services from different options fixed by the state through risk adjusted premiums (Abadia and Oviedo, 2009: 1154). The Act 100 [1993] created a System of Social Security in Health (GSSSH) comprised of two regimes, the contributory regime (CR) and the subsidiary regime (SR). The CR is composed by waged and retired workers and independent workers with annual income above a minimum salary (281 USD monthly). The SR affiliates people without regular or sufficient income. In 2010 system’s coverage was 39.7% and 51.4% respectively.

A group of health policy experts supported the technical design and political implementation of this reform in Colombia. These ‘technocrats’ have been health ministers (Juan Luis Londoño, Mauricio Santamaría, Beatriz Londoño, Alejandro Gaviria) or ministerial advisors to different Colombian governments since Cesar Gaviria’s presidency (1990-1994). Within this group Juan Luis Londoño was a key protagonist in the organisation of the current healthcare system, firstly, as part of the team that designed the Act 100 [1993], secondly as global health expert at Harvard with Julio Frenk in the

conceptual definition of ‘structured pluralism’, and finally, as Minister of Health in the presidency of Alvaro Uribe (2002-2003). Health technocrats in Latin America such as Londoño introduced these local reforms into an international network of global health policies and technical resources by mediating the technical cooperation from ‘calculation centres’, such as the Harvard School of Public Health, and by offering to these networks a laboratory in which test models and conceptual tools. In Colombia, starting in 1994, a team of experts dubbed ‘the Harvard Group’—due to the consulting support from the Harvard School of Public Health—provided technical assistance to the reform in the following years. ‘These experts and consultants produced what is known as “The Harvard Report” (Colombia Health Sector Reform Project 1996), a plan that included a blueprint for implementing the reform’ (Dargent, 2015: 191).

In spite of the emphasis on healthcare modernisation by the opening up of the system to the market, the Act 100 [1993] is a particular blend of narratives about equity and efficiency. In fact, in this framework these principles are not mutually exclusive. On the contrary, the efficiency provided by the market is a key element in the use of public resources and in the promotion of equity. However, this reform was envisaged as a long-term process, in which initial structural economic transformations would allow the future improvement of health services and equity in their access. The initial concern of the reform was to improve the access to basic health services. At the same time, it was expected that the Colombian State would increase its technical capacities to regulate the quality of the services by grading evidence about effectiveness and safety of the healthcare supply.

The healthcare supply of drugs and treatments was defined by a mandatory plan (POS, acronym in Spanish) that established the minimum insured services. It described diseases, treatments and medicaments. According to the Colombian regulation, the POS provides a guide for healthcare attention that covers prevention, surgical and medical care and essential drugs (Act 100 of 1993, art. 156 p. C). Nevertheless, in practice the definition of this set of procedures and drugs has been highly contested and has pushed the system into a financial and political crisis.

Despite Colombian health care system being ranked as the best in the Americas in overall performance and first in the world in fairness in financial contribution (WHO, 2000) (Abadia and Oviedo, 2009: 1155), currently there is an extended perception of crisis. Such crisis has been attributed to corruption, interference by the courts in the definition of POS services and the reduced size of the contributory regime. Such crisis has been related to several factors, “including increases in preventable diseases associated with a decline in vaccination rates, the end of prevention and public health programs, the collapsing of the public health care networks represented by the closing of many public hospitals, the

revoking of healthcare workers rights, and the promotion of a market mentality that has shifted the focus away from healthcare” (Abadia and Oviedo, 2009: 1155). Additionally, it is perceived that the system is focused on coverage instead quality of services.

For supporters of the system’s model, the interference of high courts and legal decisions has been a key factor in the sustainability crisis. Some economists in Colombia such as Jaramillo (2011), Gaviria (2010), Nuñez and Zapata (2012) have criticized the fiscal impact of the High Courts’ rulings on healthcare public expenditure. Jaramillo argues that the additional cost of sentences is 1% of Colombian GDP (Jaramillo, 2011, Nuñez and Zapata, 2012). On the other hand, they note, health insurance companies have acted as a cartel in their interaction with the Colombian State. Instead of competing in a market, these companies have controlled prices and restricted the quality of services. Moreover, some of them have used legal strategies to increase the government payments in the subsidiary regime.

For critics of the system, the use of legal instruments by patients is a consequence of the limitations in the supply of health services. Lawsuits against the State (Tutelas) have had an important impact in health care provision. Patients can demand drugs and procedures that are not included in the healthcare plan, when the lack of such treatment breaks a fundamental right. The Constitutional Court has an important tradition of ruling in favour of the recognition of health as a fundamental Right (T 238 of 1998, SU 819 of 1999, SU 480 of 1997, T 906 of 2004, T 597 of 2010, T 760 of 2008, among others).

The Colombian Constitution provides legal mechanisms to protect citizens’ cultural, social, political and health rights. Tutelas (writs for the protection of constitutional rights) are the most common legal action used by citizens to ask the judiciary system for protection. Of the 1.067.070 writs initiated by Colombians between 1999 and 2005 (most current data), 30.76% (328.191) asked to grant the right to health specifically (Abadia and Oviedo, 2009: 1155).

This situation has focused the attention of the government on mechanisms to make and to justify decisions about drugs, treatments and funding thresholds. The Mandatory Healthcare Plan (POS) was defined in 2007 by the National Council in Health Social Security (NCHSS). Such approval should be based on the assessment of changes in the demographic structure, the national epidemiologic profile, the effectiveness and the cost of the procedures. However, the capability of this committee to deal with the High Courts’ rulings and with the increasing supply of new technologies, was very limited. In that context, medical communities asked for more evidence and efficiency in the definition of the policy. Evidence based medicine will appear as the right strategy to overcome such crisis.

In Colombia, evidence and efficiency have been claimed as principles for the healthcare system since its “modernisation” in the 1990s (Act 100 [1993], Agreement 117 [1998] and Agreement 232 [2002]). This regulative framework has presented an ideal of policy based on efficiency, evidence and the proper management of information. Accordingly a good policy is the result of the right data and the right calculation tools. Despite this normative approach, the first attempts to create an institution devoted to the collection and definition of evidence for healthcare policymaking did not happen until 2007 with the establishment of the CRES (Health Regulatory Commission). The CRES introduced the EBM repertoire into Colombian health policy. This commission made the first attempts to develop health technology assessments (HTA) to justify the inclusion or exclusion of drugs and medical procedures. Moreover, with the support of the Inter American Development Bank (IADB), the CRES negotiated with NICE International a cooperation plan to train economists and health professionals in cost-effectiveness analysis, particularly in the use of QALY and DALYS.

Despite, the initial enthusiasm of the government, the CRES was closed in 2012 after a debate about its technical competence and impartiality. Some politicians accused the CRES directives of being corrupted by the pharmaceutical industry. The CRES was replaced by IETS (Institute of Health Technologies Assessment) a public-private organisation based on the model of NICE (National Institute for Health and Care Excellence) in the United Kingdom. IETS will have an important role in the contemporary reform of the Colombian healthcare system. The Act 1751 [2015] changes the dynamics of inclusion of medicines and treatments. The government will define cost-effectiveness thresholds to decide about the provision of healthcare instead of defining a closed list of goods and services. It is expected the IETS will provide evidence about health technologies cost-effectiveness to guarantee healthcare sustainability.

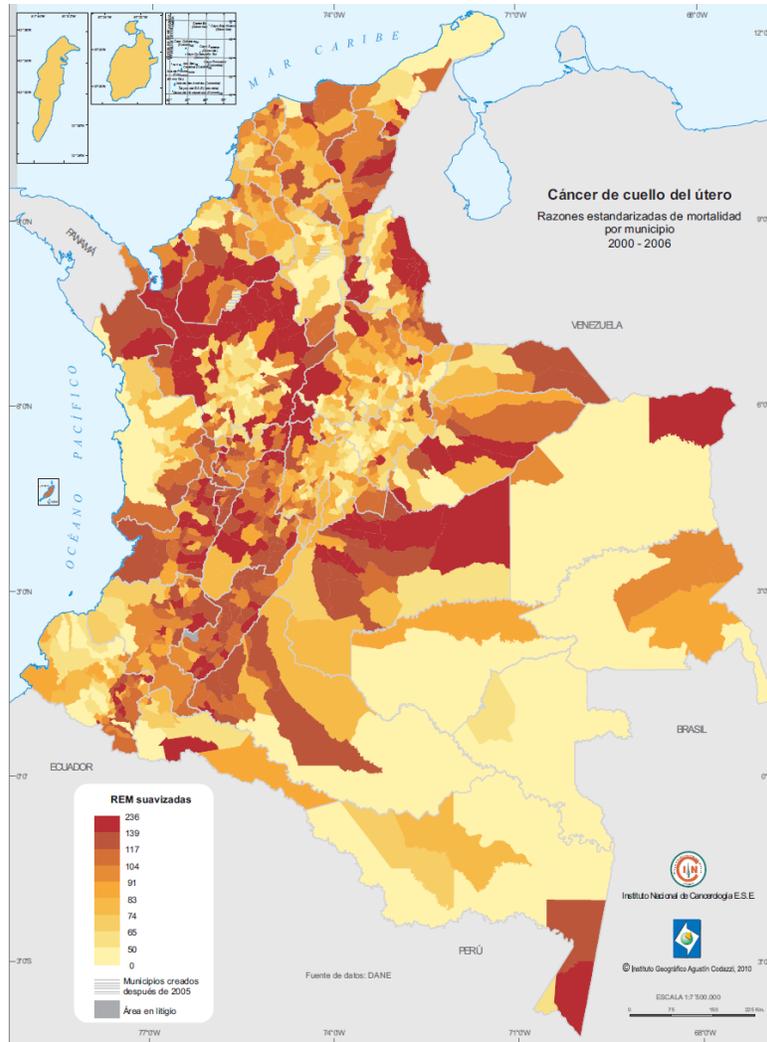
This state of affairs is showing the tensions inside the market reforms in healthcare, particularly between making visible social and collective gains and discourses about individual consumption and privatisation. EBM has been portrayed as a strategy to deal with the contradictions of the current healthcare system without making a radical transformation. Evidence promises to solve the contradictions that healthcare reform created by means of its own instruments. EBM promises to improve the position of the state in a marketised environment through better knowledge and better regulation.

Replicating global difference at national scale

These narratives about the relationship between cervical cancer and development are also reproduced at the national scale. The differences in healthcare infrastructure and development depicted in an international scenario are identified as well at national level. In Colombia, cervical cancer has been

presented in terms of its geographical distribution in the country and has been associated with a development gap between regions. Map 2, produced by Instituto Nacional de Cancerología (INC) and Instituto Geográfico Agustín Codazzi in 2010, presents cervical cancer mortality in Colombia distributed by towns. The scale of colours is almost the same used in Globocan's map in which the darkest colour represents the highest mortality by cervical cancer. In this case is hard to identify a particular region in which the burden of cervical cancer is concentrated. Nevertheless, a closer view shows that the towns with a higher mortality are concentrated in the northwest of Colombia; this region is called Middle-Magdalena. This has been a historically deprived region with a long history of political and criminal violence. However, almost all the regions outside Bogota have presented a high mortality from cervical cancer.

These maps give risk factors a geographical location. In this narrative, the populations that dwell in those places are considered priority targets of State intervention. Although cervical cancer and HPV contagion are present in the whole population, cervical cancer is defined in policies and government interventions as a problem of particular segments of society by means of the attribution of risk factors. Many of the so-called risk factors describe behaviour that is common to many people regardless their social and economic position. However, to the extent that some risks are stigmatised they are only recognized in marginalised groups or individuals. The production of stigma is part of the dynamic of global health. Some issues are rendered visible through practices of security and medical discourse whilst others are not. As Brown and colleagues have noted, “vulnerable populations are themselves redefined in sometimes problematic ways through the production of statistics or the mapping of epidemiology onto geopolitical and historical understanding of behaviour” (Brown et al., 2012: 1187).



Map 2 Cervical cancer, mortality standardised ratio by town 2000-2006
Instituto Nacional de Cancerología-Instituto Geográfico Agustín Codazzi 2010

These narratives have framed decision making in relation to the introduction of HPV vaccines in Colombia. Vaccines and political institutions have had a long-standing relation (Colgrove et al., 2010). Vaccination involves practices of population governance which make it an object of primary interest for governments and politicians. Public speeches at campaign launches have presented HPV vaccines as one of the many ways in which the Colombian State promotes equity. In a campaign launching speech in Sincelejo (August 2011) President Santos included HPV vaccination as one of the policies to fight poverty, closing social gaps between classes and regions, and promoting equity.

Fortunately, many deaths will be avoided with this vaccine. This is part of our policy; our policy is to give more and more tools and helps in order to Colombians' welfare. This policy has many aspects, but this one (vaccination) is fundamental because disease prevention is the most effective policy. Prevention is less

expensive, cheaper and many times more effective (President Santos, 8th August 2012).

Such narratives have been reproduced by other agents involved with HPV vaccination within the Colombian State. For instance, the Colombian Congress in the debates to approve Act 1626 [2013] (that guarantees vaccination funding) addressed these vaccines as an affirmative action. The Colombian Congress has assumed risk factors of cervical cancer are indicators of the association of this disease with social disadvantages. On the other hand, HPV vaccines have been framed as part of a long-standing tradition that presents vaccination as one of the few material manifestations of the Colombian State that reaches completely its territory. Such paternalism has portrayed vaccination not only as a right but also as a gift.

Vaccination campaigns have been understood by politicians and local health authorities as a social policy whose main beneficiaries are the population with highest odds of having cervical cancer. These populations are the poorest in country, who dwell precisely in “the regions” (those zones outside the economic and political centres of the Colombian big cities: Bogotá, Medellín and Cali). At the same time such attention has contributed to the “naturalisation” of risk factors as intrinsic features of those social groups.

Conclusion: providing a context for the production of evidence

This chapter has had two goals. Firstly, to present a brief description of the different events that have constituted the introduction of HPV vaccines in Colombia. These events have introduced a set of actors, institutions and objects that will be analysed in the next chapters. Within this narrative I have emphasised the role of the technical studies made by Universidad Nacional de Colombia in the production of the objects that legitimise HPV vaccines as the right strategy to deal with cervical cancer in the country. The importance of these studies is related to the demonstration of vaccines’ efficiency and pertinence. Secondly, this chapter has depicted different landscapes in which is possible to locate the introduction of these vaccines. These landscapes provide a set of contexts to understand the particularity of producing evidence for vaccines, to tackle cervical cancer, in a country like Colombia. Each landscape has presented different narratives linked with these different objects: cervical cancer as disease, vaccine as cure, and Colombia as geopolitical location. These narratives have shaped the technical and political discussion on vaccines. They have an important role in the definition of policy goals, in rendering visible particular objects and bodies and in making others invisible.

Cervical cancer has been constituted as the intervention object of the HPV vaccination in Colombia. The contemporary representation of this disease has been configured by its relation with sexuality and

difference, poverty and economic development. In Colombia cervical cancer is perceived as a public health priority by medical communities and national health authorities and therefore HPV vaccines have been depicted as an urgent and necessary intervention. However, as I will show in next chapters, the interest of pharmaceutical companies in promoting HPV vaccines has been an important factor in the rise of awareness about the importance of cervical cancer.

HPV vaccines have inherited many tensions from the historical development of vaccines as healthcare technologies. They are perceived as promising interventions that prevent illness, suffering and death. On the other hand, an increasing awareness of their potential risks has generated anxiety amongst parents and children. The trade-off between risks and benefits has made vaccines' social contract a matter of discussion. On the other hand, HPV vaccines have introduced sexuality at the heart of discussions about immunisation and have created new targets for vaccination: young people.

Finally, these narratives and tensions have reached a particular configuration in Colombia. From the perspective of global health governance, diseases and medicines are framed by the classifications and discourses of social and economic development. In this ordering, Colombia has been classified as a middle income country. This category has had effects not only in terms of international funding and global health policy, but it also has been assimilated by national experts and local decision makers to depict the economic and technical profile of the country. Such portrayal is characterised by a set of contradictions between being fast growing economies with persistent inequity and unfair social distribution. These contradictions in terms of healthcare have meant the existence of new diseases related to improving quality of life and the persistence of infectious diseases related to the lack of basic medical attention.

All these narratives, objects and tensions constitute the repertoire used by experts, journalists, politicians, practitioners and decision makers in introducing HPV vaccines in Colombia. The making of evidence about the pertinence, safety and cost-effectiveness of HPV vaccines has reproduced many of these representations and at the same time has reshaped them by presenting them as figures, numbers and numerical measurements. In the following chapters I will undertake a detailed analysis of the ways in which these practices of calculation manage the tensions that HPV vaccines entail and justify them as the right intervention to tackle cervical cancer in Colombia. In the next chapter, before starting the empirical analysis of these objects, however, I would like to present some conceptual and methodological tools to study the relationships between policymaking, evidence and calculation.

Chapter Two

Textuality, calculation and value

Tools to study policy, quantification and governance in HPV vaccines introduction

Introduction

This chapter presents the conceptual and methodological tools that I have used to analyse the introduction of HPV vaccines in Colombia. As I noted in Chapter One, my main interest is to understand the ways in which evidence and efficiency are produced and to explore their role in the justification of a policy. This involves, firstly, defining a heterogeneous set of objects and agents that constitute a policy and tracing their movement and translation amongst the diverse arenas involved in decision making; and secondly, reading, interpreting and following numbers, figures and other numerically-quantified expressions.

This chapter presents the concepts and the methods I use to study the production and political use of evidence. These methods emphasise the role of documents and their intertextuality with other discursive practices in the assemblage of institutions and policies. This research is based on diverse sources such as policy papers, regulations, websites, scientific papers, software, news, committee minutes, conferences reports, forms, budgets, interviews, participant observations in workshops and statistical reports, among others. My analysis involves tracing the role of policy actors, such as committees, experts and decision makers in the production, circulation and use of documents.

Drawing on science and technology studies, I introduce a methodological strategy to analyse the role of calculation practices and devices in the production of evidence. As different authors have noted, calculation and numerical operations play a key role in contemporary governance, promising objective, unbiased and reliable information for rational and trustworthy policy making (Hacking, 1975; Porter, 1995, Ashmore et al, 1989; Espeland and Stevens, 2009, Mackenzie, 1981; 2006; Verran, 2012a, 2012b). The methodology of this thesis relies on identifying devices of calculation and on approaching numbers

and quantified expressions as material-semiotic objects (Peirce, 1982; Verran, 2012a, 2012b). These objects are traced in scientific articles, technical reports, minutes, memoranda, regulations and campaign materials. Dealing with technical literature, statistics and simulations has led me to engage with some calculation processes and technologies. Here, I explore the role of learning practices as a research tool.

Finally, I explore the relationship between policy and the production of value. Evidence and efficiency are produced through methodological assemblages that involve practices to render visible the value of some decisions amongst different alternatives. In the introduction of HPV vaccines in Colombia, such methodologies come from the fields of health economics and evidence-based medicine. A pragmatist approach to the production of value allows us to trace the role of economic methods in the legitimation of policy decisions. This thesis offers a method to study such methods, their uses and consequences in the area of healthcare decision making. This framework is a strategy to understand the relationships between calculation and governance, emphasising multiple and different aspects of the relations between knowledge and legitimacy.

Studying policy

Policy as documents, telling stories through documents: an institutional cartography

What is a policy? According to Wikipedia a policy is a guideline for rational action, whilst a public policy “is the principled guide to action taken by the administrative executive branches of the state with regard to a class of issues in a manner consistent with law and institutional customs” (Wikipedia: Public policy). In a more material sense, policies are worlds of paper. Institutional and political decisions are embodied in technical and political documents. In my approach to health policy and specifically to HPV vaccination in Colombia, I have had to deal with bundles of regulations, decrees, policy papers, lawsuits, technical reports, forms, words and numbers. Although some piles of documents nowadays have a digital existence; after months gathering these texts in a portable document format (pdf) and trying to organize them in bundles within my computer, the sensation is the same.

Of course, a policy in action has many more elements that enable it to work. A policy isolated is just an inert set of documents. For instance, a vaccination policy involves the socio-technical arrangement of heterogeneous elements such as regulations (law, decree), money (national budget, PAHO revolving fund), vaccines, health professionals, cold chain, bureaucrats, information systems, needles and syringes, among others. However, as Dorothy Smith (2001) has noted, the articulation among these different elements is textually mediated. Within the bureaucratic worlds (public and private sectors) the

interactions and relations between the different parts involved in the development of a policy or a particular action are textually mediated.

I have witnessed such mediation in my own experience as “policymaker”. Such experience has been very important in determining my approach to policy and the sensibility toward documents and the practices of writing and reading that are associated with them. I spent a couple of years working for the Colombian Government in the department in charge of the policy in science, technology and innovation (Colciencias) before I started my Ph.D. In this position I could be part of the process of production of technical documents and I could see their movement and transformation through committees, offices, lawyers’ corrections, press advisors and politician’s speeches. Despite the additional complexity of vaccination (because of the diversity of elements it entails), documents have an important role in mediating policy production. For instance, different documents are made to register the movement and the distribution of vaccines through the cold chain, from central warehouses to regional hospitals and vaccination centres. Many of these documents have acquired the format of online reports embedded into databases and different kinds of software.

In the previous chapter the introduction of HPV vaccines was presented as a timeline, a succession of relatively related events. This first enactment rendered visible different agents that converged in the introduction of HPV vaccines: Congress, Council of State, Ministry of Health, INVIMA, CRES, amongst others. Most of them are institutions of the Colombian State. In this chapter I present a story of this process based on the documents that I have gathered and that constitute the material and documental support of HPV vaccination as a policy. At some point all these institutions have been involved in the appreciation of HPV vaccines as objects of public interest. Despite having their own frameworks to evaluate the vaccine, all of them depend on the evidence developed by Universidad Nacional (as consultant) and its ratification by the national committee of immunisation practices (NCIP).

Figure 3 shows a graphic representation of the documents that are part of the process of introduction of HPV vaccines in Colombia. This figure shows the documents that support the decision making. This graphic is very similar to a flow diagram, a visual tool widely used in management to represent the flow of information, documents and action in particular operations. My aim with this representation is much modest; I want to provide a visual image of different fragments (documents) that contribute to the production of the idea of the policy as a coherent process. At the same time, this figure summarizes the strategy of ordering I have followed to identify key objects and movements in the analysis of the production of evidence.

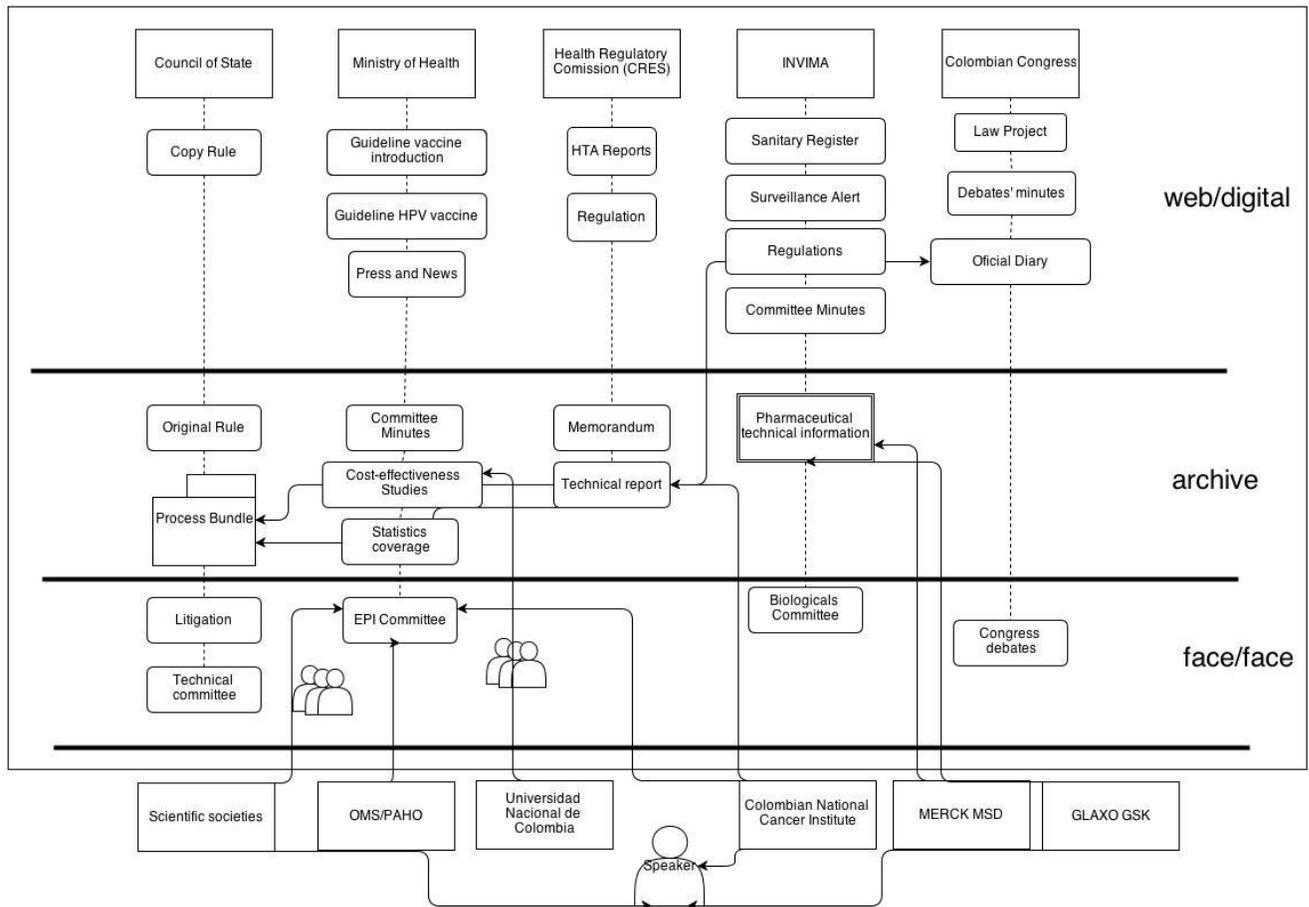


Figure 3 Documentary and institutional cartography of the introduction of HPV vaccines in Colombia

I have decided to call this representation a documentary cartography because it is an attempt to produce a map of documents, institutional boundaries and the interactions involved in this process. As a map, it is a drastic reduction of landscape's complexities; however, such simplification constitutes its usefulness. It is a guide for moving through objects' complexity and messiness. This cartography identified the material connection among these documents following the defined bureaucratic and legal path for the different involved institutions. For instance, a Bill in the Congress is linked with minutes of congress committees' debates, and such minutes are the documentary enactments of a face to face debate among congress members. On the other hand, these documents establish relations with other documents from other institutional paths. Congress decision making, for example, is based on cost-effectiveness studies and technical reports from Ministry of Health and the Health Regulatory Commission (CRES in Spanish).

This map, moreover, makes a distribution of documents taking into consideration their material support, what some linguists would call their textuality (Hayles, 2002). At the top of the diagram are located digital formats and websites; at the middle printed documents organized in archives (rooms) and at the bottom the face-to-face interactions that produce or legitimate such documents. Such textualities render visible the accountability and the transparency of decision making. Whilst some documents are published in institutional websites, others are stored in archives to which only an official procedure grants access. Others are protected by specific regulations and access to them is restricted. That is the case of pharmaceutical technical information provided by companies to obtain a licence from INVIMA. By regulation (Decree 2085 of 2002) these documents are protected for five years as industrial property.

Finally, these documents are produced by means of face-to-face interactions, meetings, committees and deliberations and claim to represent such interactions. This point is important. Most technical discussions and institutional decisions are made in either closed circles such as technical committees or representative political institutions such as the Parliament and the Congress. Political and public decisions are made in public arenas in very particular occasions. However such interactions claim to be transparent to the extent they are enacted in documents as minutes, acts, regulations, among others.

From the researcher's perspective, these interactions can be studied by means of participant observation and interviews with the members of such committees. However, sometimes because of the confidentiality of such scenarios, participant observation is not allowed. This was the case for this research²². I therefore had to depend on textual analysis and interviews with the members of the relevant technical and political committees.

Nevertheless it is important to consider that the accounts produced by interviews are different from those generated by documents, even where the interviews are about the production and reading of documents. In the case of HPV vaccine introduction, there are at least two committees that make technical decisions about this health technology: the National Committee of Immunization Practices (NCIP) at Ministry of Health and Biologicals Committee at INVIMA (Colombian Food and Drug Administration). Although I was not allowed to observe committee meetings, I could conduct interviews with different member of these committees. However as I will show in the next chapter, most of my analysis is centred on the NCIP. This committee had the responsibility of assessing the scientific evidence and the cost-

²² Although the discussions about the introduction of HPV vaccines in the National Committee of Immunization Practices (NCIP) were held at the same time I was devising this research, I asked to the committee being allowed to witness some other meetings. However, the committee informed me that because of NCIP regulations, the participation in meetings and discussions about vaccines is exclusive for committee's members.

effectiveness of vaccines in order to be introduced into the Colombian Expanded programme of Immunisations.

Documents are essential for coordinating people's activities across multiple places and times because of their properties. However, documents do not work alone. They operate embedded within a wide range of social practices and material arrangements. The concept of genre (Bazerman, 2012) is useful for describing the literary technologies and the patterns of production, diffusion and organisation of documents that favour a particular reading.²³

Textual analysis, intertextuality and genres in policymaking

My initial approach to documents is by means of textual analysis (McKee, 2003). Science and technologies studies have a long-standing empirical tradition in the analysis of documents, in particular scientific literature (Smith, 1978; Latour and Woolgar, 1986; Latour, 1987; Ashmore et al., 1989; Shapin, 1984; Shapin and Schaffer, 1985; Smith, 2001). This kind of analysis has involved the detailed study of the structure of texts, the identification of rhetorical devices and the mechanisms that texts have to induce particular readings. I have approached policy documents as literary technologies (Shapin, 1984; Haraway, 1997).

Such a starting point involves recognizing the role of intertextuality in making texts more effective as well as in shaping institutions. A revision of intertextual relations embedded into documents allows understanding of how institutions look for sources of legitimacy. As Bazerman and Prior note: "Through such relations a text evokes a representation of the discourse situation, the textual resources that bear on the situation, and how the current text positions itself and draws on other texts" (Bazerman and Prior, 2004: 309).

In the case of policy analysis, documents have an important role in the shaping of institutions as agents. The relationships that policy documents establish with other documents provide a way of tracing the relations that institutions have with other agents, organisations and objects. A policy document can be understood in relation to other texts that are addressed and presupposed. As Dorothy Smith has noted "a text is necessarily embedded complex of texts (...) investigation of organizations and institutions directs us towards the complex of texts on constitute their archi-texture (Smith, 2001: 187). The tracing of intertextual devices of documents allows us to identify "which realm of utterances" a text relies on and

²³ Genre is a set of available and familiar utterances that provides "interpretable clues that allow people to make sense of each other's utterances and to frame utterances meaningful to one's interlocutors" (Bazerman, 2012: 229).

how, an author attempts to ensure the reading of a subject by means of certain set of texts (Bazerman, 2004: 316). Texts invoke other texts in order to provide resources and support for their arguments, for identifying debates and relevant problems and for creating their own past.

Some of these intertextual connections are explicit (e.g. direct quotations and citations²⁴), whilst other remain implicit their identification depending on readers' interpretative skills. Policy documents such as regulations and technical reports have a well-established set of citation devices to cite other regulations policies and studies. As Bazerman²⁵ notes in relation to litigation surrounding phenylpropanolamine (PPA) in the United States, "In this process of selective citation, the literature gets organized around focused findings associated with particular articles. The findings or meaning of each article tends to get compacted into a single concept and citations become concept symbols" (Bazerman, 2009: 101).

Policy documents are a heterogeneous set of texts with different intertextualities and are enacted through regulations, reports, memorandum and minutes, amongst others. These documents cite legal documents (Acts, decrees, resolutions and rulings), scientific literature, technical information (e.g pharmacological description) statistics and other policies (WHO, PAHO, other countries). The selection and presentation of these references is organised following particular rules. In the case of regulations and legal documents each country has its own legal architecture which involves a documental hierarchy of acts, decrees and rules. In relation to technical and scientific literature, as I will argue in the next chapter, approaches based on evidence have developed strategies to select the most "appropriate" papers. These intertextualities between legal, bureaucratic and scientific documents allow us to trace the agents and the institutions that produce, circulate and assimilate policy, as well as, to understand how policy objects dwell in the intersection between legal, technical and bureaucratic landscapes.

Within the set of documents developed in the introduction of HPV vaccines in Colombia, the studies of cost-effectiveness made by Universidad Nacional have a fundamental role in the production of evidence

²⁴ The citation analysis -core of bibliometrics- has been an important tool in the sociology of science for identifying and constructing scientific communities and knowledge fields. This approach assumes that behind each citation there is a group of interconnected authors. These authors shape communities (invisible college) around objects and research fields (De Solla Price, 1965; Crane, 1972). On the other hand, Bazerman (2009) points out that citation styles and bibliographic tools embody academic communities' representations and ideas about how knowledge "accumulates" a collective body of disciplinary knowledge. Citations are recognition of the worth of knowledge. However some citations are negative; most articles will be never cited.

²⁵ Bazerman (2009) makes an analysis of intertextual interactions between science and law taking the litigation surrounding phenylpropanolamine (PPA) in the United States as case study. For him this kind of analysis contributes to understand how scientific knowledge is used in public policy and law. "When, how, in what form, and through what vehicle does the literature of science (embodying the knowledge of that field) enter into the textualized discussion of the differently organized domains of law, litigation, and public policy? (Bazerman, 2009: 92).

and the justification of policy's efficiency. These studies correspond to a technical genre of documents highly standardised in terms of their structure, formulae and the ways that literature is reviewed as I argue in Chapter Three. At the same time these documents are deeply local, they are produced to depict the "local" and "national" burden of the disease and to assess the best technology available according to the particularities of the country. As I noted earlier, Universidad Nacional developed two technical studies with different outcomes. The 2011 study found these vaccines cost-effective, contrasting with the results of the 2009 study. A key strategy of analysis in this thesis has been to contrast them and following the similarities and the differences they have regarding calculations and results.

Policy actors: committees, experts and decision makers

My analysis of documents has been complemented by interviews with key actors involved in the development of this policy in the country. The group of experts engaged in the introduction of HPV vaccines in Colombia is quite small and most of them have been part of the National Committee of Immunisation practices (NCIP) as consultants or full members. This committee has the duty of making decisions about the introduction of new vaccines, assessing their efficacy and safety and in some cases discussing their cost-effectiveness. It includes experts in different areas related with immunisation and vaccines, from universities, scientific associations, and research centres. Their authority relies on their expert knowledge and independence. This last feature lately has become quite controversial because of the relation that some scientists have with pharmaceuticals and the role of these companies in funding trials and basic research. Nevertheless, these committees remain composed of scientists from universities and scientific organisations. The committee acts and makes decisions as a whole, an independent actor; however such ability is linked to the institutional memberships of its individual members. In that sense, the committee's agency depends on a wider set of institutions.

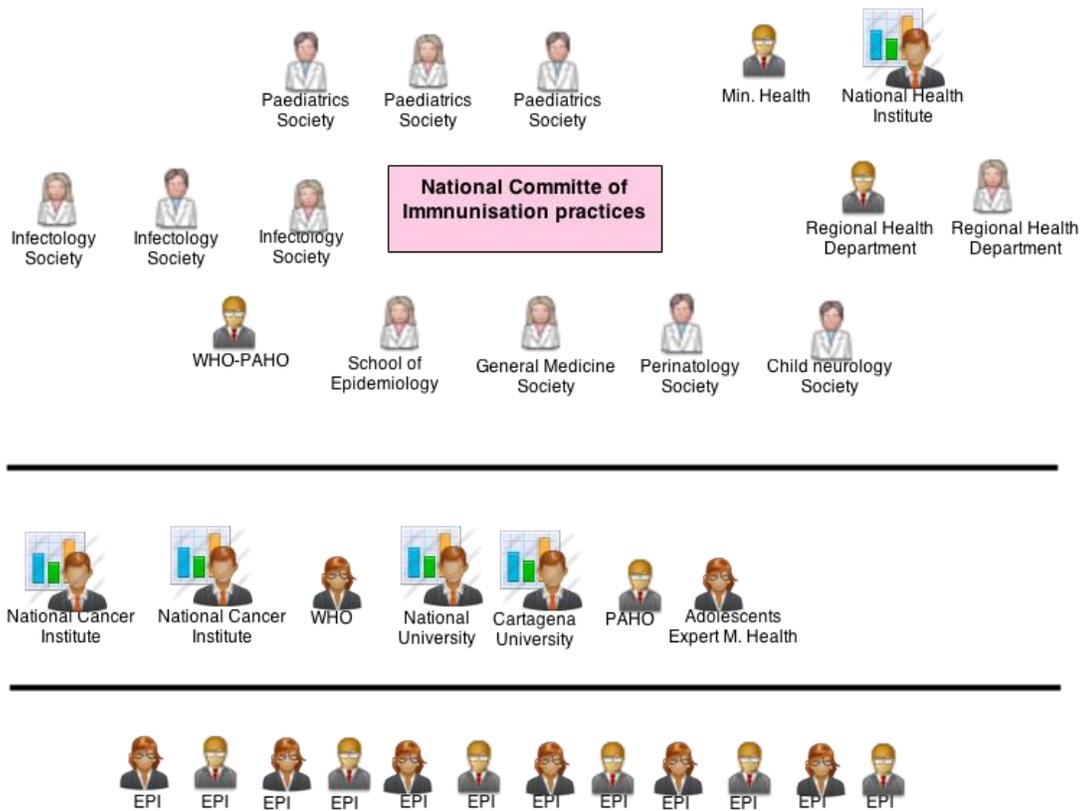


Figure 4 Composition National Committee of Immunisation Practices.
Composition according to Agreement 01 of 2011 and the Minute SGC-F03 3rd May 2012

Within this committee there are 14 members with right to speak and vote (top level). The WHO also has a delegate that can intervene in the committee without voting. Each organisation within the committee represents particular scientific or medical fields; because of the long standing relation of vaccines with children’s health; specialities such as paediatrics (three delegates), perinatology and child neurology have a significant presence. The Infectious diseases society are also members (three delegates), as are a representative of schools of Epidemiology, one from the General Medicine Society, one from the National Health Institute, and two delegates from Regional Health Departments. The National Committee of Immunisation is coordinated by the Ministry of Health Head of Health Prevention. The committee can invite other experts to present evidence and to explain particular aspects of vaccines, however, these cannot participate in discussions or vote. For the analysis of the introduction of HPV vaccines into the expanded programme of immunisations (PAI in Spanish) two experts in HPV and Cervical Cancer from National Cancer Institute, two experts from WHO-PAHO, two experts in Health Economics from Universidad Nacional and Universidad de Cartagena and an expert in adolescent healthcare from Ministry

of Health (middle of the graphic) were invited. PAI Technical staff attended this meeting as observers (at the bottom of the graphic).

In total I interviewed 21 experts, which represent almost the complete group of actors involved in the making of technical studies, clinical trials (FUTURE III) and their discussion in the NCIP. Most of these interviews were done in Bogotá (Colombia) and one in London (United Kingdom) during 2012-2014 (See appendix 2). Although the identification of these actors is relatively easy because of the size of the group and its visibility in Colombia, all quotes included here have been anonymised²⁶. Most interviewees explicitly asked for this because of confidentiality issues and legal consequences of their statements. These interviews offer a different data set to the practices that involve such documents; presenting in many cases alternative stories about the process that described by minutes and technical reports. Such differences allow tracing of specificities of documents ontologies, what they reduce from practices but also what their contribution is to the production of facts. Most of the interviews were done in Spanish. I have translated to English only the quotations that are presented in this thesis.

I would like to note some particularities of interviewing experts. As Marcus (1998) has argued, traditionally social scientists have enjoyed of a privileged position in relation to the communities and people they research. Such privilege has been based on class, race, and educational attainment amongst other factors. In many cases the social scientists represent themselves as defenders of cultural traditions and forms of knowledge that are rendered visible through a scholarly exercise of systematic writing. However sometimes, even with the best intentions, social scientists patronize the people with whom they interact.

In the case of interviewing experts and actors in a position of authority, the scenario of interaction is quite different. In the case of the members of the NCIP and its consultants, these actors are in a privileged position to talk about technical matters. During the first meetings I was considered a lay person who should be politely introduced to the complexities of “hard” science. In other cases, my expertise as a social scientist was recognised but at the same time I was associated with a range of problems and objects that are characterised as properly social, such as the anti-vaccine movement, religious opposition to vaccination and poverty. Accordingly, different experts were surprised at my interest in technical details, biology, epidemiology and simulation. At the end, the acknowledgement of my competence as a “literate”

²⁶ These interviews have followed Lancaster University research ethics policy. The participants were properly informed about the research project, its objectives, risks and results, and about the use and storage of the information. They signed the university ethics' forms and their names have been anonymised.

interlocutor in technical matters was the result of the detail of some questions and the subtle exposition of my knowledge about debates, controversies and grey areas within HPV vaccine science.

Studying calculation and quantification in policymaking: numbers and words

Contemporary technical decision making is based on calculation and the quantitative enactment of the realities that pretend to govern. Calculation is a strategy to manage uncertainty and “to pacify” the things involved in decision making (Moreira, 2007). Numbers have a very important role in the rhetoric of objectivity in policy and government decision making (Porter, 1995). Technical documentation is a key object through which to explore the politics of economic rationality exemplified in the textual rendering of a particular policy (Pinch, Ashmore and Mulkay, 2000).

Within technical and policy documents, numbers and calculations are often presented as black boxes. Data, statistics, costs and budgets are presented as the result of a process of calculation and modelling that is developed in scientific papers, (even more) technical papers and software (Christley et al., 2013). In order to open these boxes it is necessary to follow calculations-in-the-making through the assemblages that produce them (Çalışkan and Callon, 2010). Calculation and quantification in policymaking have an important role in the two-way transit of objects from matters of fact to matters of concern (Latour, 2004b); in the shaping of data and objects of knowledge as a matter of public interest and in the transformation of social and political claims in data, figures and “objects” of knowledge.

Calculation and quantification are political tools: numbers and numerical operations have been used as strategies to soften political controversies and to produce rhetorically objectivity. Calculation has been depicted in policymaking as “one of the most convincing ways by which a democracy can reach an effective decision in cases of potential controversy, while simultaneously avoiding coercion and minimizing the disorderly effects of vigorous public involvement” (Porter, 1995: 206). The rise of quantitative rhetoric is linked with the development of statistics as governance tool. In his book *Trust in Numbers* (1995), Porter describes how different professional groups (accountants, engineers, actuaries, economists and statisticians) constructed their expert authority around the use of numbers and quantitative models and the impact of such “technologies of trust” in State’s governance. According to Porter, calculation enacts objectivity; its political use depends on such capacity. “Bureaucratic use of these numbers presupposes their objectivity but not their truth” (Porter, 1995: 206). Different forms of quantification, but in particular statistics, have been adopted as the language of the modern state. Policymakers know and represent the society through numbers and figures; statistics is a key tool in debates, in the assessment of policy choices, and, increasingly, in the evaluation of government

performance (Clark, 2005: 404). The integration of quantification as strategy of governance relies on configurations that are nationally segmented. National regulations, government structures and the history of the relationship between governments and their citizens shape the role of quantification in governance (Jasanoff, 2004). The extensive development and use of information technologies has increased the production of quantified data in different realms of government and has facilitated the execution of convoluted calculations by means of a wide range of software.²⁷

The perception of quantification and numbers in social science has changed from considering them as “objective” methods to appreciate them as objects of analysis.²⁸ The analysis of numbers’ authority involves studying their practical uses and the ways in which are related to wider networks of practices (Espeland and Stevens: 406). As the French statistician Alain Desrosières, argues most successful numerical images influence the ontology of the things they represent (Desrosières, 1998). In that regard, “numerical pictures are important mechanisms through which quantification holds things together. They give form to things that otherwise would be hard to comprehend” (Espeland and Stevens, 2009: 428).

In this thesis the analysis of policy documents and the texts generated by means of interviews has been focused on discourses, rhetorical devices and representations, emphasising the ‘performative’ character of these narratives and their condition as literary technologies. The analysis of the production and the circulation of numbers and quantified expressions in the introduction of HPV vaccines in Colombia has demanded a further methodological strategy. This strategy has been to follow the production and circulation of information and results between documents, tracking the transformation of data and numbers, their disentanglement from the calculation spaces in which they are produced and their re-entanglement in new texts by new institutions. These documents and the objects that they produce have been analysed taking into account their movement and translations through different institutions and arenas.

In many ways this exercise can be understood as *reverse engineering*. I have traced papers and documents that are quoted as references to support particular claims and data, and I have re-enacted some

²⁷ Although these approaches to calculation have been very effective in identifying how technical governance and calculation practices have coproduced modern versions of the state; these analyses suggest an image of calculation and quantification as crude simplification. There is the temptation of dismiss quantification and calculation, that is to understand calculation as reduction, a cold cut of richness and diversity of qualities of objects and phenomena. On the contrary, in this analysis I want to emphasise the discursive nature of quantified objects and texts, they enact particular versions of material objects: algorithms, codes, formulas, charts, tables, among others. Through such arrangements, calculation extends reality.

²⁸ A useful synthesis of the recent interest in quantification in sociology is developed by Wendy Espeland and Mitchell Stevens in their paper: A sociology of quantification (2009). In this paper, they understand “quantification as social action that, akin to speech, can have multiple purposes and meaning. Many of the most consequential uses of numbers entail commensurations (Espeland and Stevens, 2009: 406).

calculations in order to understand the origin and use of some of these results. In classic STS terms, I have been opening the black box of technical decision making. Within this set of documents, institutions and collective agents, one technical committee, its minutes and memoranda have demanded special attention; the National Committee of Immunisations Practices (NCIP), which has the responsibility of assessing the findings of the technical studies produced by Universidad Nacional. Its deliberations are transcribed in minutes which become the official voice of the committee, enacting this agent as an independent entity. These minutes are the basis for writing official memoranda that will be read by the Ministry of Health and the Congress.

In what follows I will present some concepts that have a fundamental role in the analysis of numbers and quantified expressions; particularly in the study of the ways in which they produce evidence and efficiency for the introduction of HPV vaccines in Colombia. These tools involve a material-semiotic approach to calculation and numbers. Firstly, I introduce some working categories that have helped me to understand the relationship between calculation and governance: calculation, device, icon, symbol and index. Secondly, I present a map that shows the ways in which these categories offer a strategy of ordering of the different practices of calculation involved in the enactment of evidence and efficiency in my case study.

Looking at devices

Calculation is often associated with quantification, computation and rationality. In many contexts these different words are used interchangeably. Calculation, moreover, is commonly described as an input/output process in which different elements are transformed and expressed as results with variable change (Wikipedia: Calculation).

STS interest in calculation is related to the description of the practices and material objects involved in calculating (Muniesa, Milo and Callon, 2007; Callon and Law, 2005; Azimont and Araujo, 2010). From this perspective, calculation can be addressed as a process in which entities are detached from other contexts, reworked, displayed, related, manipulated, transformed, and summarised in a single space²⁹

²⁹ In detail, this can be described as a three-step process. “First the relevant entities are sorted out, detached, and displayed within a single space. Note that the space may come in a wide variety of forms or shapes: a sheet of paper, a spreadsheet, a supermarket shelf, or a court of law, all of these and many more are possibilities. Second, those entities are manipulated and transformed. Relations are created between them, again in a range of forms and shapes: movements up and down lines; from one place to another; scrolling; pushing a trolley, summing up the evidence. And third a result is extracted. A new entity is produced. A ranking, a sum, a decision. A judgment. A calculation. And this new entity corresponds precisely to – is nothing other than – the relations and manipulations that have been performed along the way” (Callon and Law, 2005: 719).

(Callon and Law, 2005: 730). The key element in this definition is the understanding of calculation in terms of relational materialism. In the case of calculation, Callon and Law (2005) have pointed out the objects are detached from original sets of relations and then re-attached in new ones through calculative spaces³⁰.

In the analysis of calculation³¹ and quantification, the concept ‘device’ occupies a central place in the description of orderings, practices and transformation of entities. Singleton and Law (2013) have pointed out that the use of ‘device’ in STS has been widely metaphorical, describing machine-like entities which perform specific transformations in other entities. They argue that although many devices are in fact artefacts, not all the devices are necessarily machine-like. For them, a device, “can be understood as a set of implicit and explicit strategies that work more or less repetitively to order, sort, define and arrange a heterogeneous but relatively discrete social and material field” (Singleton and Law, 2013: 260). Muniesa, Milo and Callon (2007) define devices as objects with agency: “Devices that do things” (2007: 3), they write. Devices can help (minimalist version) or force (maximalist) the production of particular arrangements. Devices act or make others act³². However, Muniesa and colleagues note that the distributed agency of these arrangements is the result of the interactions and relations that emerge in the encounter of these entities (Muniesa, Milo and Callon, 2007: 3).

In relation to the working definition of calculation adopted in this thesis, devices can be assimilated to what Law and Callon (2005) have called “calculative spaces”. These are not empty spaces waiting for

³⁰ Following Karen Barad’s (2007) material semiotics is possible to understand calculation as a process of constant disentanglement and entanglement. In relation to entanglements, she notes: “To be entangled is not simply to be intertwined with another, as in the joining of separate entities, but to lack an independent, self-contained existence. Existence is not an individual affair. Individuals do not preexist their interactions; rather, individuals emerge through and as part of their entangled intra-relating” (Barad, 2007: ix). This implies that once the objects are disentangled to be ordered into calculative spaces they are disintegrated, they lost an “original” set of relations which involves its radical transformation. On the other hand, they are reconstituted through new sets of relations, in relation to the different devices or apparatus of calculation.

³¹ The definition of quantification of Desrosières (1998) -developed in his book *The politics of large numbers: a history of statistical reasoning*- coincides with the notion of calculation of Callon and Law (2005). In relation to statistical work Desrosières notes, its objective is to make separated things hold together, extending the reality and the complexity of such objects. As it is noted by Espeland and Stevens, “by simplifying, excluding and integrating information, quantification expands the comprehensibility and comparability of social phenomena in ways that permit strict and dispersed surveillance (Espeland and Stevens, 2009: 428).

³² These notions of device are very close to the concept apparatus of Karen Barad (2003). For her, “apparatuses are dynamic (re)configurings of the world, specific agential practices/intra-actions/performances through which specific exclusionary boundaries are enacted” (2003: 816). Beyond the particular use of the language in Barad’s account, the apparatus that she describes can be thought as objects that produce effects in other entities, however, such objects “are not inscription devices, scientific instruments set in place before the action happens, or machines that mediate the dialectic of resistance and accommodation” (2003: 816). Apparatus and devices are simultaneously produced through the practices and the entities that they produce. In that sense, Barad understands apparatus as open-ended practices.

objects to be located; they have a material shape which materialises ordering principles, classification rules and operations.

In order to operate a device needs to materialise the ordering rules that constitute it as a space of calculation with the capacity to gather objects, reorganise them and summarise them in the form of results. Some of the devices of calculation that I analyse here are intentionally designed to be machine-like. The Markov chain simulation, for instance, is the result of a cybernetic project to produce calculative “virtual” machines. Others, like evidence tables, enact ordering and classification rules in the simplicity of a Word file or Excel spreadsheet (*Hoja de cálculo*, in Spanish). Other devices such as systematic reviews and cost-effectiveness analysis work through the production of classifications or the translation of entities into quantified measurements.

Performativity and calculation

An important issue in relation to quantification devices is the extent to which they can produce effects in the world. As Singleton and Law argue, the concept of device implicitly assumes the *performativity* of particular objects.³³ Practices and calculation devices enact different versions of reality. However, some of these enactments have more material and temporal permanence. Such permanence can be understood in terms of performative effects. In my analysis the terms to *perform* and to *enact* work well to express the generative effect of practices. However, I have reserved “to *perform*” to describe those enactments whose permanence is visible. It is important to note that such permanence is very contingent and it has to be maintained through repetition and the mobilisation of other agents and resources.

Authors such as Donald Mackenzie (2006) and Tiago Moreira (2012b) have demonstrated the role of economics in the shaping of contemporary governance and our understanding of the social and the market through its devices of calculation and practices of quantification. “The academic discipline of economics,” Mackenzie writes, “does not always stand outside the economy, analyzing it as an external thing; sometimes it is an intrinsic part of economic processes” (Mackenzie, 2006: 16). Latin American

³³ The idea of performativity –whose origin is the classification of Speech Acts (1955) developed by J.L. Austin- has had an important role in the discussion about the practical and material effects of languages and representational objects. It is necessary to clarify that in this thesis I have used the verbs enact and perform to express the effects of particular relational entities in the production of particular versions of the reality. My understanding of these notions has been shaped by Mol’s praxiology. Annemarie Mol in the *Body Multiple* (2002) discusses the differences between perform and enact; for her these verbs express agency of objects and entities in the extension of reality. Mol argues that performativity as sociological notion has a long history in ethnomethodology and symbolic interactionism, within these frameworks this notion has been associated with dramaturgic metaphors. Although she considers performativity offers a way of expressing the ways in which reality is produced in practice; she notes the notion implicitly invokes a “backstage”, something more real behind actors’ actions. She considers enact and enactment fit in fine with her praxiology. “This suggest that activities take place –but leaves actors vague. ‘Enact’ also suggests that in the act, and only then and there something is –being enacted” (Mol, 2002: 32).

countries, possibly, have experienced one of the most direct interventions of professional and academic economists in the configuration of policy, government and social institutions. The most famous case is “The Chicago Boys” in Chile³⁴, however, as Dezalay and Garth (2002) have noted, such technocratic style of governing was intensively promoted through the whole region.

Calculative devices from economics³⁵ produce a wide range of effects in decision making by means of concepts, models, data or algorithms that shape the market and economic practices. Calculation devices and concepts developed by economics have reshaped contemporary healthcare governance and practice in Western Europe and North America (Moreira, 2012b). This transformation influences the development of healthcare reforms in middle income countries by means of technical cooperation and academic exchange. Moreira identifies three realms that should be taken in consideration to understand the logic of contemporary healthcare: the market, the laboratory and the forum. Each one of these realms has been shaped by particular devices of calculation and technical repertoires from health economics, evidence based medicine and public deliberation.

Material semiotics of numbers: indexes, symbols and icons

As I have previously noted, at the heart of calculation is the production of results. These results operate as summaries of the orderings that produce them. In relation to quantification, numbers have been privileged entities to communicate results. The analysis of numbers is challenging, they are deeply entangled in our experience of the world—as words—but at the same time they are considered abstract. Numbers are understood as signs and entities that represent other entities, but at the same time numbers act as entities in their own right³⁶. This thesis analyses the social functioning of number, as material-semiotic objects³⁷ (Verran, 2012a: 112) and its role in a case of public decision making.

³⁴ The Chicago Boys (c. 1970) were a group of young economists, mostly trained at the Department of Economics of the University of Chicago under Milton Friedman. Upon their return to Chile they were key actors in the development of neoliberal reforms. They occupied leading positions during Pinochet’s dictatorship in government and business.

³⁵ One of the most insightful studies about quantification and its capacity to constitute socio-material arrangements is the book of Donald Mackenzie (2006), *An Engine, Not A Camera: how financial models shape markets*. Mackenzie relates two stories, the transformation of financial markets during the last 30 years and the emergence of contemporary finance theory. “Markets” provided economists with data against to produce and to test their models; on the other hand, economists’ theories shaped through calculation and normative regulation the interactions that constitute such markets (Mackenzie, 2006: 5). Mackenzie shows the ways in which “the economic theory of derivatives and the “actual practice” of derivatives markets are interwoven too intimately” (2006: 263).

³⁶ Helen Verran analyses the impact of evidence based policy repertoires in the transformation of calculations to define environmental policies in Australia. For her, “when governments buy measures and values in generating evidence based policy it is the customer – the government (not ‘nature’) – that provides warranty and guarantee” (Verran, 2012b: 69). Consultants within evidence framework generate calculation and indexical numbers that are used in policy intervention; however, the indexicality of those numerical entities is not kept “alive”. Measurement

Numbers are generated by practices of calculation. Numeric calculation can be understood as a three-step development, a game of entanglements and disentanglements. When produced as enumerated, entities follow a process of ordering, measuring and generalisation³⁸. In this process numbers are indices of a partial order, then they become measures of value and finally express a naturalized order. As Verran has noted, understanding the ways in which numbers are produced and transformed is very important in tracing the transformation of contemporary governance (2012b: 65).

Drawing on the semiotics of C.S. Peirce (1982) Verran proposes a typology to address the different relations that numbers can display in relation to the arrangements in which they were produced. Peirce's semiotics classifies signs according to the relations they have with their objects as symbols, indexes and icons. The differences between these types of signs rely on the ways in which they bring together ordering, measuring and the "naturalisation" of such orders. Icons, indices and symbols involve different intensity in their connections between 'sign', 'object' and 'interpretant'³⁹. In other words, each kind of sign entails particular dynamics of signification.

Verran argues that in the analysis of the role of numbers in contemporary governance, indices are crucial. An index is a sign in which the relations that constitute it are open and available for changes and reworking: "It is thus in the indexical zone that the three-step epistemic dance of 'modern facts' is most easily undone" (2012: 66). The other two types of signs, symbols and icons, partially hide or render invisible their own process of production. Symbols can be understood as those types of signs that need a theory, an explicit set of categories, to be meaningful. For instance, those numbers in technical reports that are justified as faithful accomplishments of formulae; these formulae are a set of relations between

and values become iconic in favour of calculation based on efficiency and customer tailored solutions. "Those indexes that had ephemeral life as the consultants hurried about doing this and that, inventing categories and assembling values, come to be visible as icons, but in this glare of visibility, the enumerated entities are rendered lifeless" (Verran, 2012b: 68).

³⁷ Verran argues that in the analysis of numbers is necessary do not treat them as universal abstractions or mere culturally relative social constructions. She notes that numbers and who uses them should be thought in practice, as present in the here and now, through the relations that quantification entails to signify the world. "Expressing formal relations working simultaneously the distinction same/different and the idea of ratio, numbers partially configure the ongoing emergency of our worlds" (Verran, 2012a: 112).

³⁸ "In the first step (1) categories are derived as parts of a vague whole (this is the process of ordering); in the second step, (2) categories are (measured and) valued as parts become specified units or elements and are collected; and in the third step (3) the categories derived in step one, and valued in the second, are universalized as how things are" (Verran, 2012b: 65).

³⁹ Peirce defines his theory of sign in the following terms: "I define a sign as anything which is so determined by something else, called its Object, and so determines an effect upon a person, which effect I call its interpretant, that the later is thereby mediately determined by the former. (Peirce, 1998: 478)".

several abstract concepts. Although the formula does not reveal the material process of producing numbers; it makes explicit the categories that render them.

The icon involves a complete black boxing in which all the meaning of the sign relies on itself. Verran argues that iconic numbers have a close relation with religious icons. “An icon is precious because in the actual practices of many religions the image is the god or spirit pictured, and is treated as such” (2012a: 112). The most quoted example of an iconic number is GDP (Gross Domestic Product). GDP is the result of highly contingent and complex practices of calculation that involve the production and gathering of data about economic activities and sectors in a particular country. However, such contingency is rendered invisible. Once the number is produced, it becomes an icon of the national economy, its growth and capacity. This icon later is used to define budgets, aims of growth and national policies.

Sign type	Definition (Peirce, 1982; Verran, 2012)
Index	Sign in which the relations that constitute it are open and available for changes and reworking.
Symbol	Those types of signs that need a theory, an explicit set of categories, to be meaningful.
Icon	The icon involves a complete black boxing in which all the meaning of the sign relies on itself. Iconic signs have a close relation with the icon in a religious sense. An icon is precious because in the actual practices of many religions the image is the god or spirit pictured, and is treated as such.

Table 1 Verran’s Signs typology based on Peirce

In contrast, indexical numbers allow what is invisible in iconic numbers and taken for granted in symbolic ones to be seen: that is “the need to wrestle with the always and already overwhelming, blooming, buzzing real. Some numbers are so open about that they call themselves indexes, not worrying about letting the messy work of rendering them as such show” (Verran, 2012a: 120). Verran calls the process of numbers’ production and calculation their *zone of indexicality*.

In this zone, numbers show the tensions and “liveness” of the attribution of measures and values and the socio-material entanglements that such dynamic entails. Measurement and value are “organically co-constituting” (Verran, 2012a: 117) in the zone of indexicality. Both are deeply related, “you cannot have one without the other and changes to one side are inevitably expressed, sometimes in unexpected ways, in the other” (Verran, 2012b: 68). However, this *liveness* is limited to the time of calculation. Verran argues that indexes have “zero temporal extension”. Once they are solidified, they become a symbol or a value icon.

The material-semiotic analysis of numbers provides a methodological and conceptual framework to describe in detail the processes of black-boxing of numbers' production and quantification and their consequences in the shaping of contemporary political configurations. Numbers are open to almost infinite modes of ordering, measuring and valuation. Mathematics offers rich and complex fields with diverse rules, languages, operations and entities in which numbers can get specific shapes. However, numeric ordering is not limited to mathematics, numbers as signs can be entangled in diverse relations; for instance, moral and affective in the case of economic transactions, aesthetic and religious (e.g. gematria and sacred numbers) among others. Moreover, numbers' production in practice involves heterogeneous assemblages of entities and rules; some of them "mathematical" but others related with alternative modes of ordering and other realms.

However, in the case of decision making based on "evidence" the concept that has had most impact in the shaping of practices and devices of calculation is probability⁴⁰. Statistical probability has become the basis of the production of objectivity and the management of uncertainty (Hacking, 1990). On the other hand, the development of a statistical understanding of change and uncertainty based on probability has been a key element in the contemporary notion of evidence, the same that has been used by EBM. The management of uncertainty based on probabilistic methods is common-place in contemporary health governance.

Thinking a strategy of ordering

Figure 5 summarises the methodological strategy I used to reconstruct the processes of calculation and the objects and effects that produce. The starting point is the identification of the main devices of calculation that are used in the production of technical reports and data about safety, cost-effectiveness and efficiency of HPV vaccines in Colombia. These devices are systematic reviews, cost-effectiveness analysis and the simulation of the natural history of cervical cancer in a cohort of Colombian women. These devices order and classify a diverse set of data and objects -clinical trials, scientific literature and data bases- which are ordered following particular calculative rules. These orderings are summarised in the form of results; in the case of systematic reviews in lists and hierarchies of documents, in cost-effectiveness analysis in

⁴⁰ Ian Hacking (1975) offers in his book *The emergency of probability* a detailed analysis of the origins and development of the concept of probability and its impact in the contemporary notions of uncertainty and objectivity. Hacking argues that probability has allowed the taming of uncertainty and chance. Before the calculative options that probability entails, change and uncertainty represented threats to knowledge. With the emergency of probability, the recognition of uncertainty has meant the recognition of the objectivity of knowledge. "The whole point of probability is that we may not be able to establish a proposition with certainty; we can at best measure the extent to which data warrant our inferences" (Hacking, 1975: 90).

health currencies such as DALYs and QALYS, and in the simulation by means of estimated rate of mortality and burden of the disease. These results are presented in the technical reports of Universidad Nacional and are discussed in the National Committee of Immunisation Practices. Some of them will move to other spaces of decision making, such as the Ministry of Health and the Congress, in minutes, letters and memoranda. Just a couple of numbers and data will reach a wider audience, in news, speeches and campaign materials.

In this process of circulation, these objects are transformed. Numbers and quantified expressions—such as measurements of the burden of the disease, cost-effectiveness ratio, prices and estimations of mortality—change in their travel through calculation practices, technical documents, committees and press releases. Although they may not change in terms of content, the expression ‘6.500 DALYS’ or ‘14 USD’ can remain the same from computer modelling to inclusion in a speech by President Santos. To the extent that these expressions get entangled with new elements, they are not the same. This thesis shows the transformation of these elements from the indexical zones in which they are produced to their use as symbols and icons in political scenarios. The following chapters present a detailed analysis of the different calculation devices that are used to enact HPV vaccines as an efficient and safe intervention. I also analyse the appropriation that pharmaceutical companies have made of these tools in order to justify the value of their products and to negotiate prices with governments in the language of evidence.

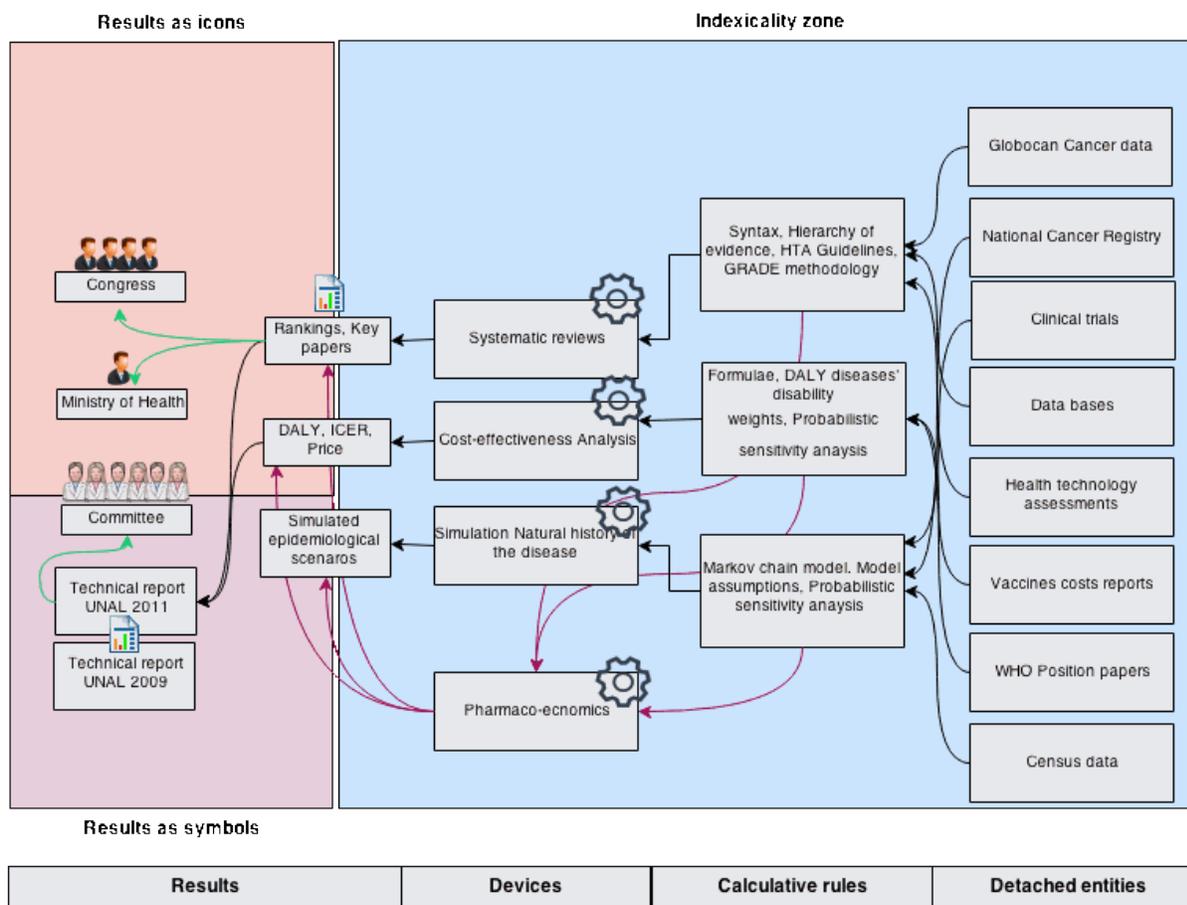


Figure 5 Devices of calculation and decision making in the introduction of HPV vaccines in Colombia.

A material-semiotic approach to the enacting of evidence and efficiency

Studying value as enacted in policy

In the last section of this chapter, I discuss an additional dimension around practices and devices of calculation: their role in the production and justification of value. Once we render visible the entanglements that calculation entails, it is clear that the generation of data and objects performs/enacts values at the same time. As noted by Karen Barad, “if phenomena, not things, are the objective referent then the apparatus that produces data and things also produces values and meanings” (Barad, 2012: 11). The different devices that I analyse demonstrate the value of vaccination in terms of economic efficiency and public health pertinence. These practices organize different studies about pharmacological performance and safety, the burden of the disease and the costs of diseases and health procedures. The operations and the relations established between these heterogeneous elements produce value.

Pragmatist and axiological approaches to value

The practices and devices of calculation I analysed in this thesis, such as systematic reviews, cost-effectiveness analysis, epidemiological modelling and pricing, produce enactments of evidence, whose aim is to demonstrate the value of vaccination in terms of economic efficiency and public health pertinence.

This thesis follows a pragmatist analysis⁴¹ of value (Dewey, 1939) that is a consequence of understanding calculation as a socio-material practice. Such approach involves understanding the production of value (valuation) as an activity that is present in everyday life; in the different considerations that people make in particular situations and that are expressed in terms of good-bad, right-wrong, admirable-blameworthy, amongst others. As Dewey has noted, the starting point to analyse valuation is to consider the linguistic expressions associated with value. Value (in English) is both a noun and a verb. The noun 'value' designates what common speech calls a valuable something that is the object of a certain kind of activity. The verb 'value' implies an activity of rating, an act that involves comparison (Dewey, 1939: 4). To value as practice is related with the emotional appreciation of a particular good and the development of rating practices that allow comparison of the relational properties of the objects.

The analysis of value (as a singular noun) points our attention to the dominance of economic value in government. The social study of value in contemporary societies should focus on how economic practices have become hegemonic in the identification and production of value. This approach involves taking into account valuation as practice. Value is enacted through practices of classification, calculation, organisations and the complex interaction between different actors, human and non-humans; valuation as other social practices depends on socio-technical arrangements (Kjellberg and Mallard, 2013: 18).

This approach contrasts with other understandings of value in social science that could be called axiological.⁴² The problem of value has been addressed from a different perspective by different

⁴¹ One of the earliest and most influential reflections about value and valuation –at least from a pragmatist perspective- was developed by John Dewey (1939) in his book *Theory of Valuation*. According to Dewey, in the beginning of XX century, value had become a contested issue; positivist pretensions of a free-value natural science raised a debate about the nature of value and the possibility of a human activity free of any kind of valuation. In this debate Dewey identifies a range of views on the subject, “from the belief, at one extreme, that so-called "values" are but emotional epithets or mere ejaculations, to the belief, at the other extreme, that a priori necessary standardized, rational values are the principles upon which art, science, and morals depend for their validity” (Dewey, 1939: 19).

⁴² Drawing on Dewey’s framework David Stark (2009) in his book *The sense of dissonance: accounts of worth in economic life* offers a critique on the place of value in social science and the importance of a focus on practices of economical valuation. For him, “the polisemic character of the term -worth- signals concerns with fundamental

disciplines amongst them sociology and economics. Sociologists –at least classical ones- have conceived values (in plural) as irrational ends that motivate social action or individuals’ behaviour. Values are not explained in themselves; rather they are a source of explanation of different kinds of actions and social behaviours (Stark, 2009: 12). Within this framework values are multiple, each social group, institutions and even individuals have a set of values that motivate and guide their actions⁴³. On the contrary, economics have developed a concept of value (in singular) with the theory of price. Value in classical economics is enacted through decisions and trade-offs between goods that makes a rational agent (the consumer). The equilibrium between supply and demand and the willingness to pay render visible agents’ estimations of value⁴⁴. While sociology and social science have assumed values as an independent analytic variable, as cause and motive for the action; economics has developed a theory of value linked to consumption and free choice of moral and non-moral goods (Stark, 2009: 9).

Value –in economics- emerges from considerations around demand, supply, willingness and cost of opportunity. Such concept of value (singular) has a massive dominance in contemporary societies, the sociotechnical arrangements through which it is produced have developed “major infrastructures of contemporary life, like housing, circulation, healthcare institutions, etc., many of which play a crucial role in determining our modes of existence” (Kjellberg and Mallard, 2013: 17). The analysis of valuation involves unpacking implicit and explicit normative assumptions that are “blackboxed” through different technical infrastructures” (Kjellberg and Mallard, 2013: 17). Technical systems and metrologies have a decisive role in the characterization of value; in healthcare for instance, EBM and its practices of calculation define the value of healthcare through measuring quality and performance of services (See Figure 6).

problems of value while recognizing that all economies have a moral component. Rather than then static fixtures of value and values, it focuses instead on ongoing process of valuation” (Stark, 2009: 7). For him, social science research interest should be the conditions and practices of production of value, understanding it as process, which are the valuation regimes.

⁴³ Although, the Theory of Value of Marx constitutes one of the most important reflections about the material origins of value; I have intentionally avoided its discussion. Value for Marx is economic value; this is objective and the result of the transformation of nature through work. This definition has generated an enormous set of scholarly work that exceeds the limits of this thesis. In contrast, the notion of value that I am presenting in this work is relational, is the result of valuation, not an objective quality of the entities. In STS, Kaushik Sunder Rajan in his book *Biocapital* (2006) provides an analysis of the role of contemporary capitalism in the development of genomic research, using an approach highly influenced by Marx’s theory of value. He describes the ways in which “scientific” objects have been transformed in commodities in contemporary organisation of genomic laboratories and companies.

⁴⁴ According to the law of demand, other things equal, when the price of a good rises, the quantity demanded of the good falls, and when the price falls, the quantity demanded rises. As Greg Mankiw has noted, in his *Introduction to Economics* –a textbook extensively used for introducing economics students into their discipline: “Because people face trade-offs, making decisions requires comparing the costs and benefits of alternative courses of action. In many cases, however, the cost of some action is not as obvious as it might first appear” (Mankiw, 2010).

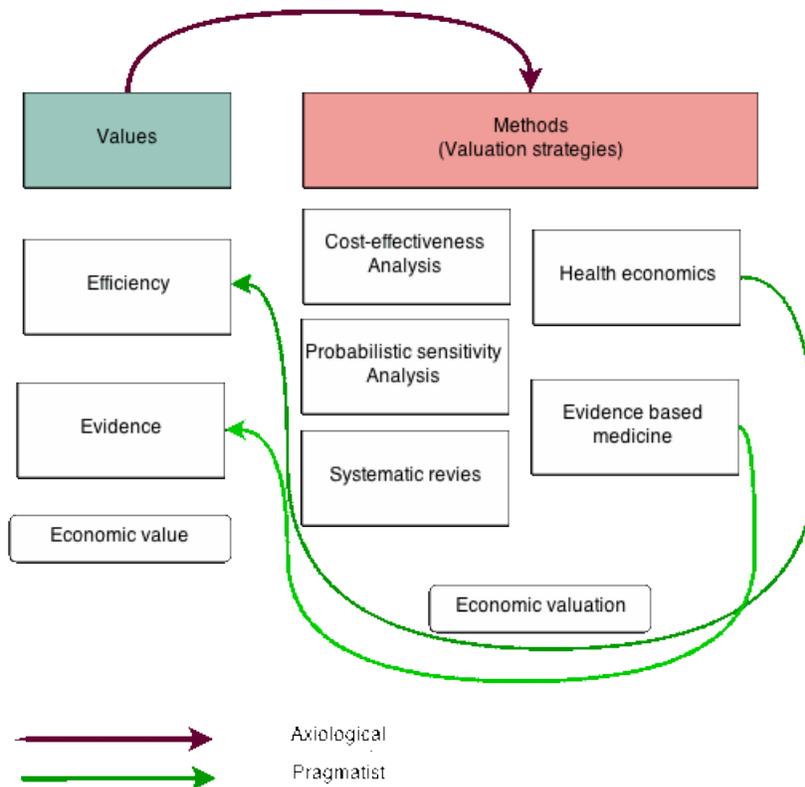


Figure 6 Values and Methods of valuation.
Axiological and pragmatic perspectives on the production of value.

To value is a question of method

The study of value is the study of practices of valuation. Valuation practices could be understood as the metrics, the rules and the practices that allow particular values or versions of value to be enacted. Economic valuation has reached a hegemonic position as valuation regime in contemporary societies; however this does not mean that other regimes do not exist (Kjellberg and Mallard, 2013: 15). Even economic valuation is multiple, it encompasses different regimes of value⁴⁵.

⁴⁵ Luc Boltanski and Laurent Thévenot (2006) in their book *On Justification*, economies of worth develop a sociological theory of value, which identifies different valuation regimes in contemporary economies which coexist and compete and interact between them: market rationality, industrial rationality, civic logic, loyalty, inspiration and fame. For them, there is not just one way of making value but that modern economies have multiple principles of evaluation. For them modern economy is not a social order but contains multiple “orders of worth” (Boltanski and Thévenot, 2006: 23). Boltanski and Thévenot also emphasise the relationship between valuation and calculation, they argue that there is a connection between cognitive framing and ideas of justice. “In this view, rational calculation is not opposed to moral judgement; instead, rationality works within orders of worth” (Boltanski and Thévenot, 2006: 23).

John Law (2004) describes a tension that I want to take into consideration regarding the performative character of methods and its boundaries in the production of value.

Method is not (...) a more or less successful set of procedures for reporting on a given reality. Rather it is performative. It helps to produce realities. It does not do so freely and at whim. There is a hinterland of realities, of manifest absences and Othernesses, resonances and patterns of one kind or another, already being enacted, and it cannot ignore these. At the same time, however, it is also creative. It re-works and re-bundles these and as it does so re-crafts realities and creates new versions of the world (Law, 2004: 143).

The elements that I have noted as context (narratives and material arrangements about cancer and vaccines in Colombia) can be assimilated with ‘a hinterland of realities’ that interfere in valuation methods’ enactment. In the case of the introduction of HPV vaccines in the Colombian healthcare system, decision making spins around cost-effectiveness analysis and evidence based medicine, such analysis involves a set of methods for evaluating if the expenditure in this technology is justifiable. Such assessment is done in relation to some values that are enacted by these same practices. However, this exercise does not completely recreate such values; other enactments of health, safety, equity, efficiency interfere by means of regulation, organisation and agents’ experience with them.

Conclusion: policy, modes of calculation and modes of ordering

The analysis of calculation is the study of the ways in which a particular kind of method performs reality. In the context of calculation for policy making such methods constitute strategies of ordering, assessment and legitimacy. The framework that I have presented provides a heterogeneous set of tools to trace the tensions between practices of calculation and governance. In spite of the particularities and diverse origins of these concepts they have in common their engagement with materiality and practices. I consider this framework a pragmatist one because of its interest in thinking about objects as verbs rather than nouns (Law, 1994; Suchman, 2000). Such approach changes the way as institutions and policies are understood. As Suchman notes:

The focus is on organizations as ongoing performances involving heterogeneous modes of action and materialization, both of which must be actively affiliated and aligned across a range of often unruly contingencies (Suchman, 2000: 313).

Despite the multiplicity and diversity of documents, practices and devices of calculation, it is possible to identify a particular strategy in the ordering of data and objects of interest for policy. I have decided to call such strategy a mode, following John Law's definition of modes of ordering:

If an organisation is a materially heterogeneous process of arranging and ordering, than that process may be understood as strategy: not, to be sure, necessarily (or indeed often) an explicit strategy but rather an as implicit strategy or as a mode of ordering. The argument is that a mode of ordering is like a Foucauldian mini-discourse which runs through, shaping, and being carried in the materially heterogeneous processes which make up the organisation (Law, 2001: 1).

The production of evidence for policy is a mode of ordering, a mode of calculation. In the following chapters I describe the shaping of this mode of calculation through technical studies, governmental documentation and policy discussions that legitimate the introduction of HPV vaccines in Colombia. This mode operates by means of devices of calculation including systematic literature review; cost-effectiveness analysis; Markov chain modelling; and pharmaco-economics and pricing. Each one of these devices involves a particular gathering of objects and their re-ordering through practices of calculation. Most importantly, this mode involves producing particular kinds of results that travel through institutional paths and several scenarios, such as media, national congress, High Courts among others. Finally, this mode of calculating involves different ways of ordering and quantifying a quite heterogeneous set of objects to produce justifications for policymaking based on efficiency and evidence.

These devices enact not only versions of disease and technology (vaccines), but also provide stories about the values and government priorities in relation to healthcare. As I argue in the next chapter, these devices produce assemblages that allow heterogeneous entities to be traded in order to define some policy options at the expense of others. These strategies render visible the tensions between different practices of valuation, in particular the exchanges between techniques and metrics from economics and healthcare. This relation allows me to trace how values as Health, Wellbeing and Care are enacted and the tensions that they entail in contexts where financial sustainability and profit are requirements.

Chapter Three

Making HPV vaccines evident

Evidence, systematic review and other technologies of legitimation

Evidence-based policy is public policy informed by rigorously established objective evidence. It is an extension of the idea of evidence-based medicine to all areas of public policy. An important aspect of evidence-based policy is **the use of scientifically rigorous studies such as randomized controlled trials to identify programs and practices capable of improving policy relevant outcomes**. However, some areas of knowledge are not well serviced by quantitative research, leading to debate about the methods and instruments that are considered critical for the collection of relevant evidence. **Good data, analytical skills and political support, as such, are seen as the important elements** (Wikipedia).

Introduction

Before the Carmen de Bolívar outbreak in which hundreds of girls were hospitalised after receiving the vaccine, the vaccination programme had not generated any highly visible controversy amongst Colombian media. The vaccination campaign has been highly praised by most of the journalists in the country, there has been a broad consensus around the benefits of the vaccine, even amongst women's rights movements and organisations. Only two issues had generated any "critical" attention from the media, one was the case of a girl in Arauca⁴⁶ who fell sick after being vaccinated (23rd May 2013); another, the possibility of extending the vaccination programme to men in relation to U.S. actor Michael Douglas's announcement that his throat cancer was caused by Human Papillomavirus (3rd June 2013). Despite the gravity of Carmen de Bolívar's event, the Government has kept to the same declaration: the vaccine is safe and effective in the prevention of cervical cancer, the vaccination programme is preventing one of the biggest causes of female mortality in Colombia which is cervical cancer.

The Government has constantly pointed out that its decisions are based on evidence. In a radio interview, the Head of the Expanded Programme of Immunisation argues:

The Ministry of Health has a national committee of immunisation practices, which is an external and independent advisory body. It encompasses academic and scientific societies of the country, among them:

⁴⁶ http://en.wikipedia.org/wiki/Arauca,_Arauca

the Colombian Society of Paediatrics, infectious diseases, internal medicine, neurology, gynaecology, among others. They recommended last year the introduction of the vaccine against human papillomavirus to all the girls. Initially the programme started with fourth grade elementary school girls. nine years old is the age of first vaccination approved for this vaccine (W radio, 3rd June 2013).

The Ministry spokesman carefully, points out that decisions are based on the advice of an expert committee which represents the most important medical and scientific societies of the country. Despite the power of this argument, this is not enough; evidence needs to be enacted through numbers and papers (studies and articles). In the same interview, he notes:

This decision is made because we want mainly to prevent cervical cancer, whose necessary cause is the infection by HPV. This does not happen in men with HPV, if we talk e.g. anal cancer, penile cancer or cancer oral-pharyngeal—the issue of the day—the association is not a necessary condition. Just 30% of these cancers have an association with HPV. Likewise if we check the burden of disease, which are studies that were done in the Ministry for the introduction of new vaccines, we can say cervical cancer has an impact on the Colombian population of 28 cases per 100,000 women. That means about 6.900 new cases of cervical cancer in the country. In contrast, oral-pharyngeal cancer's incidence is 0.8 per 100.000 which are just new 250 cases (W radio, 3rd June 2013).

In this public declaration data are disentangled from the practices in which they were produced, the textual laboratory (Moreira, 2007). Such numbers are the result of modelling and the systematic review of literature. In this context of production numbers and data render visible the conditions of their materialisation. Once data and numbers leave this space they are entangled in new configurations, they are read in new contexts and in relation to other objects and concerns. Evidence and its politics are produced through the different entanglements and disentanglements involved in the movement of data and objects from technical studies and systematic literature review (textual laboratory) to technical committees, courts, media and vaccination campaigns.

In this chapter I will discuss how *evidence* has been enacted in the introduction of HPV vaccines in Colombia. This process has been presented by the government as one of the first experiences of policy based on evidence (EBM) in the country. Evidence based medicine has developed sets of instructions and practices to identify pertinent and reliable evidence for decision makers. Such evidence is enacted through practices and devices of calculation that produce connections between realms and objects, as well as establish hierarchies and orders. The systematic review is considered by EBM the most important tool to

develop policies based on evidence. Systematic reviews are devices of calculation whose main enactments are *evidence*.

In what follows I will describe how evidence based policy is an extension of the evidence based medicine movement (EBM) and the role of systematic review in the production of evidence for policy. Then, I analyse the systematic review as a device of calculation. This is a process where entities such as papers, tables and data are detached from their “original” context, classified, and ordered within a single space (new tables, Health Technology Assessments: HTA forms). These entities are compared, manipulated, and transformed according to particular rules, in this case: searching syntax, the hierarchy of evidence, HTA Guidelines, grading methodologies and evidence checklists. Finally, results such as rankings are produced both to summarize and to represent the entities in the calculative space. In the case of systematic reviews the result is *evidence* enacted as a selection of ‘pertinent’ papers. Some of them will become iconic papers and repositories of ‘trustworthy’ data. Following Moreira’s analysis (2007) of the systematic review I have called this calculative space the *textual laboratory*.

Nevertheless, evidence enactments are not limited to technical documents. Evidence is multiple, it travels through –in the case of policymaking- institutional pathways where it is reproduced, re-enacted and transformed. In this case, an institutional pathway is a highly standardised (often regulated) procedure that plots the movement and the sequence that objects should follow to enact a particular action. In the case of policy and bureaucratic procedures such pathways are defined by regulatory commitments. I will present the ways in which the evidence about HPV vaccines is enacted in different institutional pathways of the Colombian State. Each one involves the disentanglement of the entities that were produced within the textual laboratory and their re-entanglement with other objects, practices and narratives. In this chapter I present different versions of evidence that are enacted in the movement of data from systematic reviews to the discussions in the technical committee of the Expanded Programme of Immunisations (NCIP).

Health policy based on evidence: promises for a system in crisis

Health Technology Assessment (HTA), clinical guidelines and cost-effectiveness analysis (CEA) are some of the most widespread tools of evidence based medicine (EBM) that have been integrated into health policy making. Archie Cochrane (1971), one of the ‘fathers’ of this movement, defines EBM in the following terms:

Evidence-based health care is the conscientious use of current best evidence in making decisions about the care of individual patients or the delivery of health services (Cochrane, 1971: 10).

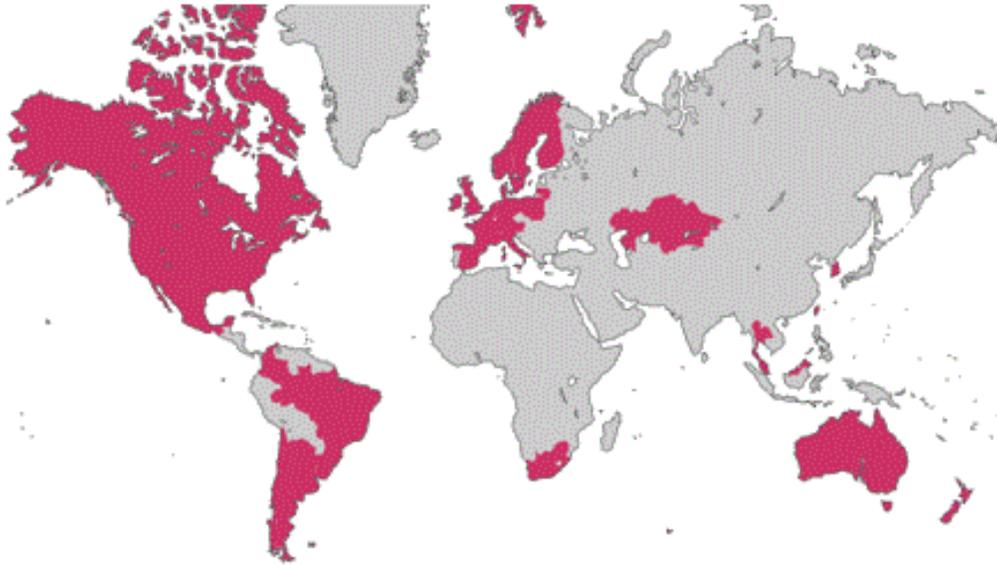
EBM can be characterised as a social movement of practitioners, scientists, policymakers and patients that advocates for the use of scientific evidence in the shaping of healthcare practice and policy. For the EBM movement, evidence means relevant information from relevant and valid research about effects, potential harm, accuracy and prognosis factors of healthcare technologies and procedures. Although EBM has grown as a social movement within healthcare professional and medical communities, policymakers and governments around the world have adopted these discourses and practices to make decisions about selection and relevance of health technologies.

Timmermans and Berg (2003) have noted that the adoption of EBM by policymakers, healthcare institutions and international bodies begun around 1980's as a response to claims of efficiency in a context of growing costs and budget restrictions. They moreover point out that EBM is a consequence of challenges to medical authority and the erosion of trust in medical knowledge. In response, a set of assessment tools emerged such as systematic practice guidelines, hierarchies of scientific knowledge and statistical meta-analysis (Timmermans and Berg, 2003: 4).

As different authors (Timmermans and Berg, 2003; Epstein, 2007; Mol, 2008; Moreira, 2012a) have noted, EBM has become a powerful movement that has promised to solve the dilemma between the introduction of new healthcare technologies and reducing or controlling costs. EBM has been materialised in an extended international network of institutions such as the Cochrane Collaboration, the National Institute for Health and Care Excellence (NICE) in the UK, the Agency for Healthcare Research and Quality (AHRQ) in the U.S; College voor Zorgverzekeringen (The Netherlands); Gemeinsamer Bundesausschuss (Germany); Haute Autorité de Santé (France); Tandvårds och Läkemedelsförmånsverket (TLV Sweden); amongst others in Europe and North America.

Outside North America and Europe a set of technical agencies have been created in the last decade, mainly in “middle income countries” and new developed Asian countries (Taiwan, Singapore, South Korea, Malaysia). In Latin America these agencies have been created in the contexts of healthcare reforms; for instance, Centro Nacional de Excelencia Tecnológica en Salud (Mexico), DECIT-CGATS - Coordenação Geral de Avaliação de Tecnologias em Saúde – CGATS (Brazil); ETESA - Department of Quality and Patient Safety of the Ministry Health of Chile (Chile); IECS - Institute for Clinical Effectiveness and Health Policy (Argentina) and IETS - Instituto de Evaluación Tecnológica en Salud (Colombia). These organisations in the South have received technical assistance from international bodies such as the World Health Organisation (within the programme CHOosing Interventions that are Cost-

Effective: CHOICE), the International Network of Agencies for Health Technology Assessment (INAHTA) and NICE International (International division of NICE-UK).



Map 3 Members of the International Network of Agencies for Health Technology Assessment (INAHTA)
Source: <http://www.inahta.org/Members/>

As Timmermans and Berg have noted, EBM has created a powerful network of allies and funding agencies that has enthusiastically communicated the promises of evidence in policymaking. Such promises for governments and insurers are more open medical decision making (less based on medical authority) and unfolding new strategies of cost control. EBM through the rationalisation of assessment practices has had a deep regulatory impact. “The same guidelines that explicate optimal decision-making procedures can of course be used to regulate those processes” (Timmermans and Berg, 2003: 17). As I have presented in chapter one, in the case of Colombia EBM principles have shaped the regulatory framework that defines the main features of the Colombian healthcare system and the technical procedures of decision making.

EBM has produced a hierarchy of evidence that sorts different outcomes of scientific research (See Table 2). This structure establishes levels of validity of research findings which are defined by the presence of randomized controlled trials (RCT). Currently, randomized clinical trials are perceived by regulation authorities as the gold standard in the definition of evidence for healthcare (Timmermans and Berg, 2003:

24). The RCT is conceived as the standard that defines the reliability and the contingency of other forms of evidence. Only systematic reviews, as meta-analyses of RCT, would offer a superior level of validity.

Level of validity of findings	Type of research
I	Strong evidence from at least one systematic review of multiple well-designed randomised controlled trials
II	Strong evidence from at least one properly designed randomised controlled trial of appropriate size
III	Evidence from well-designed non randomised trials, single group pre-post cohort, time series or matched case-controlled studies
IV	Evidence from well-designed non-experimental studies from more than one centre or research group
V	Opinions of respected authorities based on clinical evidence, descriptive studies or reports of expert committees.

Table 2 Hierarchy of evidence.

Source: Canadian Task Force (1979) cited by Harrison, 1998

Even the logo of the Cochrane Collaboration makes visible the importance of RCT and systematic reviews in EBM discourse. This illustrates a meta-analysis of data from seven randomized controlled trials (RCTs), comparing one health care treatment with a placebo in a forest plot⁴⁷.

⁴⁷ According to Wikipedia, the logo (Image 4) shows the results of a systematic review on inexpensive course of a corticosteroid given to women about to give birth too early, “the evidence on effectiveness that would have been revealed had the available RCTs been reviewed systematically a decade earlier” (Wikipedia: Cochrane Collaboration).



Image 4 Cochrane Collaboration logo

Source: <http://www.cochrane.org/about-us/history/our-logo>

The impact of EBM in healthcare policy making has been controversial. It has been perceived as the exacerbation of expert power in public policy, some kind of technocratic nightmare. Evidence has been seen by practitioners as an over-simplification of the kinds of decision making processes and practices deployed by them in diagnosis and treating individual patients (Moreira, 2012b: 87). Moreover, because of data dependency of EBM, “policies are skewed toward ‘well documented’ and funded health care problems to the detriment of less visible, singular conditions” (Moreira and Will, 2010). To the contrary, EBM supporters have pointed out that evidence is a response to the limitations and hazards of policies and decisions based on opinion. They claim that evidence protects citizens, providing the best knowledge available to solve social and health problems.

Evidence is not evident without the mediation of systematic reviews. EBM practitioners argue that scientific knowledge is useful for decision making when it has been sorted out as evidence. Without such mediation, the “scientific” information regarding an issue of interest is messy and contradictory. Systematic reviews and the meta-analysis of information from RCTs are presented as the top of the evidence pyramid (Figure 7), which is the main input that should be used in decision making.

However, as I will present, it seems that beyond the world of the systematic reviews the EBM pyramid works in an inverted direction. What is evident depends on the entanglements that allow such evidence to be read. Committee and expert opinions render visible the findings of the systematic review beyond the

textual laboratory by bringing new objects that highlight particular aspects of this text. Experts and evidence professionals produce particular contexts in which systematic review's evidence is read. As Timmermans and Berg have noted, one of the great attractions and weaknesses of evidence-based medicine is that while experts might have decided what is best, it remains up to the professionals to acquaint themselves with the clinical guidelines and follow the consolidated advice (2003:21).



Figure 7 Evidence Pyramid⁴⁸

Source: http://www.ebbp.org/course_outlines/searching_for_evidence/

Rising costs and financial sustainability are important factors that have promoted the use of EBM in healthcare policy. EBM has opened up the unfolding of regulation through rationalisation that has been a characteristic of neoliberal governance (Mirowski, 2011) and the rise of political ontologies based on market. As Moreira (2013) has noted many EBM practices have been addressed by governments as an attempt to reshape healthcare as a market. Such transformation has involved new sociotechnical arrangements to produce knowledge to organize healthcare. In the case of countries such as Colombia, this commitment has been overlapped with narratives and practices of *development* and *modernisation* (See Chapter One).

This close relation between EBM and economic decision making has meant that data about cost-benefit and cost-effectiveness are increasingly being included in the evidence upon which guidelines are based (Timmermans and Berg, 2003: 4). EBM is a source of new orderings, during its development and through the socio-material arrangements that generates once policy is implemented. The entanglements between

⁴⁸ It is important to note that qualitative research is excluded from this classification. Although the systematic reviews are qualitative analyses, they are expressed through algorithms and a highly formalised language.

EBM and policy have an important role in the production of new categories and in the reinforcement of previous classification systems within biomedical regimes (Epstein, 2007). Within these different entanglements cost-effectiveness and cost-benefit analysis of health technologies have had a central role in the transformation of healthcare policy through the pricing and valuation of health and human life. In the next chapter I will describe with more detail the features of economic valuation within EBM and its implications in the valuation of health technologies such as vaccines.

Systematic literature reviews: calculating inside the HPV textual laboratory

Systematic literature reviews are a response to one of the most challenging issues of EBM in relation to policymaking: how to provide reliable, trustworthy but simple information to policymakers about scientific evidence? This is a big task, just in relation HPV and cervical cancer, the database *Web of knowledge* reports 9,382 papers published in the period (1987-2011). Within this enormous universe of papers and references it is very difficult to identify points of reference. Literature review has been developed as a scientific genre to organize such messiness.

Authors such as Latour and Woolgar (1986), Myers (1996) and Restrepo (2003) have noted the role of literature reviews in the production of scientific fields. “Reviewers produce the fields that they avow to describe. They do this as they define what is included and what is excluded from the field” (Restrepo, 2003: 279). In the case of EBM, the adjective ‘systematic’ is introduced in the title of the literature review to denote the reshaping of this practice under the principles of *evidence* (Moreira, 2007).

Moreira (2007) has ethnographically depicted the practices of calculation and ordering that are involved in the production of systematic reviews in a British research unit dedicated to this purpose. He argues that knowledge in systematic reviews is structured in a parallel process of disentanglement and qualification of data. “In disentanglement, knowledge practices attempt to extricate data from the milieus in which they are commonly found (databases, texts, other research centres, etc.” (Moreira, 2007: 180). By qualification, Moreira understands the process of re-entanglement where data are endowed with new qualities (precision, objectivity, fairness) by means of the use of devices such as templates, graphics and their embedding into techno-political debates. Such framework is a development of the definition of calculation by Law and Callon (2005) which has been adapted in this thesis as working concept (See Chapter Two).

Institutions such as INAHTA, Cochrane Collaboration, NICE and WHO have developed methodologies to write these reviews, most of these methodologies point out the importance of rendering visible the

searching process, which means presenting information about the database used and the searching syntax. Then the results are assessed using a checklist for Health Technology Assessment (HTA) reports (See Table 6). The methodologies have framed the development of systematic reviews in Colombia.

There are at least four technical studies that were used by the Colombian Government to introduce HPV vaccines into national immunisation programmes: two were developed by Universidad Nacional for the Ministry of Health, one was written by the Sabin Institute for the Panamerican Health Organisation – PAHO- and a further was developed by INC (Colombian National Cancer Institute) for CRES (Health Regulatory Commission⁴⁹). For this analysis I have chosen the studies from Universidad Nacional (2009; 2011) and INC (2011). The Universidad Nacional studies were the technical support for the discussion in the National Committee of Immunisations (NCIP) and the INC study, although it was not part of official technical documents, was developed by INC (Colombian National Cancer Institute) the institution responsible for cancer control policy in Colombia.

In the case that I am presenting, these reviews were not made by research units dedicated “full time” to the production of systematic reviews. These were the result of consultant teams, one from Universidad Nacional (epidemiologists and health economists) and another from Colombian National Cancer Institute (INC) (oncologists, public health analysts and epidemiologists). Although both studies are framed in the discourse of EBM, the results of their literature reviews are quite different.

INC followed the Cochrane and INAHTA procedures to make Health Technology Assessments (HTA). Instead of evaluating directly scientific literature from research papers, they analysed other systematic reviews from the databases of National Institute for Health Research (NIHR) and the Database of Abstracts of Reviews of Effects (DARE). In the systematic reviews the transcript of the syntax used in the searching of information is an important element because it is assumed that this guarantees its replicability. Syntax is a tool to guarantee that the exploration in databases can lead to the same results if the right sequence of query terms is done. In the case of the INC review the information was searched using syntax Ovid SP⁵⁰. Table 3 presents the terminology used in the INC review.

⁴⁹ CRES was eliminated by Ministry of Health in 2012 after an intense political debate about its role in the sustainability and funding crisis of the Colombian healthcare system. It was replaced by IETS (Institute of Health Technology Assessment).

⁵⁰ <http://site.ovid.com/site/help/documentation/ospa/en/syntax.htm>

1.	Vaccines/	10.	exp Alphapapillomavirus/
2.	vaccin\$.mp.	11.	or/8-10
3.	Vaccination/	12.	7 and 11
4.	exp Immunization/	13.	Papillomavirus Vaccines/
5.	exp Immunization Programs/	14.	Cancer Vaccines/
6.	immuni\$.mp.	15.	(VPH adj3 vaccin\$.mp
7.	or/1-6	16.	or/12-15
8.	(Human adj2 papillomavirus).mp.	17.	((uter\$ adj3 cervi\$) or cervix or cervical) adj3 (cancer\$1 or malignanc\$ or carcinoma\$ or adeno\$ or neoplas\$ or tumo?r\$)).mp.
9.	HPV.mp.	18.	16 and 17

*Table 3 Systematic review terminology. Informe No 24 ETES
HTA (Health Technology Assessment) CRES 2011*

This enquiry looked for “evidence” about vaccines, HPV (7, 11, 8, 10, 16 and 17) and cervical cancer. The results were 15 studies: 5 systematic reviews, 1 government report and 9 HTAs. Table 4 presents the studies that were taken into consideration after contrasting them with the checklist for HTA (see Table 5) and after checking their language, this review only considered studies in English and Spanish.

No.	Title	Agency	Year	Country	Language	Inclusion	Cause exclusion
1	Ökonomische Evaluation der Impfung gegen humane Papillomaviren (HPV-Impfung) in sterreich	Ludwig Boltzmann Institute for Health Technology Assessment (LBIHTA)	2007	Austria	German	No	Language (German)
2	Reduction in the risk of cervical cancer by vaccination against Human Papillomavirus (HPV)	National Board of Health, Danish Centre for Health Technology Assessment	2007	Denmark	English	Yes	NA
3	The role of human papillomavirus vaccine in reducing the risk of cervical cancer in Ireland	Health Information and Quality Authority	2008	Ireland	English	Yes	NA
4	The Health Technology Assessment of bivalent HPV vaccine Cervarix® in Italy	Health Technology Assessment Public Health Unit, Institute of Hygiene, Catholic University of the Sacred Heart	2010	Italy	English	Yes	Text in Italian
5	Human papillomavirus (HPV) vaccination for the prevention of HPV 16/18 induced cervical cancer and its precursors	GMS Health Technology Assessment /Deutsche Agentur für Health Technology Assessment	2009	Germany	Summary in English	Yes	Text in German
6	General Childhood Vaccination Against HPV 16 and 18 Aimed at Preventing Cervical Cancer	SBU – Alert – Early Assessment of new health technologies	2008	Sweden	Summary in English	No	Text in Swedish
7	HPV Vaccination for the Prevention of Cervical Cancer in Belgium: Health Technology Assessment	Belgian Health Care Knowledge Centre	2007	Belgium	English	Yes	NA
8	Human Papillomavirus (HPV) Vaccines: A Canadian Update	The Canadian Agency for Drugs and Technologies in Health (CADTH)	2007	Canada	English	No	Just abstract
9	Human papillomavirus vaccines for prevention of cervical cancer	SD	2006	US	English	No	Just abstract

*Table 4 HTA Summary. Informe No 24 ETES
HTA (Health Technology Assessment) CRES 2011*

Systematic reviews -as you have seen in this chapter- are full of tables. In their simplicity tables are a very effective device of calculation. They define axis and create a space for sorting out the elements that will be transformed through different operations. Through tables, objects such as HTAs and the studies are detached from their original contexts (databases, institutional setting) and they are reordered in this new space. As Moreira has noted, tables are technologies of abstraction, they enact the function that has been assigned to meta-analysis, which is “to summarize the enormous amount of information that is produced about health interventions and to evaluate the significance of possibly conflicting sets of information” (Moreira, 2007: 182).

In the case of the INC review, this new space is a summary of the international “evidence” of the introduction of HPV vaccines; each study, individually, does not constitute evidence. ‘International evidence’ emerges from the comparison between documents, summarized within the limits of tables and forms. Tables are tools of classification but also they are instruments of assessments and valuation. Table 5 presents a checklist of the basic elements that should be taken into consideration for the inclusion of studies into the systematic review. Some of these criteria are related to the basic quality of the document (item 1-5), other to its relation with policies (6-9); other are related to methods (10-11) and finally to the quality of conclusions and assessments. If these formal criteria are fulfilled then the content of the study is assumed to be reliable.

At the same time, reviewers’ representation of the texts as data is an effort to make them docile (Lynch, 1985; Moreira, 2007). These texts are produced with objectives and contexts that are different from those intended in reviews and classifications. Systematic reviews are devices to neutralise texts’ rhetorical power; this is done through selection criteria and tabled comparison between studies (Moreira, 2007: 187). In this case, the papers are transformed in sentences about country, strategy of vaccination, population target and assessment of vaccines safety and efficacy.

Item	Yes	Partly	No			
Preliminary						
1. Appropriate contact details for further information?						
2. Authors identified?						
3. Statement regarding conflict of interest?						
4. Statement on whether report externally reviewed?						
5. Short summary in non-technical language?						
Why?						
6. Reference to the policy question that is addressed?						
7. Reference to the research question(s) that is/are addressed?						
8. Scope of the assessment specified?						
9. Description of the assessed health technology?						
How?						
10. Details on sources of information and literature search strategies provided?						
Search strategy	Databases	Year range	Language restriction	Primary data	Other kind of information resources	
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Complete reference list of included studies	List of excluded studies	Inclusion criteria	Exclusion criteria			
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>			
11. Information on basis for the assessment and interpretation of selected data and information?						
Method of data extraction described?	Critical appraisal method (for quality assessment of the literature) described?	Method of data synthesis described?	Results of the assessment clearly presented, e.g. in the form of evidence tables?			
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>			
Context? (may or may not apply to each HTA)						
(Medico-) legal implications considered?	Economic analysis provided?	Ethical implications considered?	Social implications considered?	Other perspectives (stakeholders, patients, consumers) considered?		
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>		
What then?				Yes	Partly	No
12. Findings of the assessment discussed?						
13. Conclusions from assessment clearly stated?						
14. Suggestions for further action?						

Table 5 Checklist for health technology assessment reports (Health Technology Assessment)
INAHTA 2007, CRES 2011

In the systematic review produced by Universidad Nacional (UNAL), the search strategy was quite different. Instead of focusing on HTA and HTA databases; this review directly dealt with research papers and scientific journals. The UNAL review looked for studies in Medline (PubMed), Scielo (Latin America and Caribbean journal database) and LILACS⁵¹. As you can see in Table 6, the search syntax is MeSH⁵² terminology (Medical Subject Headings), the searching introduces geographic terms that limit the search to studies with information about Colombia.

<p>The disease: (Uterine Cervical Neoplasms OR Uterine Cervical Dysplasia OR Cervical Intraepithelial Neoplasia OR Papillomavirus Infections OR Alphapapillomavirus)</p> <p>The virus OR (Papillomavirus Infections OR Alphapapillomavirus)</p> <p>Epidemiological terminology AND (Prevalence OR Incidence OR Epidemiology)</p> <p>Geographic terms AND (Colombia)</p>

*Table 6 Systematic review terminology
Cost-effectiveness study UNAL 2011*

As result 21 articles were obtained from Medline and 13 were selected for complete reading (UNAL, 2009; 2011). This selection was based on the expertise of the reviewers; Universidad Nacional’s selection of papers was based explicitly on experts’ discretion unlike INC review which relies on HTA checklist and EBM criteria. Table 7 shows the papers that are reviewed. In this review all the papers are about Colombia or involve Colombian scientists. In the country a group of researchers has formed around HPV and cervical cancer since 1970. This local ‘scientific community’ has been engaged in large scale research projects on cancer (IARC World Cancer Epidemiology) and clinical trials such as FUTURE⁵³ and PATRICIA⁵⁴. Most of these researchers are or have been affiliated to INC (Colombian National Cancer Institute).

⁵¹ “LILACS is the most important and comprehensive index of scientific and technical literature of Latin America and the Caribbean. For 27 years contributing to increase visibility, access and quality of health information in the Region.” <http://lilacs.bvsalud.org/en/>

⁵² http://learntech.physiol.ox.ac.uk/cochrane_tutorial/cochlibd0e914.php

⁵³ Immunogenicity and Safety of Quadrivalent HPV L1 Virus-Like Particle (VLP) Vaccine in 16- to 23-Year-Old Women When Administered Alone or Concomitantly With Hepatitis B Vaccine (Recombinant)--the F.U.T.U.R.E. Study (Females United to Unilaterally Reduce Endo/Ectocervical Disease. <http://clinicaltrials.gov/show/NCT00517309>

⁵⁴ Human Papilloma Virus (HPV) Vaccine Efficacy Trial Against Cervical Pre-cancer in Young Adults With GlaxoSmithKline (GSK) Biologicals HPV-16/18. PATRICIA (PApilloma TRIal against Cancer In young Adults) <http://clinicaltrials.gov/show/NCT00122681>

1	Piñeros M, Ferlay J, Murillo R. Cancer incidence estimates at the national and district levels in Colombia. <i>Salud Pública de Mexico</i> 2006; 48(6): 455-465.
2	Mendez F, Muñoz N, Posso H et al. Cervical coinfection with human papillomavirus (HPV) types and possible implications for the prevention of cervical cancer by HPV vaccines. <i>The Journal of Infectious Diseases</i> 2005; 192(7):1158-65.
3	Muñoz N, Mendez F, Posso H et al. Incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results. <i>The Journal of Infectious Diseases</i> 2004; 190(12):2077-87.
4	Molano M, Posso H, Weiderpass E et al. Prevalence and determinants of HPV infection among Colombian women with normal cytology. <i>British Journal of Cancer</i> 2002; 87(3):324-33.
5	Castellsagué X, Ghaffari A, Daniel RW, Bosch FX, Muñoz N, Shah K. Prevalence of penile human papillomavirus DNA in husbands of women with and without cervical neoplasia: a study in Spain and Colombia. <i>The Journal of Infectious Diseases</i> 1997; 176(2):353-61.
6	De Sanjosé S, Bosch FX, Muñoz N et al. Socioeconomic differences in cervical cancer: two case-control studies in Colombia and Spain. <i>American Journal of Public Health</i> 1996; 86(11):1532-8.
7	Muñoz N, Castellsagué X, Bosch F et al. Difficulty in elucidating the male role in cervical cancer in Colombia, a high-risk area for the disease. <i>Journal of the National Cancer Institute</i> 1996; 88(15):1068-75.
8	Bosch F, Muñoz N, De Sanjosé S et al. Human papillomavirus and cervical intraepithelial neoplasia grade III/carcinoma in situ: a case-control study in Spain and Colombia. <i>Cáncer Epidemiology, Biomarkers & Prevention</i> 1993; 2(5):415-22.
9	Sierra C, Acosta M, Orejuela L. Papilomavirus y factores asociados a Neoplasia Intraepitelial Cervical de Alto Grado en Cauca, Colombia. <i>Revista de salud pública</i> 2006; Sup. 8 (1): 47-58.
10	Urdaneta H, Calderón O, Amórtegui A. Prevalencia de los genotipos del virus del papiloma humano en neoplasia intraepitelial cervical y cáncer cervical en Bogotá. <i>Revista Colombiana de Obstetricia y Ginecología</i> 1994; 45(3): 219-224.
11	Molano M, Van den Brule A, Posso H et al. Low Grade Squamous intra-epithelial lesions and human papillomavirus infection in Colombian women. <i>British Journal of Cancer</i> 2002; 87: 1417- 1421.
12	Molano M, Posso S, Mendez F. Historia natural de la infección por el virus del papiloma humano en una cohorte de Bogotá, D.C., Colombia. <i>Revista colombiana de Cancerología</i> 2005; 9(4): 209-226.
13	Muñoz N, Kato I, Bosch FX et al. Risk factors for HPV DNA detection in middle-aged women. <i>Sexually Transmitted Diseases</i> 1996; 23(6): 504-10.

Table 7 Articles selected to complete reading
Cost-effectiveness study UNAL 2011

As I have noted before, systematic reviews are devices to enact evidence. But what is evident? First, evidence is what is visible. The systematic review makes visible a set of documents that are picked up from a massive set of scientific production which is present in databases. These documents become the framework of discussion about benefits and risks of these technologies. Such visibility at the same time enacts the field that is represented; such selection is understood as a sample that gathers the best knowledge from a universe of papers. Second, evidence means the best knowledge available to solve a particular problem. Systematic reviews are assessments of the available knowledge about a particular subject. The basic assumption of such practice is that scientific production is not homogeneous in terms of quality and pertinence; therefore it is necessary to select the best to make decisions.

A comparison between the systematic reviews developed in the context of introducing HPV vaccines in Colombia allows us to identify how such selection is deeply contingent, that means it is the consequence of assumptions about what is pertinent that are not very explicit within EBM and the objectivistic rhetoric of HTA. In that regard, systematic reviews provide a tool for the management of contingency. Assumptions such as the understanding of HPV vaccines as drugs to prevent cervical cancer and, therefore, as a matter of women's health become almost invisible, search syntax and the formalisation of information's query moves the attention of the reader toward the "objectivity" of the production of evidence.

In the case of the INC review, what is enacted as evidence is basically information about effectiveness and safety of HPV vaccines. This review concludes that both vaccines are effective in preventing infection of HPV 16 and 18 (plus 6 and 11 in the case of quadrivalent) and in the prevention of adenocarcinoma in situ, neoplasia (CIN II-III), that is the earliest stages of cervical cancer. Moreover, it points out that the target of vaccination should be women between 12-14 years old. These data come from studies done in European countries such as Denmark, Ireland, Italy, Germany and Belgium, whose epidemiological profiles are quite different from developing countries such as Colombia. The INC study is aware of this and the epidemiological data that are used to run the model of natural history of disease come from different literature (IARC and Cohort Bogotá, see Chapter Five).

If this "evidence" is not about data that can be used to characterise the particular conditions of HPV infection incidence and cervical cancer in Colombia, what is its value? In the case of the INC systematic review what is discussed is not the performance of HPV vaccines in relation to different epidemiological profiles of HPV infection; but the "trust" in the safety and the efficacy of these vaccines that regulatory authorities and healthcare institutions have. The systematic review, in this case, is a device to introduce local (Colombian) policymaking into an extended network of institutions and policies. This international support provides legitimacy to the national introduction of the vaccine.

In contrast, UNAL report did not provide a direct conclusion from the literature review. This is presented as the state of the art of the research about HPV in Colombia. As is pointed out in the document:

The research in Colombia about HPV has some degree of development, though most studies have been done by INC with the support of IARC in a cohort of women in Bogotá. In addition to this study, there are just two more studies about HPV and cervical cancer, one in Cauca and another in Bogotá. But each one was done on a different population. INC studies encompass a wide range of aspects of HPV meanwhile the

others just evaluate the frequency of HPV in cervical lesions (UNAL, 2009:21).

Despite the limitations, this information will be used as source data to run the different modelling of disease, costing and natural history by a Markov chain simulation (See Chapter Five). As is noted in the review, data about HPV and cervical cancer are far from being considered evidence in the sense denoted by EBM (hard data in terms of consistency and statistical quality). On the contrary, these data are fragmented and locally situated; other ways of calculation should be developed in order to deal with this contingency.

A last note before leaving the textual laboratory. Both systematic reviews were focused on cervical cancer and precancerous lesions and HPV vaccines but neither addressed the issue of genital warts and other cancers linked to HPV infection. As I will argue in the following, this is an important issue; the burden of genital warts will be a key factor in the choice of Gardasil (quadrivalent HPV vaccine) against Cervarix (bivalent vaccine) as the vaccine for public vaccination programmes in Colombia. The relation between other cancers related to HPV infection—such as throat and anal cancer—and vaccines remains very ambiguous in policymakers' discourse. Sometimes it is used to strengthen the link between cancer prevention and vaccines; however most of the time it is kept invisible because of its relation with non hetero-normative sexualities like anal and oral sex (Epstein, 2007).

Systematic reviews outside the textual laboratory: the political and legal entanglements of the National Committee of Immunisations

Systematic reviews entangle their calculated entities (papers and data) within the social and political relations that such devices mediate. They are “valued for their role in maintaining an appropriated boundary between biomedical science and health politics” (Moreira, 2007: 192). The political qualification of a systematic review weaves together its calculations and the political distributions that best fit them (Moreira, 2007: 192). The political trajectory of data from systematic reviews toward committees and other scenarios depends on the ways in which some political configurations are supported by the goal they attain with meta-analytic calculations.

What follows is a development of Moreira's invitation (2007) to trace how systematic reviews are reconfigured and reshaped within the practices of health politics itself. I will present how evidence and in particular the systematic reviews are dis/entangled in the National Committee of Immunisation Practices (NCIP) in relation to the selection of Gardasil® instead Cervarix®. In a scenario where both vaccines have similar price, genital warts became a key factor in adding value to Gardasil. As I will show, such

consideration meant the reshaping of the meaning of evidence and the authority of scientific papers in relation to the political configuration of the debate.

This analysis is done following the institutional pathways of vaccination programme policymaking (See Figure 8). I have undertaken a textual analysis of the documents framed within these policy processes. The strategy has been to follow the movement and transformation of calculated entities such as data, figures and references within different documents. Furthermore, I have conducted interviews with different people that have been involved in these practices; most of them have been protagonists as members of technical committees or as experts in the production of evidence (See Chapter Two).

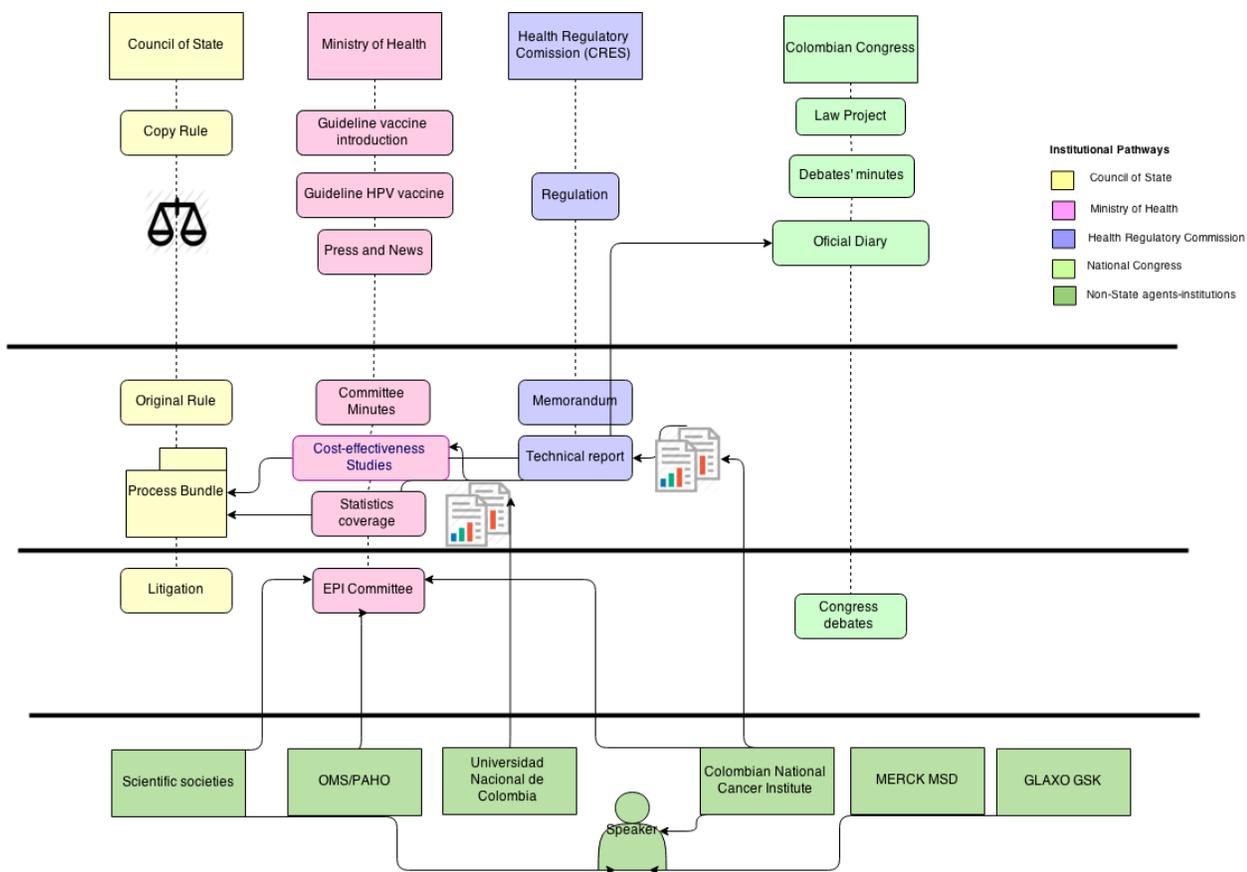


Figure 8 Institutional pathways in the introduction of HPV vaccines into Extended Programme of Immunisation

Technologies of legitimation, technical committees and consensus rhetorics

Technical studies are conceived as tools for decision making. Such tools in very particular cases interfere directly in decision makers' interventions. Most of the time, these documents are a fundamental input for the discussion of advisory bodies such as technical committees which translate, disentangle and reshape

evidence in order to give advice to politicians and bureaucrats. Committees are a very interesting case to understand how agency is enacted through distributed agents. The National Committee of Immunisation Practices (NCIP) is the main scenario of discussion about vaccination programmes in Colombia. There, many uncertainties that experts and policymakers try to move away from public opinion and media are visible. Discussions about the right vaccine (Gardasil® or Cervarix®) for public programmes involved not only considerations about prevention and disease burden, but also a particular management of the uncertainties that each vaccine entails. Although some committee members had pointed out worries about the duration of protection and about the character of genital warts as a public health issue, after decisions are made these concerns are not rendered visible in order to favour ‘consensus’.

The committee should determine its decisions on evidence; such evidence is enacted through data, figures and different studies. The committee’s agency is distributed through these studies, figures, calculations, papers and data bases. At the same time, the committee itself enacts its ability to make decision through documents and texts, such as technical reports and minutes⁵⁵. These documents are the *official voice* of committee and a material register that confers permanence (existence in time) to its actions. The main function of the committee is to manage evidence and to give advice to the Ministry of Health based on that. The existence of the committee is based on the necessity of having a technical and deliberative organism that discusses and formulates directions with the best scientific evidence at stake, with the aim of achieving a better orientation of the National Programme of Vaccination by the Ministry of Health (Agreement 01 of 2011, art: 2). This kind of organisation has been replicated in different locations around the world and it is an important part of the global governance of vaccines. As I noted before in Chapter Two, the function of the committee is to provide directions with the best scientific evidence, in order to achieve this goal the committee is composed of delegates of medical and scientific associations (See Chapter Two).

STS has developed a set of contributions regarding expertise and policymaking in which committees have an important role as object of study and scenario of controversy and consensus construction (Hilgartner, 2000; Jasanoff, 2004, Wynne, 2010, Hedgecoe, 2009, 2012). STS has described the entanglements between politics, science and technology, regulations and media and more radically the ways in which nature and politics are coproduced. Much STS work about committees has followed an ethnographic approach in order to depict the interactions among their members and the ways that consensus and trust

⁵⁵ In this particular case, the considerations of NCIP regarding HPV vaccines in Colombia can be traced in the Meeting minute SGC-F03. “Definition of introduction of vaccine against HPV and Hepatitis A into Extended Programme of Immunisations”. National Committee of Immunisation Practices, 3rd May 2012. Bogotá: Ministry of Health.

are produced (Hedgecoe, 2009, 2012). In this thesis such an approach involves many difficulties. The meetings that are important to understand the development of this policy happened some years ago, on the other hand some of these committees are closed in the sense that the discussions are confidential.

However, in parallel to the analysis of contingency and the controversies to reach *consensus*, my interest is focused on the performative role of committees in policy making. In other words, I describe the ways in which committees enact legitimacy; how they act as organisation technologies that introduce particular enactments of transparency, legitimacy and accountability. As I previously noted institutions are constituted by heterogeneous association between human and non-human actors. The extended agency of institutions and large-scale organisation is the result of material and discursive assemblages (see Chapter Two).

New calculative spaces, minutes as literary technologies

Minutes as literary technologies (Shapin and Schaffer, 1985) are one of the most important tools to enact the values that are supposed to define the work of the National Committee of Immunisations in Colombia: that is, excellence, transparency, independence and confidentiality (Agreement 01 of 2011). These documents produce a linear account of decision making from presentation of evidence, deliberation to consensus achievement. On the other hand minutes have a role as tools of accountability; they are part of the chain of documents which allows us to trace legal and political responsibility regarding the consequences of these decisions. Although minutes are based on transcription of notes of meetings, these are not an exact reproduction of members' interventions and discussions.

The minute (SGC-F03 3rd May 2012) of the meeting that defined the introduction of HPV vaccines in the Expanded Programme of Immunisation (PAI) summarizes the presentations of cost-effectiveness studies and the systematic literature review about vaccines safety and efficacy. This document, moreover, presents the main topics of discussion and the decision of the committee. This document illustrates some of the ways in which evidence is reshaped through its interaction with other entities once it leaves the textual laboratory.

Minutes allow us to locate the ways in which the systematic review is transformed in committees and deliberations. I want to illustrate such dynamics through the analysis of the selection of Gardasil®, presenting how such decision is enacted and legitimated in the Committee minutes. Such selection was made after a discussion about cost-effectiveness, burden of disease, price and safety. These issues are addressed in different chapters of this thesis, nevertheless, here I would like to present the role of

systematic reviews and scientific papers in the production of these enactments of evidence. On the other hand, through interviews with committee members and invited professionals I describe how what counts as evidence becomes extremely contingent during committee discussion. However, after the decision is enacted, such evidence becomes strong enough to legitimate the committee role of providing the “best scientific evidence at stake”. The following table summarizes technical features that were taken into consideration in the selection of the vaccines.

	HPV 16/18 vaccine Cervarix (Bivalent)	HPV 6/11/16/18 vaccine Gardasil
Manufacturer	GlaxoSmithKline	Merck MSD
Volume	Per dose 0.5 ml	Per dose 0.5 mL
Adjuvant	AS04: Al(OH) ₃ 500 µg MPL® 50 µg	Aluminium sulphate® 225 µg
Antigens	L1 HPV 16 20 µg L1 HPV 18 20 µg	L1 HPV 6 20 µg L1 HPV 11 40 µg L1 HPV 16 40 µg L1 HPV 18 20 µg
Expression System	Hi-5 Baculovirus	Yeast
Schedule	Intramuscular 0,1,6 mths	Intramuscular 0,2,6 mths
Indications	Prevention of HPV-16 and HPV-18 infections, and for the prevention of cervical intraepithelial neoplasia grade 1 (CIN1), CIN2, and CIN3.	Prevention of HPV-16 and HPV-18 infections, and for the prevention of cervical intraepithelial neoplasia grade 1 (CIN1), CIN2, and CIN3. Prevention of vaginal and vulvar neoplasia, genital warts in females and, recently, to the prevention of genital warts in males.
Duration of protection ⁵⁶	9,5 years study phase II 4 years study phase III	8,5 years monovalent vaccine HPV 16 5 years study phase II 4 years study phase III 3 years study phase III in men
Price for Colombian government	14USD (2011 prices) Through PAHO Revolving fund.	16USD (2011 prices) Through PAHO Revolving fund.

Table 8 Technical description of HPV vaccines

This table -as calculative device- unavoidably reduces the different aspects that such comparison involves, however, it is quite useful to present the most contested aspects of the debate which are related with the indications, the duration of the protection and the price. After a closed vote (Bivalent: 5 and

⁵⁶ According to the Minute SGC-F03 3rd May 2012. These data were provided by the PAHO consultant using this literature: Villa et al. 2006. Br J Cancer 95:1459-66; Kajel et al. 2009, Cancer Prev Res 2:868:78; Rowhani-Rahbar et al. 2009, Vaccine 27: 5612-9; Lehtinen et al. 2009, Vaccine 27: 5612-9; Lehtinen et al. 2012, Lancet Oncol 13:89-99.

quadrivalent: 6), “the committee, based on the **best available and current evidence**, decides to recommend the introduction of the quadrivalent HPV vaccine into the Expanded Programme of Immunisations” (SGC-F03 3rd May 2012).

Evidence in controversy, extending calculation accounts and confronting valuation strategies

What is the “best available and current evidence”? That is the conundrum. In an interview one of the committee members pointed out the difficulty of talking about evidence in this context:

Oscar Maldonado (OM): According to the minutes, the decision was very close and very contested (5 to 6); wasn't it?

Committee member (Sr Epidemiologist 1): Yes, it was. A lot of people considered that the best option was the bivalent vaccine. Basically because it costs 2 USD less by shot and also because there is a recent study that supposedly showed a bigger effect against serotypes in most advanced stages of cancer. However, some members—in particular those from the regions—considered that the effect on genital warts was an important issue. I mean, that issue was very important for the people that work locally in the departments⁵⁷. In that sense, they thought that to deal with genital warts could be a visionary intervention.

OM: What was their evidence? Was that based on their own experience?

Committee member (Sr. Epid 1): Indeed, everyone in that discussion had their own theory but none had proper population data to contest such estimations. The only new information -after our study was done- was a study published in January (2012). This study apparently showed that bivalent vaccine had an additional effect on cervical cancer, in terms of bigger protection. But this study was not a comparison between bivalent and quadrivalent vaccines; it was just data about bivalent. So some people in the committee interpreted this study as if it demonstrated the superiority of one vaccine over the other; but as a matter of fact, there was no study at that stage about both vaccines. But that study was determinant. Many people voted in favour of bivalent vaccine (Cervarix) because they thought such a study contributed important additional information.

The Committee epidemiologist is referring to two studies published in *The Lancet Oncology* that were presented by one of the experts from National Cancer Institute (INC) in relation to cross protective

⁵⁷ “Colombia is divided into 32 departments and one capital district, which is treated as a department (Bogotá also serves as the capital of the department of Cundinamarca). Departments are subdivided into municipalities, each of which is assigned a municipal seat, and municipalities are in turn subdivided into corregimientos. Each department has a local government with a governor and assembly directly elected to four-year terms. Each municipality is headed by a mayor and council, and each corregimiento by an elected corregidor, or local leader” (Wikipedia: Colombia).

efficacy. That is the development of immunity against other types of oncogenic HPV that are not the primary target of the vaccine. These are the journal articles presented in the discussion:

Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncology*. 2012 Jan;13(1):100-10.

Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncol*. 2012 Jan;13(1):89-99.

Cross protective efficacy is a factor that can produce difference between vaccines and, therefore, add value to them. Both studies are part of the PATRICIA trial (PApilloma TRIal against Cancer In young Adults) sponsored by GlaxoSmithKline to demonstrate efficacy and safety of its vaccine (Cervarix). Nevertheless, according to committee's minute these studies were not considered as evidence of technical superiority of this vaccine:

In this regard, the committee argued that the objective of those studies was not to analyse cross protection, therefore these are non-intended findings, whose validity is questionable (Meeting minute SGC-F03 3rd May 2012).

There is a gap between the consensus enacted in the minutes and the controversy that can be reconstructed through interviews with committee members. Such a gap allows the confrontation between valuation strategies of HPV vaccines to be traced and the reinterpretation of the systematic review evidence within this debate. On one hand, Gardasil supporters have focused their evidence on the prevention of genital warts as an added value. On the other hand, Cervarix supporters have centred their argumentation in the cross protective efficacy of the vaccine against other oncogenic HPV types. Of course, each one of these claims involves the mobilisation of arguments to undermine the other's strategy. From the perspective of Gardasil supporters, that meant associating the choice of Cervarix as an issue of money, a minor saving of 2USD in comparison with the "massive" impact of preventing genital warts. An analysis of the construction of data about genital warts will be presented in Chapter Five, however it is important to point out there are little data about incidence and burden of genital warts in Colombia, most of data comes from international literature. Accordingly, the discussion about genital warts within the committee was based on the "clinical" experience of some members, those from the "regions", who pointed out that genital warts is a recurrent issue, in particular in war zones where soldiers are specially

affected. The regions are very important for the Expanded Programme of Immunisation. In terms of political support, the impact of vaccination has been perceived as greater outside the larger cities and metropolitan areas.

However, such reference to local and clinical experience hardly fits into the EBM repertoire which shapes the rhetoric, the narratives and the calculation practices that are materialised in the committee minutes. As discussed before, the committee ‘tames’ the papers presented in favour of Cervarix by pointing out that the findings of cross protective effectiveness were unintended. Therefore, such results are not strong enough to be considered as proper evidence. This is not an easy move, as I have presented in the first part of this chapter EBM conceives RCT -Randomized Controlled Trials- as the most reliable form of evidence, and the paper about cross efficacy is the result of the RCT PATRICIA. But in practice the definition of reliable and pertinent evidence is much more complex.

Committees can be understood as technologies of legitimation (Harrison and Mort, 1998) that confer political support to policy making by managing uncertainty and reshaping evidence. As one of the PAI epidemiologists points out, the committee has to consider a diverse set of factors that are beyond literature. Such flexibility makes decision-making operative, however, at the same time it introduces contingency, making visible as Latour would argue that matters of facts are matters of concern (Latour, 2004b).

The members of the committee that supported Cervarix argued that the main issues that should be discussed regarding HPV vaccines are cross protective effectiveness and the duration of the protection effect. The first because HPV 16 and 18 just are present in the 70% of cases of cervical cancer in the world and in Colombia their prevalence is around 65% (see Chapter Five); the second because if the duration of the protection is too short, an additional boost could be required increasing vaccination costs. For Cervarix supporters in both issues the performance of this vaccine is superior. As it is noted by one of the members of the committee:

Committee member 2: The bivalent vaccine has showed much more convincing data about its effect which is not limited to HPV 16 and 18 but also to other virus types that produce cancer. However, for some people that is negligible. It is a hard decision (...)

Producers of the quadrivalent vaccine have formulated the vaccination of men which is not recommended by WHO (...) Nowadays the research is focused on establishing the long term protection of the vaccine, how long the effect will last and if it is necessary and additional boost.

The debate between these groups in the committee was intense and critical. Some members of the committee perceived that the systematic review produced by Universidad Nacional was extremely partial, that maximised explicitly the burden of genital warts and minimised the problem of cross protective efficacy. Some members even perceived that such omissions could be unethical within the committee.

Committee member 2: In the second presentation—it was when the decision about which vaccine was done—I think they (UNAL advisors) maximised the issue of the warts and minimised the cross protective efficacy. They say they did alternative analysis but for me, my impression, there was not a fair consideration of the alternatives that each group formulated. Actually, in the presentation they showed data with a bigger cross protective efficacy for the quadrivalent than for the bivalent vaccine. I think I know why such confusion... They said later, they were sorry; it was just a mistake in the presentation. For me it is curious that in a presentation where a big decision for the country will be made, you say that you made a mistake with the data. It is at least inappropriate. Is it not?

On the other hand, the debate about the choice of vaccine can be understood as a controversy between institutions about expertise of the groups and the institutions behind the development of the systematic reviews. For the experts from INC, the Universidad Nacional study fails to provide the right evidence because of a lack of knowledge about the health problem they are analysing. For them the group from Universidad Nacional is outside HPV and cervical cancer's research world and the technological advances around this issue, because their experience is mainly about childhood vaccines. INC experts claim they have superior knowledge of HPV vaccines.

This controversy shows a clash between strategies of production of value. The perspective accepted as official, will be enacted as *evidence* meanwhile the other will disappear in order to keep an image of relatively stable consensus. Despite the controversy, members of the committee argue that this debate is merely technical, both vaccines are good enough to be included into the EPI. At this point the evidence enacted in minutes constitutes the “official” voice of the Ministry of Health and of the Colombian Government. Such enactment of evidence will travel through other institutional pathways; it will provide the plot of politicians' speeches, press communications and public declarations, such as the radio interview that I described in the beginning of this chapter.

Finally this movement of data and the reshaping of evidence within technical committees will create a boundary between evidence from the perspective of the experts and the information that will circulate between lay and public arenas. In the interviews that I conducted with members of the committee, some considered that they should preserve the *consensus* reached. In relation to a question about the lack of

studies regarding genital warts to support the quadrivalent vaccine (Gardasil), one of the epidemiologists of PAI pointed out:

Committee member 3 ...At the moment of making the decision -because I was there- there were theoretical argumentation and evidence about both vaccines' cost-effectiveness. And it was concluded both were equal regarding their main goal, which is reduction of cervical cancer. Either was considered useful to be introduced into a vaccination programme against cervical cancer (...)

However, at the moment of making decisions the committee considered the possibility of reducing genital warts and moreover they took that study about the herd effect. So it could be more effective to go beyond direct effect of vaccination (cervical cancer) but (the committee) said that issue (genital warts) should remain invisible, it will be not told to the public, for instance in the campaign. The focus of advertising and campaigns should be just reduction of cervical cancer. So when people started to vote -because the voting was very closed and very objective- they choose the tetravalent. That was the situation.

Oscar Maldonado: So... what were the arguments against tetravalent vaccine? Was it the lack of studies about genital warts?

Committee member 3 They said that the additional cost of the tetravalent vaccine could be used in a bigger campaign (media and advertising) and making more research, more studies... those savings could be used for that. Moreover, if the goal was preventing cervical cancer, so the vaccine and the discussion should be just about cervical cancer. But at the moment of voting, some people said it is important to consider additional factors. The economic difference is not big and one vaccine is providing a plus; on the other hand, there is money enough... so we should choose the best, and the best was the vaccine that gives a plus (beyond cervical cancer prevention).

For the committee, the cost of moving away from evidence standards is to risk its capacity to enact legitimacy. In this case, the committee's decision to extend the vaccination programme from cervical cancer to genital warts involves the introduction of new factors harder to control: promoting a vaccine against a sexual transmitted disease (STD) whose target is girls between 9-12 years old. Although such a relation is present in the cervical cancer narrative it is less explicit than in the case of genital warts. As I have noted at the beginning of this dissertation, the consequence -as it is visible in advertisement and campaigns- is to hide this relation and to focus on preventing cancer (See Chapter One).

Conclusion

Evidence has been presented by policymakers and supporters of EBM as the solution to the current crisis of healthcare; it provides a way of dealing with the increasing demand of new technologies and treatments, the transition toward new epidemiological profiles and increasing costs. Systematic reviews are one of the tools that better presents the dynamics and the orderings of evidence in healthcare.

Systematic reviews are depicted –within EBM narratives- as interfaces between the world of scientific research and the concerns and practicalities of policymaking. These reviews have promised the presentation of clear and simple information to policymakers about reliable and robust scientific knowledge in relation to policy problems. Systematic reviews, as textual laboratories, produce objects through the assemblage of entities from diverse contexts.

However, if we look in detail at the practices of production of systematic reviews and the ways in which they are read in different institutional settings, it is possible to see that the transit of objects and problems from the orderings of science to the domain of policymaking is neither linear nor unidirectional. On the contrary, systematic reviews can be understood as a practice of calculation that entangles different entities from different contexts in a singular space producing new orderings. Accordingly, systematic reviews are textual laboratories; the entities that are manipulated, reordered and transformed are texts such as scientific papers, HTA's and other systematic reviews. Systematic reviews are also literary technologies whose rhetoric enacts a modest witness, an “objective” observer of the transformation of objects that happen within the text as laboratory (Haraway, 1997: 37).

In relation to the introduction of HPV vaccines in Colombia, the analysis of the systematic reviews produced in the development of this policy shows how political concerns shape the design of the systematic review and thus interfere in the enactment of evidence. At least two alternatives of calculation were formulated in order to present the evidence gathered as legitimate. In the case of INC review a strategy is adopted that relies on the support of an international network of texts and institutions part of the EBM movement. In contrast, the Universidad Nacional review centred its gathering of data in local studies done by local communities. In this review the evidence presented is legitimate because of its local nature. In that sense, to calculate, to value and to legitimate are dimensions of the practices of production of evidence.

For this reason the main impact of systematic reviews is beyond their textual laboratory, at the moment when they are used as input and source of data and information in policymaking. Data and documents travel, reaching new contexts of reading in which new objects and practices are entangled. Technical committees are particularly important in the design of policies and in the enactment of *technical consensus* as a mechanism of legitimation. In the case of the selection of vaccines for the vaccination programme against HPV in Colombia, it is possible to see how strategies of calculation are strategies of production of value. Within each one of these strategies evidence is reworked and reshaped in order to support the claims in controversy. In the case of HPV vaccines this meant a trade-off between preventing

genital warts versus considering the cross protection efficacy of vaccines. Despite the intensity of the debate, to preserve the image of the committee as a *consensus maker*, it is necessary that just one strategy of valuation should be considered as legitimate. Finally the movement of data and the reshaping of evidence within technical committees is an important element in the production of the boundaries between experts and decision makers and lay people and citizens.

Chapter Four

Making HPV vaccines efficient

Cost-effectiveness analysis, health currencies and the economic assemblage of healthcare

Introduction

Evidence and efficiency are claims that have guided the transformation of contemporary healthcare practice and policy (Mol, 2008; Moreira, 2012b). If evidence is related with the use of the “best” scientific knowledge available to make decisions, efficiency has been envisioned as a claim for the “best” use of scarce resources. Although evidence and efficiency are deeply intertwined, each one has developed its own practices of calculation. While evidence relies on the systematic review; efficiency has been enacted through strategies of calculation such cost-benefit (CBA) and cost-effectiveness analysis. Both evidence and efficiency are expressions of logic of “optimisation” in healthcare based on management.

In this chapter I analyse a second device of calculation—cost-effectiveness analysis—and the ways in which efficiency is enacted in the introduction of HPV vaccines. Cost-effectiveness analysis (CEA) is a strategy of calculation whose main objective is to compare and make decisions about the best, the most efficient solution (costs vs. benefits) to a particular problem. In particular, the use of CEA in healthcare has been focused on the comparison between technologies and procedures with the aim of reducing costs through the rationalisation of care. To compare is never an easy task. It involves taming objects, reducing them to analytical features, and establishing standards and measurement units. In the case of healthcare and medicine such tasks are even harder, considerations about human life and healthcare value have made any attempt of rationalisation of costs based on increasing efficiency extremely contested.

However, difficult does not means impossible. CEA is a well-established technique to support decision making in health policy; it has a long tradition in Europe and North America and in the past decade it has been increasingly used in developing countries. This practice has demanded the development of particular health measurement units such as the Year Lost Life (YLL), Quality Adjusted Life Years (QALY) and

Disability Adjusted Life Years (DALY). These units act as health currencies in the sense that they are used as quantified and interchangeable measures of the value of health care interventions in terms of human life. As I will show, health currencies complete the work done by monetary estimations in the calculation of cost-effectiveness which is a ratio between costs expressed in money and benefits in terms of human life and quality of life.

The practices of calculation that make possible the definition of measurements and thresholds are complex to the extent that they involve many actors, multiple enactments and a big effort of coordination. The value of a particular thing, even human life, depends on the process of measurement of such value through particular material and discursive arrangements. As Callon and Law write, “calculation and non-calculation reside not primarily within human subjects but in material arrangements, systems of measurement, and methods of displacement or their absence” (Callon and Law, 2005). In that sense, this chapter is an analysis about how methods perform reality, in this case how CEA as methodology of comparison and valuation enacts entanglements between health, economic value, sexuality, risk, cervical cancer and HPV vaccines.

Cost-effectiveness analysis as calculation practice depends on the disentanglement of technologies and procedures from their contexts of use in healthcare; these entities are ordered in a calculative space in which they will be transformed and translated into new entanglements as results. As I presented earlier in the case of systematic reviews, such spaces are classification tables and the different orderings from the textual laboratory. In the case of CEA the new calculative space will be defined by formulae. A formula is a symbolic representation of the relation between entities that have been quantified. In the same way in which tables and rankings tell stories about modes of ordering, hierarchies, inclusions and exclusions, formulae as calculative spaces enact rules, assumptions and narratives about the entities that are calculated.

In the introduction of HPV vaccines in Colombia was central the debate of their cost-effectiveness. Security and efficacy of the vaccines were relatively taken for granted. In the systematic reviews of literature issues regarding adverse effects or problems of immunogenicity were not made explicit. The different studies used by decision makers argued that HPV vaccines are safe and effective in the prevention of cervical cancer. In contrast, cost-effectiveness has been a contested issue. During the first attempt to introduce HPV vaccines in Colombia (2008) they were not considered cost-effective by Universidad Nacional, the institution in charge of the studies for Ministry of Health. Such conclusion

generated a debate with the National Cancer Institute (INC) and even lead to a lawsuit against the Ministry of Health that was addressed by the Council of State.

HPV vaccines' cost-effectiveness has been a contested issue because of the different elements involved in its calculation. They are one of the most expensive vaccines on the market and an intervention to prevent a disease with an occurrence period of 20-30 years. Moreover HPV vaccines are 'competing' with cervical screening programmes, a complex system of diagnosis and treatment of cervical lesions. For Global health experts, cervical screening has significantly reduced mortality for cervical cancer in the countries where it has been organised (developed countries). CEA put together these different elements and translated their heterogeneity into the language of health and monetary currencies.

In this chapter I analyse the use of cost-effectiveness analysis in the introduction of Gardasil® (Quadrivalent HPV vaccine) in the Colombian Expanded Programme of Immunisations. Such studies compared four scenarios: non-intervention, cervical screening programme, only vaccination alone and vaccination plus cervical screening programme. In this chapter I present a description of CEA as calculation strategy. CEA not only provides a framework to compare healthcare interventions which in practice seem incommensurable; it also performs a set of assumptions regarding the nature of healthcare and the behaviour of individuals, such assumptions are embedded into narratives and ontologies based on market and rational choice theory.

In what follows I will discuss the role of CEA analysis in the transformation of healthcare policies toward market based decisions and in particular its role in the introduction of vaccines. I analyse the formulae involved in CEA, presenting how health currencies are calculated and the consequence of the use of DALYs as a unit of measurement of burden of disease and cost-effectiveness in Colombia. Finally I analyse how the results of CEA are interpreted in the technical reports and in other arenas such as the NCIP committee, the Colombian Congress and the Council of State.

Cost-effectiveness: Efficiency and rationalisation of public decision making

Numbers and quantification have had a deep impact in modern politics. Figures and quantified data have constituted a powerful rhetorical resource in political debates and in the enactment of policies. One of the most important transformations of contemporary policymaking has been the integration of cost-benefit analysis and cost-effectiveness analysis in governments' decision making. Cost-benefit analysis has been presented by bureaucrats and governments as a substitute for pure ad-hoc decision making (Porter, 1995: 222). Such practices have had a great impact not only because of their rationality but their impersonality (Porter, 1995: 227). As Porter has noted, the increasing use of calculation and numerical methods in social

and policy arenas is related to their capacity to reduce potential controversies in political processes through the translation of these issues into a numerical scale. Such is the case of cost-benefit analysis and its extended use in health policy making⁵⁸.

The use of these practices of calculation in health policy making have been strongly encouraged by international organisms such as the World Bank, the Inter American Development Bank –IADB- and the WHO. Cost-benefit analysis (CBA) and cost-effectiveness studies have been strongly promoted by the WHO in order to facilitate decision making in the introduction of healthcare technologies in developing countries. Since 1998, WHO has developed the project CHOICE (CHOosing Interventions that are Cost-Effective) to provide “policy makers with the evidence for deciding on the interventions and programmes which maximize health for the available resources” (WHO, 2014⁵⁹). WHO-CHOICE reports the costs and effects of a wide range of health interventions in 14 epidemiological sub-regions based on geographical location and epidemiological profiles. Furthermore, cost-effectiveness analysis has been extensively recommended by WHO in the introduction of vaccines in developing countries, in particular in relation to the introduction of new vaccines into the national immunisation programmes. In 2011 the Strategic Advisory Group of Experts (SAGE) of WHO published the *Guidance for the development of evidence-based vaccine related recommendations* which advises the use of GRADE scale to evaluate evidence and data quality to determinate cost-effectiveness of vaccines (Guyatt et al., 2011).

Cost-effectiveness analysis allows the identification and monetization of the costs and the benefits of a programme. It relates costs to specific measures of effectiveness, in the case of health economics to measures of human life’s value expressed in QALY, DALY or YLL⁶⁰. Cost-benefit (CBA) and cost-effectiveness analysis (CEA) are powerful tools in policymaking because they translate different objects

⁵⁸ Ashmore, Mulkay and Pinch (2000) have analysed the use of this scheme in the case of NHS (National Health Service) option appraisals. “Option appraisal is a relatively well-established technique both in terms of its theoretical and technical pedigree and its degree of embeddedness within the current practices of the NHS” (Ashmore et al., 2000: 4). For them, option appraisals depict the politics of rational decision making; basically such politics justify “soft decisions” through “hard numbers”. Such pretensions -for Ashmore et al., (2000) - have taken the form of “the strong programme” in health economics. This model conceives policies based on numbers and figures as the best process of decision because it entails rational decision making. At the same time, Ashmore and colleagues identify a weak model in health economics, which recognizes the limitations of calculation and quantification, because politics and evidence are deeply intertwined and are inseparable. Despite the coexistence of these models, in the case of option appraisals the rhetoric of the strong programme seems stronger.

⁵⁹ WHO-CHOICE. <http://www.who.int/choice/description/en/>

⁶⁰ Analysts can obtain a programme’s cost-effectiveness (CE) ratio by dividing costs by units of effectiveness (Cellini and Kee, 2010: 493). CEA also identifies and monetizes the costs of a programme, but it weights moreover those costs against the money (USD, I\$, GBP) value of programme benefits. “Typically, analysts subtract costs from benefits to obtain the net benefits of the policy (if the net benefits are negative, they are referred to as net costs)” (Cellini and Kee, 2010: 494).

and realms into a quantified language whose “value” is perceived as highly visible: money⁶¹. Both methods are devices of commensurability. As Ashmore and colleagues noted, “the success and credibility of techniques like cost benefit analysis lies in their ability to continually trade between the worlds of facts and figures and worlds of words and politics” (Ashmore et al., 2000: 24). Such capacity to mediate makes such practices very extended in contemporary policy assessment.

Steps in Cost-Effectiveness and Cost-Benefit Analysis
1. Set the framework for the analysis
2. Decide whose costs and benefits should be recognized
3. Identify and categorize costs and benefits
4. Project costs and benefits over the life of the program, if applicable
5. Monetize (place a dollar value on) costs
6. Quantify benefits in terms of units of effectiveness (for CEA), or monetize benefits (for CBA)
7. Discount costs and benefits to obtain present values
8. Compute a cost - effectiveness ratio (for CEA) or a net present value (for CBA)
9. Perform sensitivity analysis
10. Make a recommendation where appropriate

Table 9 Steps in Cost-Effectiveness and Cost-Benefit Analysis

Source: Cellini and Kee, 2010: 495.

Rigg and colleagues (2010) present a good summary of the steps in CEA and CBA; I have adapted them in this table. As I will present further, such process is rendered visible in decision making and its sequence is part of the construction of “objective” valuations done by health economics and analysts which is presented in closed numbers and ratios.

Another feature of cost-benefit and cost-effectiveness analysis is their capacity to enact future scenarios. This is important to decision makers because programmes’ benefits and costs are not limited to the present; on the contrary they are calculated and defined in the future. These methods provide a quantitative enactment of the anticipation regimes in contemporary biomedicine described by Adams and colleagues (Adams et al., 2009). Economic and health benefits are projected in the future, the current scenario matters because it is perceived as a stage in the enactment of the future. Although the main equations that define CBA and CEA seem relatively simple, they become more detailed when issues about

⁶¹ In Chapter 6, I will present how the complexity of such economic estimations and how the “value” of money depends on the socio-technical arrangements by which it is calculated.

time and opportunity costs are included in the analysis⁶². Most CEA and CBA use something known as a social discount rate to calculate the present value of costs and benefits. “The social discount rate is meant to reflect society’s impatience or preference for consumption today over consumption in the future” (Cellini and Kee, 2010: 518). As I will show, discount rate is a highly contested issue in the definition of health currencies such as QALY and DALY.

These different calculations are made in order to define with more detail and on a time horizon what economists have called opportunity costs, that is the value of the best alternative forgone, in a situation where choices have to be made between several mutually exclusive alternatives, given limited resources. Technical literature about CEA (Zeifel et al., 2009; Mayer, 2010; WHO, 2011b) warns about the serious ethical issues that opportunity costs entail. The most contested issue has been public health expenditure equity: if a government decides to pay for a very expensive treatment which is beneficial for few people, such government may be unable to afford other equally or more effective treatments that may help many more people. A common example in the technical literature is the comparison between bone marrow transplant and hypertension screening⁶³.

Cost-effectiveness analysis is depicted by EBM experts and policymakers as the tool that should be able to reveal if the cost of a new therapy is “worth it” or if decision makers should be paying for some other, “cheaper” or “more effective therapy”. As I will present later in relation to the definition of QALY and DALY, CEA implies deep and strong assumptions about human nature and the value of care. Most of the

⁶² A closer look at the formulae of these equations allows us to understand the ways in which temporality is entangled in this kind of analysis. In CEA, you take the present value of the costs of the project to use as the numerator in your cost-effectiveness ratio. To do this, you first aggregate the costs in each year, noting each year’s costs as C_t , where t indicates the year from 1 to T (the last year of the analysis). The values in each year need to be converted to their year 1 equivalent, and this is done by dividing C_t by $(1+r)^{t-1}$

CER is calculated taking into consideration the Present Value of Costs (PVC)

$$PVC = C_1 + \frac{C_2}{(1+r)^1} + \frac{C_3}{(1+r)^2} + \dots + \frac{C_r}{(1+r)^{r-1}} = \sum_{t=1}^T \frac{C_t}{(1+r)^{t-1}}$$

In CBA, the calculation takes the present value of the benefits and subtracts the present value of the costs. The final calculation is now referred to as the net present value (NPV), rather than net benefits (Cellini and Kee, 2010: 518).

$$NPV = \sum_{t=1}^T \frac{(B_t)}{(1+r)^{t-1}} - \sum_{t=1}^T \frac{(C_t)}{(1+r)^{t-1}}$$

⁶³ “If we fund bone marrow transplants for questionably beneficial indications, we may not be able to pay for hypertension screening leading to treatment that could prevent the need for certain other high cost therapies like kidney or heart organ transplants in the future. A bone marrow transplant may prolong one life by 6 years, yet result in loss of funds for hypertension screening and treatment programs which could prevent six new deaths from uncontrolled hypertension in that same period”(Mayer, 2010: 351).

time such assumptions are taken for granted because the analysis is focused on the particular features and implications of the technologies that are assessed, what is measured makes invisible what measures.

Before presenting the ways in which CEA is performed in the introduction of HPV vaccines in Colombia, I discuss some of the assumptions and tensions that the metrics used in this kind of calculation entail. These measurement units play a decisive role in the demonstration of HPV vaccines as efficient interventions, in particular Disability Adjusted Life Years (DALY): the measurement unit used by Universidad Nacional to express the cost-effectiveness of interventions and the burden of diseases. I will present some of the tensions that DALY entails by contrasting them with a measurement unit deeply related to its development and that has been studied with more detail by STS: Quality Adjusted Life Years (QALY).

Measuring life, the development of human health metrics

The production of evidence and efficiency involves a diverse set of calculation devices. Each one entails different practices of classification, production of calculative spaces, gathering and transformation of entities and their reshaping and reconstitution through results and summaries. The coordination of these devices demands the production of specific languages and objects. This problem is not exclusive to technical and scientific calculative practices, everyday life exchanges involve calculation, valuation and the definition of exchange media. These objects that facilitate exchange can be called currencies (Zelizer, 1998; Çalışkan and Callon, 2009; Appadurai, 1986). Currencies are not only exchange media they are signs of value as well. In contemporary societies money has had the role of being a standardised measure of value (Zelizer, 1998, Smithin, 2000), whatever value can mean.

Despite its extensive use in the valuation and assessment of healthcare technologies and procedures, monetary units have become considered extremely limited in the calculation of health and human life. In response, the notion of quality of life has gradually emerged as an accepted currency in which to express the human costs of technological interventions, as well as their effectiveness (Armstrong and Caldwell, 2004; Moreira, 2012b).

According to Armstrong and Caldwell (2004) the rise of quality of life repertoire is a counterpoint to “the dream of a technological future” in the care of patients. They argue that ambivalence towards technological progress was a key element in the surge of quality of life measurements. Simple survival data and reduction in costs expressed in money were no longer enough, “Quality of life moved towards being the new common currency of medical outcome that would allow more meaningful comparison of

surgical rates or the explanation of medical care variation” (Armstrong and Caldwell, 2004:23). Quality of life discourse has been centered on patients’ well-being, not only on their survival. The widespread use of new forms of measurement has been supported in the justification that it recognizes and gives voice to the patient beyond the traditional dominance of ‘biological’ and medico-centric outcomes in health (Armstrong and Caldwell, 2004: 22).

Armstrong and Caldwell argue that the analysis of medical interventions (e.g. renal dialysis for children and chemotherapy in the United Kingdom during the 1970s) showed that the “technological success” of these interventions was limited to the number of survival years. However, patients’ lives were being prolonged at expense of quality. There was a need to recognize that “our life saving technology of the past four decades has outstripped our health preserving technology and that the net effect has been to worsen people’s health” (Armstrong and Caldwell, 2004: 22).

Other authors such as Moreira (2012b), Harrison (1998), Ashmore, Mulkey and Pinch (1989, 2000) have noted that the development of quality of life measurement is a consequence of the introduction of management and market narratives and practices into healthcare institutions. Healthcare provision has been reshaped by the claims of efficiency and effectiveness that this setting entails. Accordingly, market and marketization practices in healthcare have been presented in policy arena as the solution against the moral dilemmas that such understanding of healthcare provision as a market creates itself⁶⁴ (Harrison, 1998: 16). In this context, not only the meaning of quality of life is discussed, but also what could be the value of healthcare and what human life is worth. From a health economics’ perspective, value is enacted through price, in the case of human life like any other consumer good, its proper price is just what people are willing to spend in order to preserve it (Zweifel, 2009).

Since the 1970s different metrics have been developed in order to deal with the value of health and human life. These measurements have been created to measure the burden of the disease and to quantify the impact of healthcare interventions in terms of human life quality and saved years. The most commonly

⁶⁴ For instance, Harrison (1998) argues that quality of life measurement within NHS management has been depicted as a rationing strategy against producer and consumer moral hazard. “Patients seek care in order to be relieved of some actual or perceived, present or potential, ‘dis-ease’. The care itself is not directly of value; it is generally inconvenient, often painful or frightening. It is difficult to avoid the conclusion that, just as beauty is proverbially in the eye of the beholder, ‘goodness’ in healthcare, as in other areas of economic activity, is in the eye of the demander”. (Harrison, 1998: 16). Regarding, producer moral hazard, “the critical one seems to be medical ethics; if, in a third party payment system, your doctor believes that an intervention would be good for you and does not have to worry about whether you can afford to pay for it, then the ethical action to take is to provide, or refer you, for intervention. From this perspective, supplier-induced demand is moral, rather than morally hazardous, behavior” (Harrison, 1998: 16).

used measures are Year of Life Lost (YLL), Quality Adjusted Life Years (QALY) and Disability Adjusted Life Years (DALY). The use of these measurements has been segmented between developed and developing countries, QALY has had an extended use in Europe and North America. In the UK for instance, QALY has been integrated routinely into the healthcare assessments of NICE. In contrast, DALY and YLL are the measurements used by the WHO in the calculation of the *Global Burden of Disease*, a technical report about the costs—in terms of human life—of many diseases around the world. Although these calculations are global, they have a particular interest in depicting the changes of the epidemiological profiles of developing countries, the transition from contagious diseases to non-contagious diseases (See Chapter One).

Metric	Formula
YLL	YLL = N x L where: N = number of deaths L = standard life expectancy at age of death in years
YLD	YLD = I x DW x L where: I = number of incident cases DW = disability weight L = average duration of the case until remission or death (years)
DALY	DALY = YLL + YLD
QALY	The years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score.

Table 10 Burden of disease metrics and QALY definition
Source: WHO 2013 and NICE 2013⁶⁵

Because of this segmentation, most STS and critical analysis of these measures have been focused on the origins and the use of QALY in healthcare practices and policies in Europe⁶⁶, particularly UK (Ashmore et al. 1989; Moreira, 2012b) and Sweden (Sjögren and Helgesson, 2007). Other measurements such as DALY and YLL have been less studied, in part because their use is relatively recent in developing countries. In Colombia, for instance, Pneumococcus and HPV vaccines were the first healthcare technologies whose introduction into public programs was based on economic valuation expressed in terms of cost-effectiveness and DALYs. Before analyzing the use of DALYs and cost-effectiveness in Colombia, I introduce a brief description of HALY (Health adjusted life years) and some STS approaches to QALY. This discussion will be helpful in creating a framework to analyze the role of DALY and particularities of the valuation of HPV vaccines in Colombia.

⁶⁵ http://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/

⁶⁶ The European Consortium in Healthcare Outcomes and Cost-Benefit research (ECHOOUTCOME), is a research programme supported by the Seventh Framework Programme (European Union). This programme has done an evaluation about the integration of cost-benefit measures into national healthcare programmes. <http://www.echoutcome.eu/index.php/en/publications.html>. This report heavily criticises the assumption in the design of QALYs because of the bias in the survey by means they are calculated.

Qualifying human life through quantification: risk, rationality and the consequences of calculability

The first appearance of the term QALY (Quality Adjusted Life Year) was in an article by Zeckhauser and Shepard (1976) describing a health outcome measurement that joins duration and quality of life (Sassi, 2006: 402). QALYs are widely integrated to the economic evaluations (CEA) performed by technical agencies in Europe, Australia and North America. QALY's main assumptions are based on multi-attribute utility theory which entails the following conditions: "utility independence between life years and health status; constant proportional trade-off; and risk neutrality on life years" (Sassi, 2006: 402).

The QALY was developed to compare the benefits of health interventions beyond survival. Health economists have argued that QALYs provide "a form of currency to assess the extent of the benefits gained from healthcare interventions, not only in terms of survival but more importantly in terms of the 'quality' of the time gained as a result of those interventions" (Moreira, 2012b: 64). QALY has provided the analytical framework to develop other measurement units such as (disability-adjusted life year) DALY. This measurement unit has been used at the same time in cost-effectiveness analysis and as measure of burden of disease⁶⁷. DALYs and QALYs express health in time (life years) and adjust such years in relation to disease. However, DALYs measure health loss and QALYs health gain, "they express an inverse value" (see Figure 9) (Qalibra software glossary⁶⁸).

DALY and QALY are different in many aspects. However, most importantly, DALY incorporates age-weighting and discounting rates. There is a debate about the assumptions and consequences of using QALYs or DALYs (Sassi, 2006) to the extent that they offer different outcomes; however, the main issue has been the distributive consequences of age weighting and discounting. According to Sassi (2006) QALY critics have noted its difficulties in making interpersonal comparisons and aggregating individual utilities, the ways in which health utility elicitation methods are based and its implicit discrimination against disabled or chronically ill people. On the other hand, DALY critics argue that age-weighting and the use of standard life expectancy have serious equity implications (Anand and Hanson, 1997).

These measures come from different disciplines, which have meant different practices of calculation.

⁶⁷ "Disease burden is the impact of a health problem as measured by financial cost, mortality, morbidity, or other indicators. It is often quantified in terms of quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs), both of which quantify the number of years lost due to disease. One DALY can be thought of as one year of healthy life lost, and the overall disease burden can be thought of as a measure of the gap between current health status and the ideal health status (where the individual lives to old age free from disease and disability)" (Wikipedia)

⁶⁸ <http://www.qalibra.eu/tool/support/page8.cfm>

DALY calculations are based on a universal standard of weighting based on experts' valuation. In the case of DALYs calculated in Colombia, such standard is defined by WHO. In contrast, QALYs often rely on "a preference-based health-related quality of life measures directly elicited from general population samples or from groups of patients" (Sassi, 2006: 404).

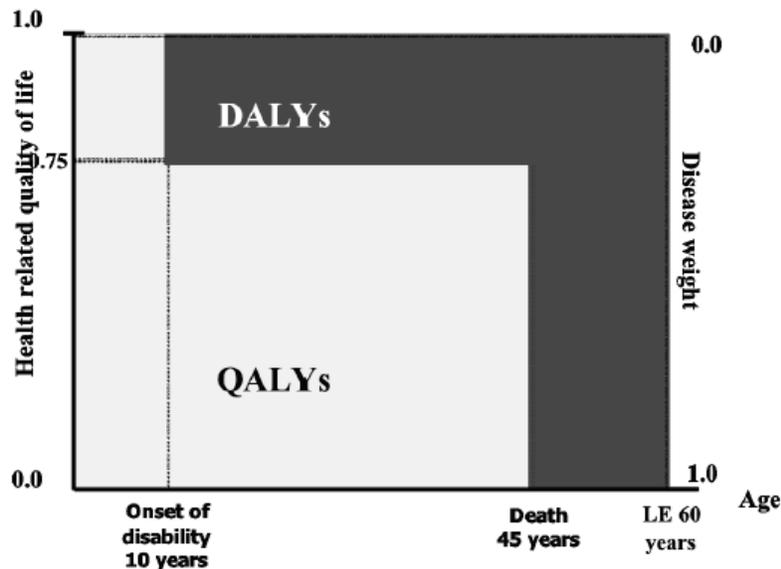


Figure 9 Graphic representation of DALY and QALY in relation to time and health

The creation of QALY and its use in policy decision making have attracted the attention of STS scholars. Early work about QALY and cost-effectiveness analysis was published in the book *Health and Efficiency* (1989). Its authors Malcolm Ashmore, Mike Mulkey and Trevor Pinch identified some explicit social assumptions upon which QALY relied. For them, QALY claims a correspondence between the analyst's evaluative categories around quality of life and 'those' of the community. Moreover, QALY assumes that decisions about health quality are stable for each individual across situations and those could be quantified. They noted QALY was developed as a strategy to tame the lack of 'normal' markets within health care (1989:88).

In his book *The Transformation of Contemporary Health Care: The market, the laboratory and the forum* Tiago Moreira develops what he calls a "biography" of the QALY. He argues that QALY is both product and source of epistemic and institutional processes associated with the use of CEA in healthcare decision making. Moreira claims that previous STS critical approaches to QALY have seen this measurement unit as a descriptive concept ignoring explicit normative dimensions that health economics try to invest in it. QALY's biography, he suggests, allows the exploration of the materialisation of sets of values and

concerns into calculation object but also traces the ways in which its articulation and implementation have reconfigured values and political positions attached to them (Moreira, 2012b: 65).

According to Moreira, mainstream economics showed a late interest in healthcare. Neoclassical economics has had an ambiguous and troubled relation with healthcare analysis in particular because of the difficulties of framing it as a market. One of the first attempts to present an economic analysis of healthcare services was the paper of D.S. Lees “Health through choice” (1962). As Moreira notes, “Lees saw prices as the most efficient and democratic process through which the standards or preferences of a society could be revealed” (Moreira, 2012b: 66). Another very influential paper presented by Moreira is *The Development of Economics for Health, Education and Welfare* written by Kenneth Arrow commissioned by The Ford Foundation in 1960. Moreira argues, that this unit of measurement is shaped by intellectual traditions such as Operational Research, in particular the work of George Torrance (1960), which is part of the technological and political transfer from war strategy to management (in the case of the relationship between cybernetics and neoclassical economics, see Mirowski, 2002). Nevertheless the main frameworks to understand QALY design are the theories of decision making and information (Moreira, 2012b), in particular the expected utility hypothesis and the Von Neumann and Morgenstern axioms (1944).

This mathematical decision theory defines how a rational individual should make decisions when faced with uncertain outcomes (Sloan, 1995). The QALY equation was defined on a von Neumann-Morgenstern utility function of expected utility. This relation between expected utility (EU) and QALY calculation is explicit in their formulae.⁶⁹ This framework has shaped QALY as a measure of the trade-offs of a rational agent.

$$EU = \sum_{h=1}^m \pi_h u(H_h, T_h).$$

⁶⁹ The terms of these formulas are described by Zweifel: “We start from a simple version of the QALY model, where there is no discounting of the future and no risk aversion with respect to the length of life. For simplicity, let all health states $H_h, h=1, \dots, m$ be *chronic*, i.e., the health state does not change up to T_h . This assumption is used only to simplify the exposition and is no inherent characteristic of the QALY model. The combination (H_h, T_h) occurs with probability π_h . Thus, an individual is confronted with a lottery of chronic conditions $(\pi_h, H_h, T_h), h = 1, \dots, m$. Assume that preferences satisfy the von-Neumann-Morgenstern axioms. If the utility of spending T_h years in the chronic condition H_h is denoted by $u(H_h, T_h)$, the preferences of the individual are therefore represented by expected utility (Zweifel, 2009: 28).

$$EU = QALYS = \sum_{h=1}^m \pi_h T_h v(H_h).$$

QALY and other health adjusted measurement units have an important role in calculating costs and efficiency of healthcare interventions and technologies, but moreover, they have an important function in the governance of healthcare. These devices are tools of regulatory objectivity (Cambrosio et al 2006: 190) which recognizes the importance of conventional forms of agreement for knowledge production and policy making. In the case of the Swedish Medicaments Agency, Sjögren and Helgesson (2007) have noted that calculating and comparing cost per QALY can be seen as a way to perform a ‘societal buyer’. This measurement unit allows the comparison of treatments which are not choice alternatives in medical practice (Sjögren and Helgesson, 2007: 235). Sjögren and Helgesson understand QALY as a device in the sense that is an assembly of instruments and rules to classify goods. “These devices qualify and render calculable, and therefore make economic evaluation possible. (Sjögren and Helgesson, 2007: 236).

The QALY is a device that facilitates the translation of ethical and political questions into technical calculation. Ashmore and colleagues (1989) argue that QALY can be addressed in terms of the ‘Strong Programme’ of health economics which argues principles of economics are the best framework to make decisions in a context of scarcity of resources and uncertainty. After two decades of debate about QALY assumptions and equity, Moreira argues that, in contrast, “health economists are aware that individuals normally could not make decisions about their own health, and that was the justification for not implementing market mechanisms in health care without careful experimentation” (Moreira, 2012b: 74). In that sense, Moreira’s interpretation of the use of QALY seems closer to what Ashmore and colleagues have called the “weak” programme in health economics, which is a set of tools to help policy makers in making decisions more accountable and efficient. As I will present, the use of Health Adjusted Life Year in the introduction of HPV vaccines in Colombia shows the coexistence of these programmes. Although a reflexive understanding of these measurement units is shown in technical reports and academic literature, in more public arenas these units are presented as objective measures of the contribution of HPV vaccines to public health.

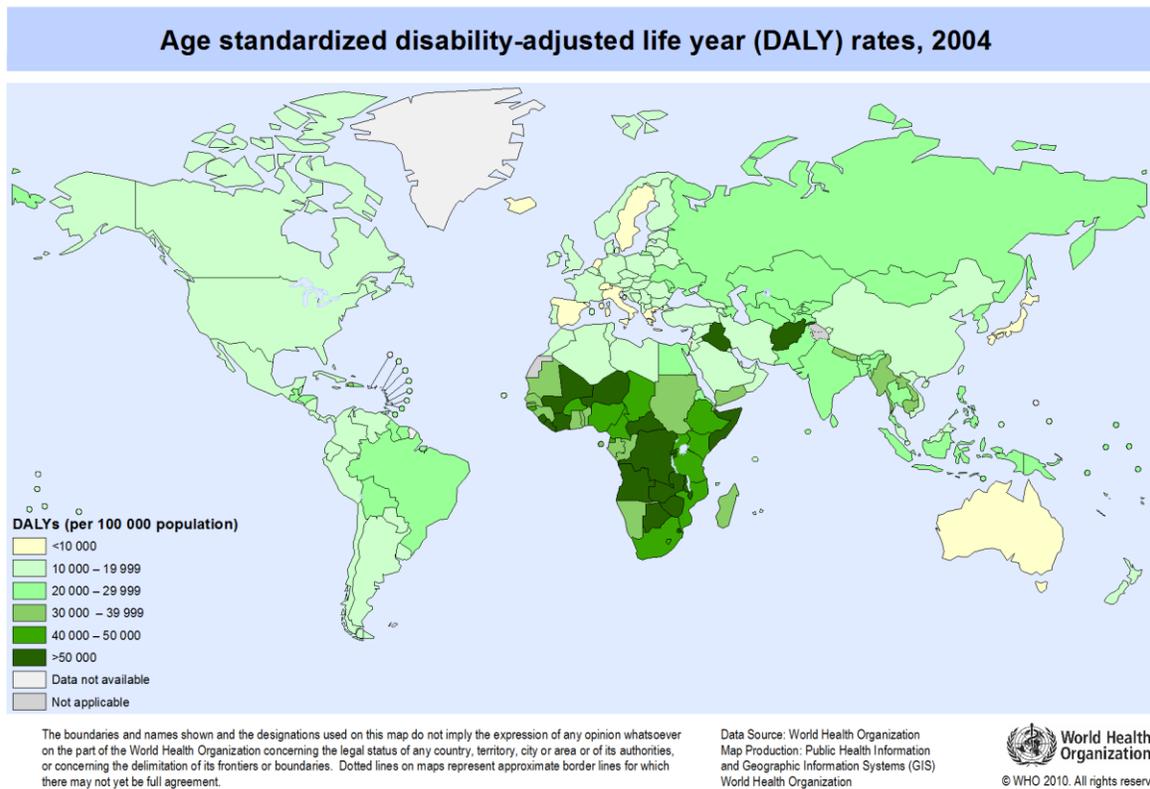
Burden of disease, development and economisation, DALY as calculation device

As I noted earlier, the cost-effectiveness of HPV vaccines in Colombia was calculated using DALY as measurement unit. DALY is the negative of QALY, not only because it measures disability instead quality of life (ability) but also because it was an experiment originated in policy institutions (WHO-World Bank) not within academia as QALY. In 1993, the World Bank published the *World Development Report: Investing in Health*. This document discussed the importance of reforming and transforming healthcare

mainly in the developing world, through the modernisation of national healthcare systems. This report was a landmark of the spread of market based reforms in developing countries during the 1990s; such policy transformations are called “neoliberal reforms”. In this context DALY as unit of measurement was born.

DALY was presented as a unit to measure the burden of disease and as a tool to calculate cost-effectiveness of procedures and healthcare technologies. Such calculation practices have been depicted as a solution to guarantee the sustainability and the efficiency of healthcare. The World Bank noted that developing countries were facing rising health system costs as high-income countries have experienced. “Governments need to promote greater diversity and competition in the financing and delivery of health services” (World Bank, 1993: iii).

The World Bank’s discourse and the calculation devices that promotes are organised around a political commitment to efficiency. Within this framework, efficiency is understood as the extent of optimality in the distribution of resources among competing alternatives, but also the extent to which input resources produce a specific health output at lowest cost (World Bank, 1993: 25). Accordingly, cost-effectiveness analysis is promoted as right the strategy to measure efficiency in healthcare. The World Bank proposal is to measure the gain in health or the reduction in disease burden resulting from an intervention in relation to the cost expressed in dollars per DALY.



Map 4 Global Burden of disease, DALY rates, 2004

The Global Burden of Disease (GBD), first published in 1996, constituted the most comprehensive and consistent set of estimates of mortality and morbidity yet produced (Murray & Lopez, 1996), and World Health Organisation regularly develops GBD estimates at regional and global level for a set of more than 135 causes of disease and injury (WHO, 2002a). Source: <http://viz.healthmetricsandevaluation.org/gbd-compare/>

Nevertheless the primary use of DALY in the World Bank report was to measure the burden of disease (See map, updated data for 2004). DALY combines (healthy) life years lost because of premature mortality with those lost as a result of disability. DALYs by definition are a bad that should be minimized (Anad and Hanson, 1997: 689). Because DALYs are calculated using life expectancy there is a huge variation in per person loss of DALYs across regions. Life expectancy has been extensively associated with quality of life. The total loss of DALYs is referred as the global burden of disease (GBD). Japanese life expectancy is used as time horizon in the calculations, because it is the highest in the world. This report concludes governments should expand the measurement of burden of disease to determine the most cost-effective public health initiatives. The World Bank, for instance, recommends interventions that it considers highly cost-effective, where the cost of gaining one DALY is relatively low (around \$25), such as immunizations (EPI), school-based health services and information and selected services for family planning and nutrition (World Bank, 1993: 25).

This discourse has been persistent in the last 20 years, in particular through the different World Health Reports which are presented by WHO annually. For instance, Murray and Frenk (2000) in a presentation of the ‘World Health Report 2000: a step towards evidence-based health policy’ in *The Lancet* argue that their “emphasis is not on more money for health but on more health for money” (2000: 689). Cost-effectiveness analysis and DALYs are put at the heart of the debate on the achievements and efficiency of health systems and its accountability. For them, society should be concerned about attainment of such standards.

QALY and DALY as metrics have promised “to revolutionize the ways in which we measure the impact of disease, how we choose interventions, and how we track the success or failure of our intervention” (Foege, 1994: 1705 quoted by Anand and Hanson, 1997: 686). The World Bank and DALY designers argue this metric opens the black box of decision makers’ values to public scrutiny and influence. Despite its extending use in policymaking, DALY has been a matter of debate between health economists. The main controversy has been set around the political and social consequences of these calculations. Anand and Hanson (1997), for instance, have developed a detailed critique of DALY’s conceptual and technical assumptions. They criticize the idea of burden of disease, and the “fairness” of resource allocation based on DALYs.

DALY measures the effects of a disease in reducing “human function”. Such reduction is mapped from 0 (perfect health) to 1 (death); different weights are assigned to different diseases based on the loss of “ability” that such diseases produce. In the DALY framework the effects of illness are captured through seven disability classes that define increasing weights associated with the extent of loss of physical functionality. However, as Anand and Hanson have argued, the ways in which burden of disease is measured does not reflect individuals’ differential ability to cope with disability, neither the burden on family, friends and society at large (Anand and Hanson, 1997: 689). On the other hand, the differences between life expectancy for men and women could affect the value assigned to DALYs. This gender gap in life expectancy may have serious implications for the estimation of women’s burden of disease relative to that of men. In the DALY calculations, men’s years of life can have a bigger value than women.

Nevertheless, the most controversial issue regarding DALY’s design has been the impact of age-weighting, which assigns a different value to the lived time at different ages, in a possible distribution of resources based on the burden of disease. From a utilitarian perspective, for instance in a human capital framework, such differentiation is justified in terms of differential productivity of an individual at

different stages in his/her life (Anand and Hanson, 1997: 691). Such framework is explicitly rejected by Murray (1994) and the World Bank (1993) arguing that age-weighting is an attempt to capture different social roles at different ages, the consequences are the same: monetarising human life.

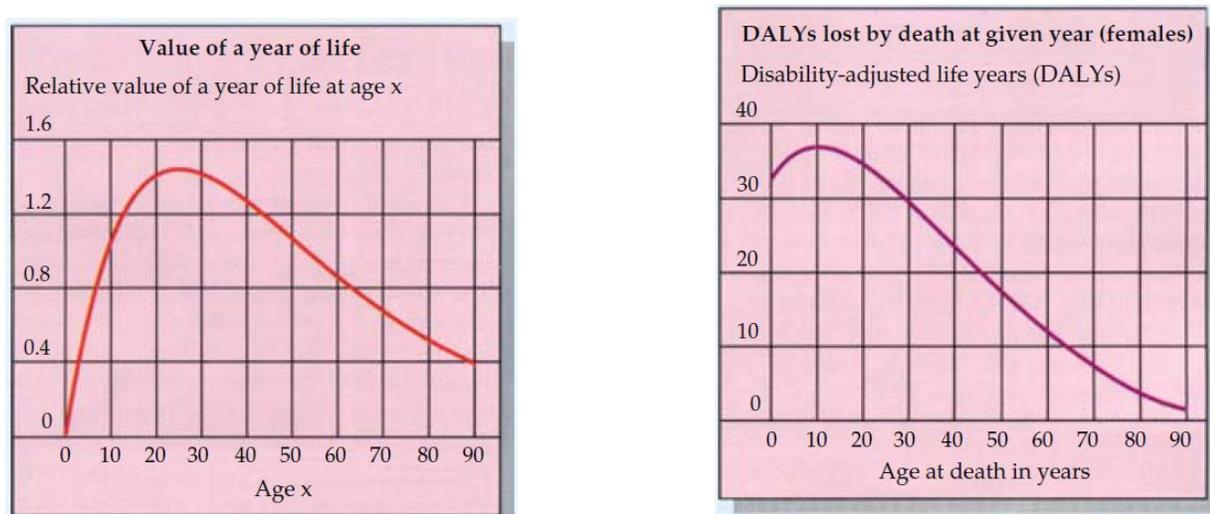


Figure 10 Age-weighting DALY

Source: World Bank, 1997

On the other hand, in the DALY formula future years of life lived are valued less than present years. As Anand and Hanson have noted a “3% discount rate⁷⁰ implies that one life saved today will be worth more than five in five years” (1997: 695). Such estimations are legitimated within a human capital framework in which life would be reducible to monetary value thus discounting it is justified because of the opportunity cost of money. Life utility is understood as monetary consumption.

Locating metrics, the search for the right measure unit for Colombia

The increasing integration of health economics into healthcare decision making has involved discussions about the right unit to measure effectiveness of procedures and technologies. As I have noted before, DALYs have had a longer history than QALYS in the measurement of burden of disease and in cost-effectiveness analysis in middle and low income countries. In the studies for the introduction of HPV in Colombia the different analyses were done using DALYS to measure the burden of disease and also to determine the effectiveness of cervical screening programmes and HPV vaccines. These reports do not present arguments about the use of DALYS instead of QALYS to calculate cost-effectiveness. Nevertheless, the experts that developed these studies for the Expanded Programme of Immunization

⁷⁰ Discounting in economic evaluation implies that costs and benefits occurring at different points in time are valued differently. Discounting health with time reflects the social preference of a healthy year now, rather than in the future. To do this, the value of a year of life is generally decreased annually by a fixed percentage (Bonneux and Birnie, 2001: 123).

(PAI) have argued that DALYS are more pertinent to the context of Latin America and Colombia. One of those experts notes:

PAI Sr. Advisor: Why we do not believe in QALYS? We think QALYS are a theoretical construction too risky for Latin America without any assessment which considers the different variables. For us QALYS are not an index of quality of life but of independence, the ability of the individual to do things. For us quality of life has to do with more factors.

Maybe in developed countries, the quality of life can be measured only for the ability of a person to do things even with a disease. But here where we don't have a set of welfare services provided by the State and the people have so many difficulties to get access to healthcare services... so quality of life should be considered in a different way, thus we don't use that (QALY).

These experts perceive that QALY is integrated to a wider set of services and care infrastructures which make reasonable the assumed relationship between quality of life and independence. Outside such entanglements, a negative measurement of quality of life seems more appropriate. On the other hand, PAI experts argue pharmaceutical companies through pharma-economics have intensively used QALYS to value their own products (see Chapter Six).

PAI Sr. Advisor: We think QALYS favour pharmaceutical companies. Through QALYS many benefits have been sneaked. We think such benefits are not real in our analysis about the introduction of the vaccine. This is a realm very important for the companies, for instance, they sponsor these studies, the lawsuits in the Courts, and within these different things one can see that QALYS are prone to benefit a higher price of such products (...) On the other hand, one can see the excesses that are done with QALYS. For instance, QALYS are used to evaluate quality of life in children, what is no sense... so we almost never use QALYS; because we work with vaccines which often have children as target.

QALYS are calculated using different surveys—such as EQ-5D® and SF 36®—to determine the valuations and the trade-offs that individuals make between different health scenarios. Such information is used to assemblage 'a societal perspective' in healthcare valuation. The use of QALYS in healthcare procedures that involve children is perceived by PAI experts as inappropriate. Because it would suggest that children were able to make a trade-off between the health states that QALY suppose to reflect.

In Colombia the discussion about the right health measurement unit has continued. Despite the use of DALYS in the cost-effectiveness analysis of vaccines, the Colombian Institute for Health Technologies

Assessment (IETS) created in 2013 is developing guidelines that recommend the use of QALYS. NICE International (a division of NICE UK) has collaborated on this issue. One of the consultants from NICE International and advisor to the Colombian government describes why he considers QALYS are better than DALYS:

NICE Consultant: No... DALYs are fine. I can understand why they use them, I think they are problematic. But obviously... all these countries are using DALY. Essentially DALY is the inverse of the QALY. So, you avoid DALYs but you want to get QALYs. There is an adjustment that takes play on the life-gain there (...)

(...) Why are QALYS better? (Because) You get data or information from the patients themselves of their quality of life, and also for society what quality of life it wants to state. DALY framework does not do that. DALYs apply weightings but they are decided by a bunch of experts what they should be. But there is no relation necessarily with the society in which they should be applied. And DALYS... you can disentangle them as well. But DALYs in the traditional form, they have an implicit weighting system what which is about... at one level you can argue that they discriminate against the elderly and the very young because they are not economically productive. That is the emphasis I think it is problematic. In the QALY framework you don't have to do that.

I am not saying that QALY is perfect. But if you want to know what life you can get in full health, that is a quality of life issue, (...) I think QALY in many ways are much better in doing that. Especially if you can use patients' actual preferences, actual society weightings that refer to your country in determining what the quality adjustments are. DALYS really don't do that. That is my problem with DALYS but they are routinely used, to be fair, but they are pretty much part of the development literature, WHO, IADB...

As I noted before, QALY supporters argue that this measure reflects patients' preferences; unlike DALYS which relies on expert weighting of disability. Recently QALYS have been suggested by IETS as health measurement unit for cost-effectiveness analysis in Colombia; however because of financial limitations their calculation will be not based on social preferences surveys but in literature reviews (IETS, 2013: 40). Both QALYS and DALYS rely heavily on experts' assumption about the value of human life to determine a 'societal' perspective. According to *IETS Guidelines for Economic Valuation*, in case of calculating QALYS, it is suggested that the clinical group contributes data regarding health outcomes and the economics group data about quality of life related with health utilities (IETS, 2013: 40).

There are two additional issues regarding the ways in which health currencies are integrated in cost-effectiveness analysis and in general health decision making; one is related with the necessity of

consistency in their use; another is the definition of thresholds on what is considered the “willingness” to pay. The support of NICE International has been focused on developing a consistent framework that standardizes healthcare economic valuation in Colombia. Such consistency is understood as standardization of measurement units and as the establishment of visible connections between clinical data and economic calculation.

NICE Consultant: There is no reason not to use QALY if you want. Part of the work I have done in Colombia is to talk about QALYS and DALYS... it is up to the Colombian decision makers to decide what they prefer... they key thing is you have to have a consistent decision making framework.

(Such measures) cannot come from everywhere. The clinical evidence for the estimation of the QALYS has to be based on actual real clinical data, it is not made up. We have a consistent decision making framework. We made it completely consistent, and also critically we can decide what is cost-effective or not, because we can apply thresholds (...)

(...) for example, I have seen previously a document about economic valuation in Colombia, a manual, I've seen what they're trying to describe as a framework in Colombia. And it is all over the place, they say you can do, this way or this way... it will be a manual to guide developers... I took a look and I asked: what is it that the decision maker really wants? It seems you are offering all sorts of ways of presenting and analyzing, the outputs and the measures, how does this help decision making? It is not consistent.

The definition of thresholds is one of the most important and contested aspects in making decisions on healthcare technologies based on their cost-effectiveness. Cost-effectiveness analysis provides an assessment of healthcare technologies regarding their optimal use, it means in relation to the best obtained results at the lowest costs. However, some technologies can be very cost-effective and still very expensive to be affordable for healthcare systems. Thresholds have to be defined to decide the limits in which even a very effective technology (in terms of medical performance) cannot be integrated into healthcare services because of its price. This issue has been extremely contested and has confronted patients, health economists and healthcare professionals. As Alan Maynard has noted in an interview published in Nature about NICE thresholds in the UK: “Ideologically this isn't very pleasant but as I tell my medical students, there are two certainties in life, one is death and the other one is scarcity of resources” (Cressey, 2009: 339).

Such threshold can be assimilated to the price (economic value) that a human life has in practice, at least for the healthcare systems that defines such limit. Probably one of the organisations with most experience

in defining such limits is NICE. In the United Kingdom, there is not an official threshold expressed in GBP per QALY, however, some analysts have identified a limit around 30.000 GBP per QALY (Cressey, 2009). Such estimation is an arithmetical mean, in practice there is a flexible range of thresholds (See Table 11). According to NICE consultants, NICE has been operating with different thresholds according to each case; they argue “a likely threshold is based on real information about UK healthcare system”. Sometimes the threshold can be up to 80.000 GBP per QALY.

Drug	Condition	Cost per QALY range	Approved?
Cetuximab	Colorectal cancer	26700-33300 GBP	Yes
Alitretinoin	Eczema	15000-31000 GBP	Yes
Bevacizumab	Renal-cell carcinoma	Lowest 53800 GBP	No
Tenofovir	Chronic hepatitis B	Less than 20000 GBP	Yes
Rituximab	Chronic lymphocytic leukaemia	Less than 30000 GBP	Yes

Table 11 Example of recent NICE technology appraisals
Source: Cressey, 2009

In the case of developing (middle and low income) countries, WHO has recommended applying a threshold based on GDP per capita. In the case of middle-income countries the limit to introduce a cost-effective health technology or procedure into national programmes is 3 times GDP per capita. According to the World Bank the GDP per capita of Colombia⁷¹ (2012) is 7.752 USD. This is the framework used in the analysis of HPV vaccines in Colombia. Some health economists have considered WHO threshold as very high and potentially unsustainable. As the NICE consultant has noted:

NICE Consultant: “But what WHO worldwide has recommended to apply GDP per capita and that is really about DALYS, it can be applied to QALY, it doesn’t really matter. It is rough...it is rough enough you have to be very careful to apply it, you shouldn’t make too tight, you need flexibility around it. They shouldn’t recommended 3 times GDP per capita, maybe it is too high, I know some countries have been arguing for reimbursing drugs because of the limit of 3 times GDP per capita, I have to argue that is probably too expensive. I think they should keep 1 GDP per capita, but with flexibility (...)”

As I have noted (Chapter Three) GDP is an iconic number, which means “number and the category numbered are treated as one and the same” (Mackenzie et al., 2007 cited by Verran, 2012a: 116). If GDP enacts a country within an international ranking based on economic capacities, then GDP per capita enacts the position of its inhabitants within such order. GDP per capita homogenises income distribution

⁷¹ The GDP per capita of United Kingdom in 2012 was 41.053 USD.

and performs a ‘fair’ distribution. The results of these enactments can be perverse in the sense that they can render inequalities invisible and a ‘real’ concentration of income. The consequence is different valuations of human life based on the capacity of local healthcare institutions to afford care. In the next section I will present the ways in which these frameworks and calculation tools have been used in the analysis of cost-effectiveness of HPV vaccines in Colombia.

Cost-effectiveness studies, HPV vaccines and the economical assemblage of public health concerns

Vaccines have been one of the most preferred objects of cost-effectiveness analysis. Because most vaccines are prophylactics, drugs to create immunity, they are an excellent case to demonstrate the (economic) benefits of prevention and the utility of cost-effectiveness analysis as decision making tool. Since the 1990’s the literature about cost-effectiveness analysis of vaccines has grown, however such trends reach a particular point of increasing from the middle of 2000’s with the introduction of HPV vaccines in the market and in the public discussion about their affordability, safety and efficiency (See Figure 11).

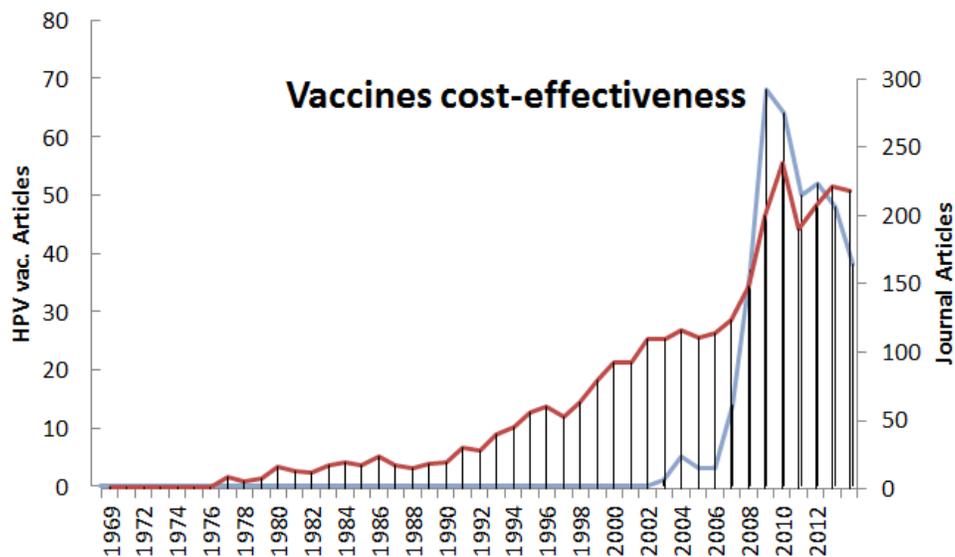


Figure 11 Journal articles about vaccines cost-effectiveness

Journal articles about vaccines cost-effectiveness (red-right axis) and about HPV vaccine cost-effectiveness (blue-left axis). Source: Pubmed 2014

Cost-effectiveness analysis of vaccines has meant the reinterpretation of prevention, its risks and anxieties, through the language and the ontologies of economic valuation. Different authors (Clarke, 2010; Leach and Fairhead, 2008; Durbach, 2005) have noted that vaccines have constituted a source of

anxiety because they are an intervention on healthy bodies in order to prevent a potential and probable disease. In the extent that infectious diseases have been overcome in contemporary societies the dangers that vaccines prevent have become invisible and have remained as risk statistically enacted in the public representation (See Chapter One). Cost-effectiveness analysis addresses vaccines in the same framework, however, through the calculation and quantification of costs and benefits such indeterminacy is transformed in economic and practical consequences for healthcare governance and policymaking. The regime of anticipation depicted by Clarke (2010), Adams and colleagues (2009), and Carpenter and Casper (2009; 2010) is materialised in the realm of health policy by cost-effectiveness analysis, by the process of calculation, quantification and monetisation that is entailed.

Price is an additional element that has interfered with the extensive use of this calculation technique in the introduction of HPV vaccines in different countries and regions around the world. HPV vaccines are the most expensive vaccines in the market (see Table 12). Despite the reduction of their price for developing countries (See Chapter Six), HPV vaccines remain a very expensive intervention if the price of other vaccines is considered and the size of the vaccination programmes that entail the use of millions of doses per year. The impact of the introduction of these technologies in government's budgets have demanded the development of "justifications" (Boltanski and Thevenot, 2006), strategies of valuation that render visible the contribution of this expense (investment) to the public good.

As I will show what is valuable and the definition of public good are enacted in the same process of valuation. In the next section I offer an analysis of the studies of cost-effectiveness developed in the introduction of HPV vaccines in Colombia. This account is limited to the studies that were commissioned by the government to support its decision (see Table 13)⁷².

⁷² The criteria that I have followed to sort out these studies are the same standards to classify them in a systematic review. These are, for instance, the criteria used by Yuen (2012) in her systematic review of cost-effectiveness analysis of the introduction of HPV vaccines in Asian countries with Chinese-Han population (Yuen, 2012). These classification criteria summarize many of the elements that these studies put together in the practices of calculation that they depict.

Vaccine	Packaging	Price PAHO revolving fund	Price CDC	Companies
BCG	10 pack - 1 dose vials	\$0.1385 \$0.115		Gen. Bulgaria Gen. India
Hepatitis A pediatric	10 pack - 1 dose vials	\$7.10	\$10.93 \$11.00	Engerix B® Recombivax HB®
DPT	10 pack - 1 dose vials	\$2.65 \$3.45		DPT Hib Lyophilized DPT Hib Liquid
Haemophilus influenzae B	10 pack - 1 dose vials	\$1.95		
Hepatitis B	10 pack - 1 dose vials	\$0.25		
Hepatitis A	10 pack - 1 dose vials	\$7.10		
Rotavirus	10 pack - 1 dose vials	\$6.50	\$92.15 \$63.961	GlaxoSmithKline Merck
Pneumococcal	10 pack - 1 dose vials	\$15.84	\$107.12	Pfizer
MMR	10 pack - 1 dose vials	\$3.60		
Yellow Fever	10 pack - 1 dose vials	\$1.10 \$0.85		France Brazil
Influenza	20 pack - 1 dose vials	\$1.50 \$1.90		Korea France
HPV	1 pack - 1 dose vials	\$13.08 \$13.79	\$107.156 \$100.85	Bivalent GSK Quadrivalent Merck

Table 12 Vaccine prices for year 2013 (Prices PAHO and CDC). Expanded programme of immunization
Source: Revolving Fund PAHO 2013 and CDC 2014

As soon as Gardasil® was approved by the FDA in United States in 2005, different voices were raised in favour of its introduction in Colombia; one particularly notable was the Colombian National Cancer Institute (INC). At the same time, the WHO and PAHO began to develop guidelines and conferences to prepare middle-income countries in the adoption of these vaccines (UNFPA-WHO, 2006)⁷³. These different voices pointed out the massive benefits of vaccination in the reduction and eventual eradication of cervical cancer, but at the same time warned about its high costs and the necessity of a careful decision making.

In 2008 the PAHO asked *The Sabin Institute* in the U.S, to study the burden of disease of cervical cancer and HPV infection in six countries of Latin America (Argentina, Brazil, Chile, Colombia, Mexico, and Peru) and conduct a cost-effectiveness analysis of the HPV vaccines at different price scenarios (See Table 13). The study concludes that only a vaccination programme under 20 USD per doses is cost-effective for these countries. In this year, Universidad Nacional de Colombia was entrusted with

⁷³ http://whqlibdoc.who.int/hq/2006/WHO_RHR_06.11_spa.pdf

developing a similar study about HPV vaccines by the Ministry of Health.

The Universidad Nacional (2009) study concluded that although vaccines could have an important impact in the reduction of the burden of cervical cancer and related lesions in Colombia, the introduction price offered at that time made the intervention not cost-effective. Universidad Nacional recommended the introduction of the vaccine into PAI only if the cost per woman (3 doses) was under \$25 (USD) and integrated to cervical screening programmes. As consequence the Committee of Immunisations (NCIP) decided to postpone the introduction of these vaccines.

As I have noted previously, this decision was widely criticised by different medical associations and the INC (Colombian National Cancer Institute). Most importantly, on September the 3rd 2010, Mrs María Teresa Tovar Rojas filed a class action against Ministry of Health because she considered the non-inclusion of the HPV vaccine into public programmes violated collective rights to Public Health and Security. This case finally was resolved in the Council of State that ruled the development of new technical studies and asked for a decision from Ministry of Health. During this time Universidad Nacional produced a second study, which included a comparison between bivalent and tetravalent vaccines and data about the impact of genital warts. These were the only changes between first and second study, the remaining aspects did not change. This was the study that supported the introduction of HPV vaccines into the Expanded Programme of Immunization (PAI) in May 2012.

Institution (author)	Universidad Nacional	Universidad Nacional	PAHO	Instituto Nacional de Cancerología
Institution (decision maker)	Ministerio de Salud (EPI)	Ministerio de Salud (EPI)	Ministries of Health PAHO countries	CRES
Year	2009	2011	2008	2011
Natural history model	Markov chain	Markov chain	Excel-based model	Markov chain
Setting	Colombia	Colombia	Argentina, Brazil, Chile, Colombia, Mexico, and Peru	Colombia
Perspective	Society and Healthcare System	Society and Healthcare System	Modified societal perspective	Payer
Vaccine	Bivalent	Bivalent (BV) Quadrivalent (QV)	Bivalent (BV) Quadrivalent (QV)	Bivalent
Disease measured	CIN 1, 2, 3 and Cervical cancer	Cervical cancer, CIN 1, 2, 3 and Genital Warts	Precancerous lesions and cervical cancer}	CIN 2, 3 and Cervical cancer
Population	Girls 14 years old	Girls 12 years old	Girls 12 years old	Girls 12 years old
Compared with	Screening Programme and non-interv.	Screening Programme (Pap-test)	Screening Programme	Screening Programme
Source and data	Bogota Cohort, Pueblo Rico Antioq study	Bogota Cohort, Mexico,	CI5C and GLOBOCAN 2002	Bogotá Cohort,
Outcome measure	DALY	DALY	DALY	LY, DALY
ICER	\$1.028,02	ICER/DALY: BV: \$5.314 (\$11.354) QV: \$5.193	40 IS/DALY	\$4.207.070
Threshold	\$7.400 (Int Dollars) (GDP/per cap)	\$6,294 (USD) (GDP/per cap) max: (GDP/per capX3)	GDP/per capita	\$12.018.370 (GDP/per capX3)
Discount rate			3% per annum	3% per annum
Protection duration	Life-Long (Life exp: 85 years old)	Life-Long (Life exp: 76 years)	Life-Long	Life-Long (Life exp: 76 years)
Cost vaccine course	\$25 (Intern Dollars)	BV: USD \$13,48 (x3) QV: USD \$15,15 (x3)	\$25 \$75 and \$360	\$98.300
Screening pattern	annually at 1st 2 visit (neg results) then triennial (1-1-3)	annually at 1st 2 visit (neg results) then triennial (1-1-3)	annually at 1st 2 visit (neg results) then triennial (1-1-3)	annually at 1st 2 visit (neg results) then triennial
Vaccine coverage rate	70%		70%	95%
Screening coverage rate	50%			60.8%
Vaccine efficacy	100%	BV 99% QV 99%	100%	95%
Money	International Dollar	US Dollars	International Dollars (2005)	COP
Conclusion	Non cost-effective	Both are cost-effective.	Many scenarios of cost-effectiveness	Very cost-effective

Table 13 Cost-effectiveness analysis HPV vaccines in Colombia
Sources: UNAL, 2009; 2011; Ministerio de Salud, 2008; CRES, 2011

Moreover, this second study was the main source of evidence used by Ministry of Health for the Congress of Colombia in the debate about the inclusion of boys into the vaccination programme. In November 2012, the Congress of Colombia asked for a technical concept to the Ministry of Health about the Bill 260

of 2012. The Bill had suggested “The National Government must to guarantee the free and mandatory vaccination against HPV for all the boys and girls between 9 to 12 years old”. The Ministry of Health through a memorandum summarized the main conclusions of 2011 Universidad Nacional study.

In all these different institutional pathways and scenarios cost-effectiveness has been the key issue that justified the inclusions and the exclusions that such technology entails. Cost-effectiveness has justified the definition of girls as the population target and the exclusion of boys from risks and benefits of this technology. Moreover, cost-effectiveness analysis has been a key instrument in the sexualising and de-sexualising of cervical cancer and HPV vaccines through the rationalisation of economic benefits.

Cost-effectiveness analysis is a calculation device to compare technologies’ performance, in this case, primarily HPV vaccines and cervical screening programmes. Such comparison is done through the modelling of the natural history of cervical cancer in a hypothetical cohort of women using a Markov chain simulation. This device will be analysed in next chapter (*Chapter Five*). The result of the simulation is information about the burden of disease in the different stages of cancer development. Costs in money and in DALYS are assigned to each stage in order to determinate cost-effectiveness of the different procedures.

I close this chapter by presenting the ways in which cost-effectiveness and its metrics are used in three different interpretative contexts, firstly, in the same technical reports and in their use by PAI technical committee (NCIP). Secondly in the Council of State lawsuit and thirdly, in the technical concept that Ministry of Health presents to the Colombian Congress regarding the Bill to support mandatory vaccination of boys and girls. As I present, although cost-effectiveness is invoked as the main framework to understand the social and economic value of HPV vaccines, the metrics that render visible such value do not travel through these different institutional settings. DALYS are very important enactments of value within technical literature and in the experts’ arena of the committee. DALYS use is deeply related with producing differential value between technical procedures, firstly between screening programmes and HPV vaccines, but more importantly between the vaccines themselves (bivalent-cervarix and tetravalent-gardasil). This will be particularly clear in the second study done by Universidad Nacional (2011) in which a comparison between the vaccines is presented.

In spite of DALYS being used to evaluate HPV vaccines, cervical screening programmes and medical attention for cervical cancer and associated neoplasias, they were decisive in the presentation of the contested public health value of genital warts. As I have noted, the genital warts’ burden of disease was

the differential element that defined the selection of the tetravalent vaccine (Gardasil) as the right tool for the Expanded Programme of Immunisations in Colombia. Curiously, DALYS and genital warts, main actors in cost-effectiveness analysis and within the textual laboratory, will be rendered invisible in the movement of data and matters of fact toward more public arenas: media, congress, courts and vaccination campaigns.

Genital Warts and DALYS, assembling matters of concern through economic valuation

As I have noted, two studies were produced by Universidad Nacional about cost-effectiveness of HPV vaccines. The first study (UNAL 2009) was focused on defining the burden of cervical cancer and HPV infection, and the potential impact of HPV vaccines in the reduction of the incidence of cervical cancer. In this study the cost-effectiveness analysis is based on loss of life years (LLY), DALYS are just used to present the burden of the disease in the Markov chain simulation. The study concludes the most cost-effective strategy is cervical screening and HPV vaccination, ICER (incremental cost-effectiveness ratio) was calculated based on YLL (See Table 14). Because the main interest is to define the impact of HPV vaccines in reducing mortality associated with cervical cancer, YLL seems enough to describe the effectiveness of these technologies.

Strategy	Costs per woman	Incremental Cost	CER	ICER
Vaccine	\$ 59,30		\$ 1.028,02	
No intervention	\$ 76,82	\$ 17,52	\$ 728,10	(Dominated)
Screening 113 + vaccine	\$ 266,43	\$ 207,12	\$ 10.522,11	\$ 6.399,45
Screening 113 ⁷⁴	\$ 313,34	\$ 46,92	\$ 6.705,29	(Dominated)

Table 14 Basic scenario comparison the four strategies
Source: (UNAL, 2009)

This study is extremely careful in declaring the limitations and contingencies of the analysis. It notes the lack of official data about national incidence and prevalence of cervical cancer and HPV infection by types. It is stated, moreover, that the frequency of HPV 16 and 18 oscillates between 52 to 64% in the Colombian female population. More importantly, the study does not “take into consideration the burden of disease produced by genital warts because these lesions are benign and there is no consensus about the degree of disability they produce” (UNAL, 2009: 44).

⁷⁴ This value includes the costs of diagnosis and treatments of CIN and cervical cancer.

After the ruling of the Council of State⁷⁵ some criteria and parameters of these studies changed, as it is possible to see in the second study (UNAL, 2011). Particularly, genital warts surged as matter of concern in relation to public health and as a decisive element in the choice of the right vaccine. Although the first study (2009) was the main source of data for the court, the Council of State rejects its conclusions (Council of State, 2012: 42). The court considers the study needs to be updated because since 2008 statistics could have changed. “Moreover, it is possible that the biologics (vaccines) have had some changes which could have a different effect regarding their cost-effectiveness” (Council of State, 2012: 44).

For the Court, another limitation of this study was that it only covered HPV effects in women and not in men; and “there is no analysis of the potential impact of HPV vaccines in other types of cancer” (Council of State, 2012: 44). As a consequence the court ordered a new study which includes an analysis of cost-effectiveness of HPV vaccines in the prevention of other cancers in men and women. Furthermore, the Ministry of Health had to present within three months of the ruling, new studies of cost-effectiveness according to the Court’s recommendations. If vaccines are cost-effective according to the new framework, then Ministry must include them into the Expanded Programme of Immunisations. The result is well known; in July of 2012, the Ministry of Health makes public the introduction of HPV vaccines into the programme.

The new study (2011) has very few changes from the first one. After three years most of technical and data limitations are the same. This study extends the analysis of burden of disease to other cancers related with HPV infection; nevertheless these data come from literature reviews, most of them are statistical estimations based on trials but not official data. The study remains focused on cervical cancer and the cost-effectiveness of strategies for its prevention and treatment. However, this study introduces two important changes; it offers a comparison between both vaccines entered the market: tetravalent (Gardasil) and bivalent (Cervarix) and calculates the impact of HPV vaccines, always, in combination with cervical screening.

In this new configuration, genital warts became a key element of differentiation and added value for tetravalent vaccines. Such context demanded metrics sensitive to subtle differences that are not perceived

⁷⁵ Courts and legal institutions have developed protocols and rules for admitting technical evidence in litigation. In the case of U.S. law, the Daubert rule has been used by the Supreme Court as gold standard for the admissibility of expert testimony (Bazerman, 2009). In the case of High Colombian courts, there are no explicit protocols or rules for assessing technical evidence. In each case the Court uses formal principle of constitutional and legal interpretation.

by measurement units such as LLY. DALY as a measurement unit of disability was considered the right tool to value the burden of a disease whose endings were not fatal.

	Costs	Increment costs	LLY	LYG	DALYS	Avoided DALYS	ICER: USD/LYG	ICER: USD/DALYS
No intervention	\$7.495.699		9.593		11.453			
Screening	\$56.114.451	48.618.752	1.191	8.402	1.506	9.947	\$5.787	\$4.888
Screening+Bivalent	\$62.754.454	55.258.755	808	8.785	1.054	10.399	\$6.290	\$5.314
Screening+Tetravalent	\$61.712.199	54.216.500	810	8.783	1.013	10.440	\$6.173	\$5.193

Table 15 Incremental cost-effectiveness HPV vaccination in Colombian women, taking into account genital Warts. Base case.

Source: (UNAL, 2011).

	Costs	Increment costs USD	LLY	LYG	DALYS	Avoided DALYS	ICER: USD/LYG	ICER: USD/DALYS
No intervention	\$7.495.699		9.593		11.453			
Screening	\$56.114.451	48.618.752	1.191	8.402	1.506	9.947	\$5.787	\$4.888
Screening+Tetravalent	\$61.712.199	5.597.748	810	381	1.013	493	\$14.692	\$11.354
Screening+Bivalent	\$62.754.454	1.042.244	808	2	1.054	-41	\$21.128	Dominated

Table 16 Incremental cost-effectiveness HPV vaccination in Colombian women, taking into account genital Warts. Competitive analysis

Source: (UNAL, 2011).

DALY allows a more visible differentiation between vaccines to be produced (see Tables 15 and 16). In terms of deaths avoided by vaccination, the performance of both vaccines is impressively similar. If tetravalent vaccine is compared with no intervention, in a cohort of 450.000 women this vaccine avoids 8.783 deaths from the 9.593 deaths that could happen without any intervention. In the same scenario, bivalent vaccine avoids 8.785 deaths. In contrast when DALYS are introduced the gap between vaccines is rendered visible. Tetravalent vaccine prevents 1.054 DALYS meanwhile bivalent vaccine 1.013 DALYS. Even though this difference is not quite wide (41 avoided DALY); it is still bigger than the gap in terms of reduction of mortality.

As I have presented, DALY is calculated through a set of weightings defined in relation to the disability that a disease produces. In the second study from Universidad Nacional (2011) such weightings are taken from the *Victorian Burden of Disease study* (1994, Australia) (See Table 17). These weightings assign an

important burden of disability to terminal stages of cervical cancer (up to 0.95 in a scale where 1 is death) and to the consequences of early treatment (0.43).

Although these data come from a context of healthcare attention completely different to Colombian one, they are widely accepted by public health experts as an approximate measure of the effects of the disease in human function. On the contrary, the nature of genital warts as a disease with an important burden has been contested. There is no defined weighting for this condition within the technical literature about burden of disease (WHO, 2012, Victorian BoD, 2001; 1994). Even the first study of Universidad Nacional pointed out that such condition is considered a “benign” affection.

Cervix cancer		
Diagnosis and primary therapy	0.430	Provisional weight based on Dutch weights
State after intentionally curative primary therapy	0.200	Provisional weight based on Dutch weights
In remission	0.200	Provisional weight based on Dutch weights
Disseminated carcinoma	0.750	Provisional weight based on Dutch weights
Terminal stage	0.930	Dutch weight for end-stage disease

Table 17 Disability weightings associated with cervical cancer
Source: UNAL, 2011

In the second study data are not provided about the assigned weight of genital warts in the calculation of DALY. Nevertheless, if the calculations are reenacted it is possible to note that the disability value assigned is very low, to 8.410 episodes of genital warts are assigned just 41 DALYS. Because genital warts are not a fatal condition it is possible to estimate that the assigned disability weight was 0.0048. This weight is slightly higher than the lowest weighting assigned to a disease by The Victorian Burden of Disease (2001), which is the long term effect of moderate burns. The concern for the disease burden of genital warts is more a consequence of the introduction of HPV vaccine and the claims of added value of Gardasil. Even within the immunisation committee, tetravalent critics argued that the genital warts burden was part of the strategy of Merck to add value to its vaccine.

In the technical reports the tables that summarize the results of modelling—as calculative spaces—preserve some of the contingency of these calculations, in particular, they render visible the narrowness of the difference and the effort of raising genital warts as a matter of public health. However, once these data

are moved from technical reports to the technical committee, such contingency and such indexicality (Verran, 2012a) disappear. The different elements that are displayed in the calculative spaces of the cost-effectiveness analysis are reordered in a coherent and linear narrative whose conclusion is the selection of tetravalent vaccine as the right tool. As is noted in the minutes of the NCIP:

In a cohort of 430.859 women, 9.137 cases of cervical cancer and 8.410 episodes of genital warts can happen without any intervention. Cervical cancer could cause 6.436 female deaths. Colombian cervical screening programme would avoid 3.744 deaths. Any alternative of vaccination is cost-effective compared with no intervention. However, in a competitive analysis, screening plus bivalent vaccine are dominated alternatives. Meanwhile, tetravalent vaccination plus screening is the most cost-effective option which is under 1 GDP per capita (ICER: 2395USD per DALY) (SGC-F03 3rd May 2012).

The Committee concludes based on this analysis that “in a competitive scenario and taking into consideration genital warts without cross effective protection, the vaccination with tetravalent is the most cost-effective strategy. ICER: 1.348USD/DALY” (SGC-F03 3rd May 2012: 10).

Iconic cost-effectiveness and closing black boxes in health decision making

Once the committee’s decision is enacted, DALYS, formulae and tables disappear. The decision will be justified in public arenas using disentangled data about the impact of cervical cancer in public health and the reduction of female mortality that HPV vaccines promise. Although cost-effectiveness will continue as a source of political legitimacy, its presence becomes iconic in the sense defined by Verran regarding numbers (2012a, 2012b). That is the category and the measurement unit are treated as undistinguishable. Numbers and figures about the cost of HPV vaccines and its estimated impact in the reduction of cervical cancer are read as evidence of the effectiveness of this technology without any further discussion about the meaning of these elements and the ways in which they were calculated.

For instance, in the technical concept (memorandum) presented by the Ministry of Health to the Congress of Colombia in relation to Bill 260 of 2012 (Rad: 201221102384491), the legitimacy of the current vaccination programme is supported through data about the costs of the current treatment of cervical cancer and genital warts and the savings that HPV vaccine could generate.

Universidad Nacional estimated that the costs of attention in a female cohort for genital warts are \$5.8 million of USD, \$1.0 million of USD for CIN⁷⁶ I (Low risk), \$24 millions of USD for CIN II and III and

⁷⁶ Cervical intraepithelial neoplasia. “Cancer of the cervix usually takes many years to develop. Before it does, the cells in the cervix often show changes known as cervical intraepithelial neoplasia (CIN) or, less commonly, cervical glandular intraepithelial neoplasia (CGIN). CIN and CGIN are pre-cancerous conditions. Pre-cancerous conditions

13.4 millions of USD for cervical cancer at any stage. The addition of costs of prevention and treatment of this disease are 117.6 millions of USD per year.

In this memorandum the cost-effectiveness of the Colombian vaccination programme is not explained using measurements of cost-effectiveness such as ICER, but the Ministry of Health presents a selection of key papers which argue that the vaccination of boys against HPV is not cost effective.



**PROSPERIDAD
PARA TODOS**

201221102384491

Al contestar por favor cite estos datos:

Radicado No.: 201221102384491

Fecha: 06-11-2012

Página 3 de 6

La meta de Colombia en términos de reducción de mortalidad por CCU, es lograr una tasa ajustada de mortalidad (TAJ) de 6,8 por 100.000 mujeres en 2015 (Objetivos de Desarrollo del Milenio para Colombia). En el estudio de carga de la enfermedad, contratado por el MSPS en 2011 y realizado por la Universidad Nacional de Colombia, se estimó que el costo de la atención de la enfermedad para cada cohorte de mujeres asciende a US\$ 5,8 millones por atención de verrugas genitales, US\$ 1 millón por tratamiento de Neoplasias Intraepiteliales Cervicales (NIC) 1 de bajo riesgo, US\$ 24 millones por NIC 1 de alto riesgo o NIC 2/3 y US\$ 13,4 millones por cáncer en cualquier estado. Sumando el costo de la prevención y el costo directo de la enfermedad, representan anualmente más de 117,6 millones de dólares a valor presente.

VACUNACIÓN EN NIÑOS

El estudio "Evaluating Human Papillomavirus Vaccination Programs" publicado en *Emerging Infectious Diseases*, Volumen 10, No.11, de noviembre de 2004, concluyó que el incluir hombres en la vacunación contra el VPH, podría reducir los casos de cáncer cervical en solamente el 2.2%, haciendo el programa no costo efectivo, comparado con la vacunación en solo mujeres.

En el estudio "The value of including boys in a HPV vaccination programme: a cost-effectiveness analysis in a low-resource setting" se encontró una mayor reducción en la mortalidad por CCU al vacunar solamente niñas, que al incluir en la estrategia a los niños pre adolescentes, siendo entonces prioritario para este país (Brasil) la vacunación de niñas preadolescentes.

Según las recomendaciones de la Organización Mundial de la Salud - OMS (Position Paper 10 de abril de 2009), la vacunación contra el VPH en hombres no es recomendada debido a que las estrategias utilizadas para alcanzar una cobertura alta, son más rentables si se utilizan en la vacunación de mujeres. Por lo tanto, no es costo-efectivo la vacunación de niños contra el VPH.

En el estudio de Australia "Population-wide vaccination against human papillomavirus in adolescent boys: Australia as a case study" se demostró la existencia del efecto rebaño en niños no vacunados, luego de la implementación del programa de vacunación solamente para niñas.

La incidencia de los cánceres de genitales externos y verrugas producidos por el VPH no son representativos en la carga de enfermedad masculina en el país, por lo que no es pertinente considerar la vacunación de niños contra el VPH.

El citado proyecto de Ley pretende prevenir el CCU, evento de interés para la salud pública femenina, correspondiendo a los ODM mencionados anteriormente, y que con la implementación de la vacunación en niñas escolarizadas se da respuesta a la pretensión del proyecto de ley 260/2012.

Cra. 13 No. 32-76 Bogotá D.C.

PBX: (57-1) 3305000 - Línea gratuita: 018000-910097 Fax: (57-1) 3305050 www.minsalud.gov.co

The quoted papers are (This is the bibliographic notation used in the memo):

“Evaluating Human Papillomavirus Vaccination Programs” in: *Emerging Infectious Diseases*, 10 (11) Nov., 2004.

“The value of including boys in a HPV vaccination programme: a cost-effectiveness analysis in a low-resource setting”

WHO position paper about the introduction of HPV vaccines (2009)

“Population-wide vaccination against human papillomavirus in adolescent boys: Australia as a case study”

Figure 12 Memorandum 201221102384491. Technical concept from Ministry of Health to Colombian Congress about Bill 260 of 2012

From these studies data or figures are not selected, the studies themselves are the evidence of the loss of cost-effectiveness by extending the programme to boys. The Ministry of Health notes the vaccination in boys is not recommended because “such strategies are more cost-effective when they are focused on women to the extent that boys are protected by herd effect” (Ministry of Health, 2012: 1).

do not pose an immediate threat to a person's health, but they can potentially develop into cancer in the future. However, even if you develop CIN or CGIN, the chances of it developing into cervical cancer are very small and if the changes are discovered during cervical screening, treatment is highly successful. The progression from becoming infected with HPV to developing CIN or CGIN and then developing cervical cancer is very slow, often taking between 10 and 20 years.” <http://www.nhs.uk/Conditions/Cancer-of-the-cervix/Pages/Causes.aspx>

This last claim of the Ministry of Health materialises the inclusions and exclusions produced during the different entanglements and disentanglements that cost-effectiveness calculations entail. The emphasis on genital warts not only increased the value of the tetravalent vaccine, at the same time it overshadowed the possible impact of this vaccine on other cancers most of them related with non hetero-normative sexualities.

The promise of an extended protection to boys through the herd effect from girls' vaccination renders visible the heterosexual sexualising of HPV vaccines. Nevertheless, as I have shown before, such sexualising is just limited to decision making and experts arenas. In media and vaccination campaigns the Ministry of Health and the Expanded Programme of Immunisation have tried explicitly to de-sex HPV vaccines, presenting them as an anticipated treatment against a women's cancer and as means of empowerment for girls. The result is that genital warts a key factor in the process of decision making will return to the shadows as 'a technical detail'. Meanwhile, cervical cancer and gender inclusion will be integrated in the presentation of the vaccine in public arenas and media (See Chapter One).

Conclusion

Let me summarize very briefly the topics that were addressed in this chapter. It was an analysis of cost-effectiveness analysis (CEA) as a device of calculation whose purpose is to enact efficiency. Efficiency has reached a normative status as a principle of good governing in contemporary societies and it has had a deep impact in the reconfiguration of practices and governance in healthcare.

Cost-effectiveness analysis (CEA) as device of calculation involves the disentanglement of entities and its reordering in a new calculative space. Prices, technologies, populations and health technologies are disentangled from other contexts and reordered through the rules and dynamics enacted in formulae. Cost-effectiveness analysis has been particularly important in contemporary decision making for its capacity to transform a political process of selection of alternatives of healthcare into an "objective" calculation. Such movement of objects requires the development of languages that facilitate the translation and the commensurability of (in)commensurable entities. In everyday life such exchanges are mediated by currencies and measurement units. In the case of healthcare calculations, a set of health currencies based on the quantification of quality of human life (QALY, DALY, LLY) have been developed allowing the comparison of technologies and procedures.

These currencies have materialised many assumptions of neoclassical economics which have reshaped healthcare policy, the most important being the redefinition of human health based on opportunity cost

and marginality (Moreira, 2012b: 86). The result has been that currencies that were created to avoid the limitations of calculating healthcare efficiency just in terms of monetary units, in practice are monetised. The introduction of HPV vaccines in Colombia is a good case to trace the ways in which these calculation practices are reshaped locally. Health metrics are segmented geopolitically between developed and developing countries, DALYS are perceived by some local experts as the right tool to analyse the national specificities of cervical cancer and HPV infection.

Cost-effectiveness analysis has a very important role in the assembling of particular diseases as public health concerns and in rendering the value of healthcare procedures and technologies. This technique and other evidence based devices have had a key role in the pharmaceuticalisation of public health (Mamo and Epstein, 2014). This device of calculation and its measurement units are designed in a way that privileges pharmaceuticals as medical technologies over other approaches to public health. On the other hand, pharmaceutical companies have appropriated these strategies to increase the value of their products. For instance, the rise of genital warts as a public concern is closely related with the molecular design of Gardasil which extended the protection against HPV 6 and 11. Measurement units such as DALY have an important role in translating these features into the language of health decision making.

Nevertheless these metrics are useful in very limited contexts. Beyond expert arenas, DALYS are not used as expressions of cost-effectiveness. In more public arenas, figures and papers become iconic in the sense, that they are themselves the evidence that legitimate decision making and not the data or the entanglements that they encompass. The classical STS image of the closure of knowledge, its black-boxing (Latour and Woolgar, 1986) seems quite appropriate to describe the ways in which evidence travels and is embedded in new entanglements.

This chapter presented an analysis of cost-effectiveness as results expressed in monetary and health currencies. Nevertheless, these numbers are the result of practices of simulation that recreate the epidemiological evolution of cervical cancer, genital warts and the performance of vaccines and cervical screening programmes. In the next chapter I analyse the role of this calculation device in the enacting of anticipation regimes around cervical cancer and the promises of HPV vaccines.

Chapter Five

Making the right target for vaccination

Markov chain simulation, HPV vaccines and the enactment of a Colombian female population

Introduction

Markov chain simulation is a statistical tool used in cost-effectiveness analysis to simulate the natural history of diseases whose evolution may involve different stages. This tool has been extensively used to compare HPV vaccines and cervical screening programmes in technical studies of the introduction of HPV vaccines. Such simulation relies on a set of assumptions about population composition, HPV infection prevalence, cervical screening coverage and vaccines' effectiveness that are made explicit in the model design.

These assumptions tell a history quite different to the political and public discourses about the development of cancer, vaccines' effectiveness and the characteristics of prevention (see Chapter One). Markov modelling makes explicit the contingency, the uncertainties and the complexities of the relation between HPV and cervical cancer. In contrast, media, public and campaign narratives about cervical cancer and HPV vaccines enact a causal and unidirectional process between disease and prevention.

In Colombia, technical studies have been used to justify the introduction of HPV vaccines as the right intervention according to the national epidemiological profile of the population and the burden of the disease in the country. Markov chain simulation has an important role in assembling a specific "national" portrayal of cervical cancer dynamics. This assemblage involves data from different locations that can hardly be considered as representative of the 'Colombian female population'. Colombia is a country of regions highly diverse in terms of ethnicity and race, such variability has consequences in the definition of a 'Colombian' epidemiological profile (See Chapter One). This chapter reconstructs these contingencies and the role of this calculation device in the enacting of anticipation regimes around

cervical cancer and HPV vaccines' promises to the public and in particular the girls that are the target of this intervention.

In this chapter I describe the different elements that constitute Markov chain modelling as a device of calculation, the entities that are disentangled, the creation of calculative spaces, its rules of calculation and the ways in which results and the natural history of disease are enacted. This strategy of modelling, I argue, has meaningful consequences in the production of new entanglements between individual and social histories of the disease. In principle, the natural history of cervical cancer describes and predicts the development of this malady through different stages in a 'typical' individual; these are changes that happen in an individual body. However, through epidemiological modelling this dynamic is extended to populations through the use of cohorts. Markov chain simulation based on cohorts allows epidemiologists to produce material and semiotic connections between individual bodies and the social body. Such connections interfere with the particular narratives about risk, future and anxiety that are targeted at populations and particular groups.

Markov modelling has also been extensively used in health economics valuation because it facilitates the calculation of monetary and health costs in the development of a disease and allows health economists to compare the impact of different health technologies at different stages of a disease's development. Markov chain modelling is represented in health economics as a 'virtual' clinical trial that enacts different scenarios for each technology and procedure that is compared. This simulation has been introduced into the frameworks of evidence as an alternative to randomised controlled trials –RCT- in cases in which ethical, political and legal restrictions limit their design and application. Furthermore, Markov chain can be understood as an interface between epidemiological and economical valuations of healthcare; through this calculative device disease, costs and human lives are entangled and expressed in health currencies. Markov chain modelling is the main source of data for cost-effectiveness analysis.

In what follows I will present a brief socio-technical history of the natural history of cervical cancer in Colombia. It is an attempt to articulate the social and material origins of the data that are disentangled in the Markov chain's modelling. These data have different socio-material origins; they come from international scientific literature and clinical trials sponsored by pharmaceutical companies (FUTURE-Merck and PATRICIA-GSK) but most importantly from national sources, in the case of cervical cancer and HPV infection in Colombia, the Bogotá Cohort and the Cancer Registry from Cali.

As Bowker and Star (1999) have shown, data are the result of socio-material entanglements; they are produced through chains of translations and material interferences between different entities. In the case of data about the incidence and prevalence of HPV infection and cervical cancer in Colombia, both the Bogotá Cohort study and the Cancer Registry of Cali combine epidemiological research with information arising from healthcare attention to poor people. Different studies (Petryna et al., 2006; Petryna, 2011; Epstein, 2007; Montgomery, 2010) have noted the role of socially disadvantaged populations in the development of global health research and clinical trials. Contemporary production of evidence and scientific knowledge has been deeply related with inequalities in access to healthcare and the recruitment of vulnerable populations as research subjects. Most research and data registration about cervical cancer in Colombia has been done by public universities and research institutes which simultaneously provide healthcare services to poor urban populations. Research and healthcare attention are deeply mixed.

Markov chain modelling and in general the calculation practices of epidemiology tame these data, making their context of production invisible. Living bodies are translated into classification categories and numbers. These data disentangle the differences (intersections between race, gender and class) that shape them. In this chapter I describe the ways in which Markov chain simulation as calculative device produces “ideal” cohorts of populations; cohorts that are diverse in epidemiological and statistical senses but socially undifferentiated. Traditionally the discipline of public health has been characterised by considering social and medical aspects of health as inseparable. Nevertheless, as different scholars (Mamo and Epstein, 2014; Petryna et al., 2006) have noted, in the last 20 years public health discourses and practices have turned to pharmaceuticals as the most privileged intervention strategy for healthcare. Calculation devices such as Markov chain simulation are part of the set of practices that materialise this transformation.

Temporality and causalities: the ontology of cervical cancer

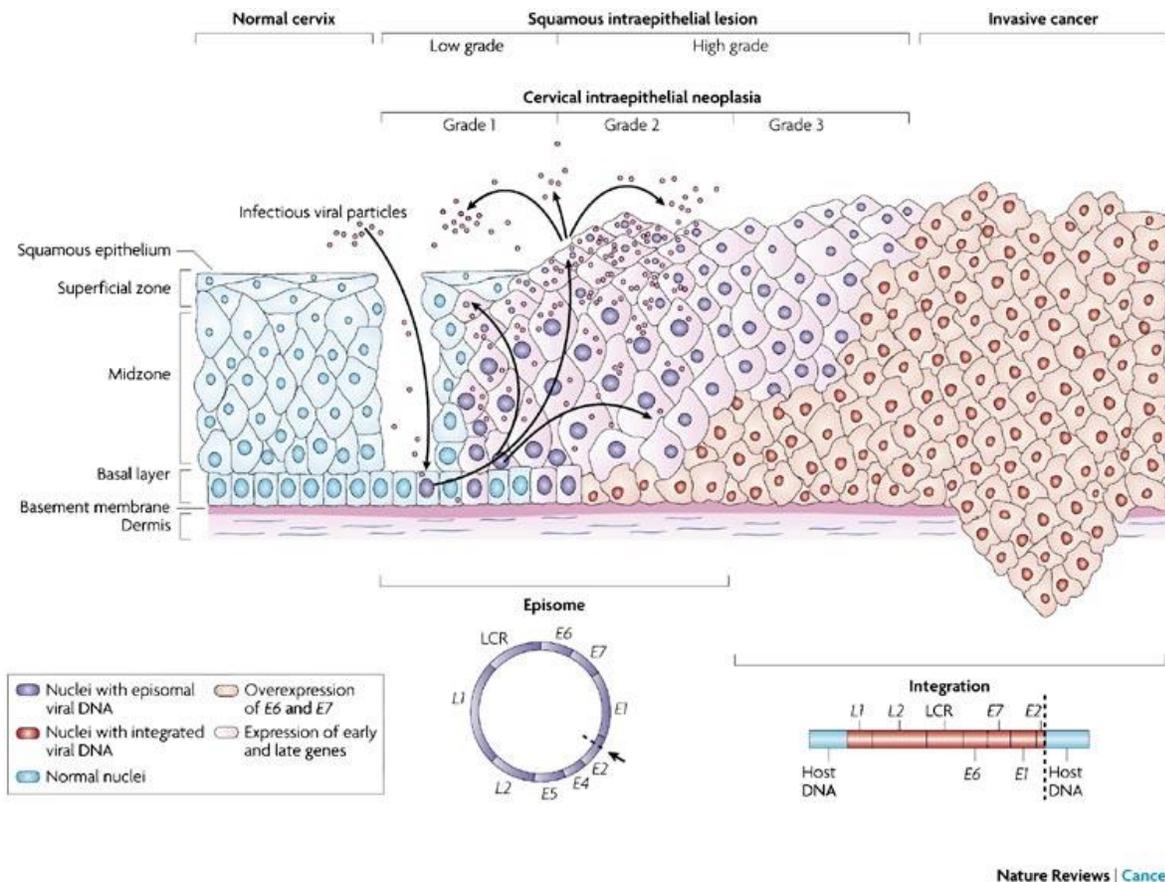
The natural history of cervical cancer –similar to many other natural histories- is a narrative without history. In this case ‘history’ is understood as a sociotechnical chain of contingencies that are enacted in a time sequence. In this section I will discuss the way in which the production of narratives about the natural history of cervical cancer is an attempt to purify social and human contingencies in the intertwining of “facts” that explain the physiological development of this malady.

The most common way of presenting this natural history - in scientific literature and popularisation materials- has been through the illustration of cervical cells’ infection with HPV. For instance, Image 5 is a visual representation of the development of cervical cancer from HPV infection through cancer and metastasis. This image was taken from a paper published in Nature Reviews Cancer about the biology of

cervical cancer (Woodman et al., 2007: 13); in the original paper the image is accompanied by the note I have transcribed below the picture (see Image 5).

This image is organised from left to right following a time sequence in which the different stages of healthy tissue's transformation are presented. These stages are used to classify the different lesions of cervical cells; such classification has been called the grade of cervical intraepithelial neoplasia (CIN). The image is organised from top to bottom as well. At the top the changes in cervical cells are rendered as a description of the grade of the resultant damage in each CIN (I, II, III). Moreover, the picture depicts the ways in which HPV 'causes' the transformation of healthy cells into dangerous neoplastic ones. At the bottom of the picture, the infection of HPV is presented as a molecular process: HPV is rendered as an assemblage of genes and HPV infection as a genetic mutation of cervical cells performed by viral proteins. HPV infection is defined as a genetic integration and drawn in the picture as a bar.

The genetic mutation of cervical cells is the cornerstone of these kinds of narratives, which have an important role in the justification of HPV vaccines as the right tool to use against cervical cancer. HPV vaccines' molecular technology are VLP (Virus Like Particles), these particles produce an immune response to the HPV proteins that cause the host cells to mutate. As Stanley writes, "The VLP is morphologically and immunologically identical to the HPV virus particle" (Stanley, 2010: 10). HPV infection in the mutation of cervical cells is considered the *necessary cause* of cervical cancer. In most of scientific literature about HPV vaccines and cervical cancer the discovery of this relation is assumed to be the most important piece in the history of technological success that HPV vaccines entail. For instance, it is frequently mentioned that in 2008, Harald Zur Hausen was awarded with the Nobel Prize in medicine for the 1983 discovery of this connection. In scientific publications, the natural history of cervical cancer is rendered as a genetic and molecular process.



Nature Reviews | Cancer

Image 5 HPV-mediated progression to cervical cancer

“Basal cells in the cervical epithelium rest on the basement membrane, which is supported by the dermis. Human papillomavirus (HPV) is thought to access the basal cells through micro-abrasions in the cervical epithelium. Following infection, the early HPV genes *E1*, *E2*, *E4*, *E5*, *E6* and *E7* are expressed and the viral DNA replicates from episomal DNA (purple nuclei). In the upper layers of epithelium (the midzone and superficial zone) the viral genome is replicated further, and the late genes *L1* and *L2*, and *E4* are expressed. *L1* and *L2* encapsidate the viral genomes to form progeny virions in the nucleus. The shed virus can then initiate a new infection. Low-grade intraepithelial lesions support productive viral replication. An unknown number of high-risk HPV infections progress to high-grade cervical intraepithelial neoplasia (HGCIN). The progression of untreated lesions to microinvasive and invasive cancer is associated with the integration of the HPV genome into the host chromosomes (red nuclei), with associated loss or disruption of *E2*, and subsequent upregulation of *E6* and *E7* oncogene expression. LCR, long control region” (Woodman et al., 2007: 13).

The molecularisation⁷⁷ of cervical cancer is a recent process if we consider the history of cervical cancer as a medical concern (Löwy, 2011; Hogarth et al., 2011; Chapter One in this thesis). This process has been closely related with the development of HPV vaccines and with the promotion of pharmaceuticals as a public health intervention. Through the molecular understanding of this malady many factors are

⁷⁷ The concept of molecularisation is related with a redefinition of life, biological process and body based on different practices and discourses from molecular biology, genetics and biochemistry. Authors as Rose (2001) and Braun (2007) argue such understanding of the body has important implications “for how we are governed and the ways in which we govern ourselves” (Braun, 2007: 3).

tamed—most of them social—that historically have characterised medical practices and treatment of cervical cancer, e.g. risk factors. Moreover different uncertainties such as genetic variability of HPV and the lack of knowledge about natural immune response are avoided because they can ‘undermine’ the public trust in the vaccine, according to the immunisation Committee (NCIP). On the other hand, this model of natural history has had a great impact in the epidemiological representation of the disease. As I will present in the next section, Markov chain simulation is the tool for the production of epidemiological futures through an individual representation of the disease.

The natural history of cervical cancer provides the foundation to attribute a causal relation between HPV infection and cervical cancer, and therefore, to legitimate the role of HPV vaccines as the best intervention for prevention. Although this relation has been proclaimed in public –media, vaccination campaigns, congress- and policymaking arenas as a straightforward connection; in the scientific and technical literature such link is much more contested and contingent. For instance, Bosch and colleagues (2002) in their influential⁷⁸ paper *The causal relation between human papillomavirus and cervical cancer* point out: cervical cancer is a rare consequence of an infection by some mucosotropic types of HPV” (Bosch et al. 2002: 244). Nevertheless, such discovery is assumed in public health terms, as important “as the discovery of the association between cigarette smoking and lung cancer, or between chronic infections with hepatitis B virus (HBV) or hepatitis C virus and the risk of liver cancer” (Bosch et al. 2002: 244).

This paper is interesting because provides a detailed review of the literature that supports the recognition of a causal link between HPV infection and cervical cancer. This connection is the result of a wide and diverse set of techniques and studies: “Prevalence surveys, natural history investigations, case-control studies and randomised intervention trials” (Bosch et al. 2002a: 244). The team that produced this paper is almost the same as the one that wrote the IARC Monograph No 90 about HPV (2007). These monographs are the official recognition that the IARC on behalf of WHO makes of an element as carcinogenic and therefore risky to humans (IARC, 2007).

Epidemiology had noted cervical cancer displayed a profile similar to sexually transmitted diseases -STD. During the second half of the 20th century the research about cervical cancer was focused on finding a cause linked to STD; syphilis, gonorrhoea and type 2 herpes simplex virus (HSV2) were hypothesis. Even sperm was considered as a possible cause, the known male factor (Reid et al., 1978; Reynolds and Tansey, 2009).

⁷⁸ This paper is often cited in technical and scientific literature about HPV vaccines to support the status of HPV as the necessary cause of cervical cancer. According to the Citation Report from Web of Science Core Collection, this paper has 1.291 cited papers and an H-index of 77.

Bosch and colleagues argue technological development in the detection of DNA is the key factor in the identification of HPV as oncogenic. In the Figure 13, they summarize the percentage of HPV-DNA detected in “cellular specimens” in relation to different technologies of detection (e.g.) FISH, filter in situ hybridisation; GP-PCR, general primer PCR; HC I–II, hybrid capture first and second generation; PCR, polymerase chain reaction; SH, Southern blot hybridisation; TS-PCR, type specific PCR. The evolution of these tests coincides with the development of particular studies, cohorts and HPV vaccines’ clinical trials that have a definitive role in the recognition of HPV as a “necessary cause” of cervical cancer.

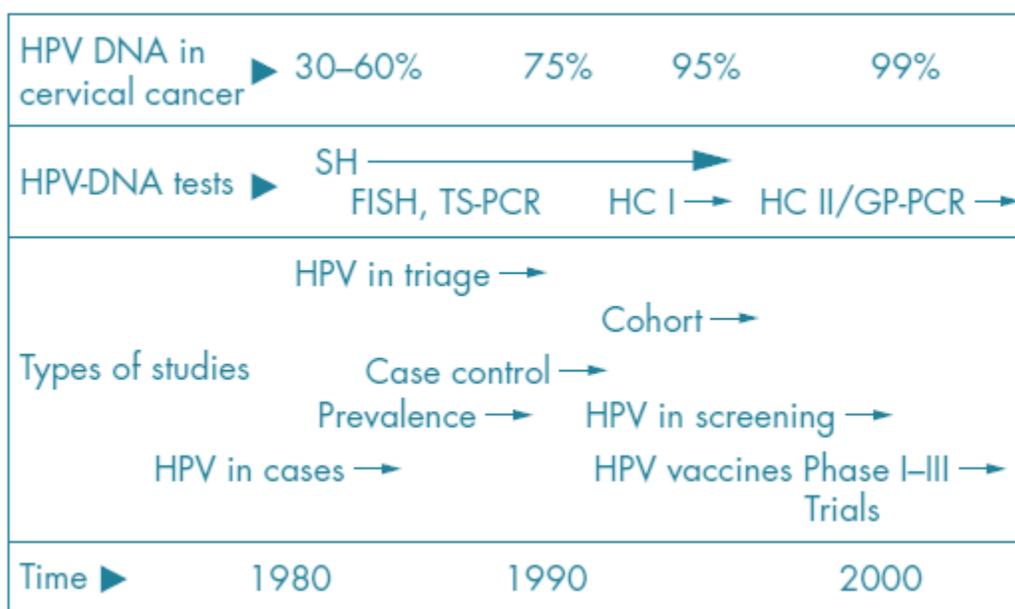


Figure 13 Evolution of epidemiological research on HPV and cervical cancer 1980-2000
Source: Bosch et al. 2002: 245.

Because cervical cancer is a chronic disease it is not easy to follow its complete development through the conventional temporalities of clinical and laboratory research. At the same time, the nature of causality, in medical research, differs from the straightforward identification of one state as producer of another. Causality in this case is more related to co-occurrence, correlation, consistency and a set of particular temporalities. Accordingly, causality is an assemblage. It is the result of entanglements between different studies which are ordered following different criteria of interpretation. In the case of cervical cancer and HPV, since the 1950s epidemiological reviews have been periodically undertaken in order to evaluate ‘evidence’ and to infer causal connection between particular agents and cancer. Bosch and colleagues

present a very interesting summary of the changes of these criteria in epidemiology before introducing their own criteria to attribute causality to HPV (Figure 14).

Lilienfeld (1959) ⁶	Sartwell (1960) ⁷	Hill (1965) ⁸	Surgeon General (1964) ⁹ and Susser (1973) ¹⁰	MacMahon and Pugh (1970) ¹¹	IARC (1995) ¹²
Magnitude of effect	Strength of association	Strength of association	Strength/magnitude of association	Strength/magnitude of association	Strength of association
Consistency	Replication	Consistency	Consistency	Consistency	Consistency
		Specificity	Specificity		Specificity
	Temporality	Temporality	Temporality	Temporality	Temporality
Dose response	Dose response	Biological gradient	Dose response	Dose response	Dose response
Biological mechanism		Biological plausibility		Biological mechanisms	Mechanisms
	Biological reasonableness	Biological coherence	Biological coherence	Consonance with existing knowledge	
Experimentation		Experimental evidence		Experimental (intervention)	Experimental (intervention)
		Analogy			
				Exclusion of alternative explanations	

Figure 14 Epidemiological considerations important for causal inference
Source: Bosch et al. 2002: 246

The ‘canon’ of criteria to define causality that is used by the IARC and Bosch and colleagues was firstly proposed by Austin Hill in 1965. According to Hill such criteria should provide elements to distinguish causal from non-causal associations. These criteria are strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence, and analogy. Table 18 provides a synopsis of the analysis done by Bosch et al. based on Hill’s criteria. The first column shows the criteria, the second one describes its definition and the third, the assessment of the evidence (cohort and clinical trials).

Strength	“Strength of association, it is the magnitude of the ratio of incidence rates. Strong associations are more likely to be causal than weak associations because if they were the result of confounding or some other bias, the biasing association would have to be even stronger and would therefore presumably be evident. Weak associations, on the other hand, are more likely to be explained by undetected biases. Nevertheless, the fact that an association is weak does not rule out a causal connection”.	“The association between HPV DNA in cervical specimens and cervical cancer is one of the strongest ever observed for a human cancer. HPV-16 accounts for almost 50% of the types identified in cervical cancer. The cancer risk for any one of at least 10 HPV types or for any combination of HPV types does not differ significantly”.
Consistency	“Consistency refers to the repeated observation of an association in different populations under different circumstances”.	“The association between HPV DNA in cervical specimens and cervical cancer is consistent in a large number of investigations in different countries and populations. There are no published studies with observations challenging

		the central hypothesis on causality”.
Specificity	“A cause should lead to a single effect, not multiple effects. However, causes of a given effect cannot be expected to be without other effects on any logical grounds. In fact, everyday experience teaches us repeatedly that single events may have many effects”.	“The association of type specific HPV DNA and cervical cancer is significantly different from random. Systematic patterns of HPV type and cervical cancer histology suggest a fair degree of specificity. Patterns are also observed when the scope of HPV and cancer expands to include the full spectrum of HPV types and the large number of additional cancer sites that have been investigated”.
Temporality	“The cause should necessarily precede the effect in time. The temporality of an association, is a sine qua non: if the “cause” does not precede the effect that is indisputable evidence that the association is not causal”.	“HPV infections precede cervical precancerous lesions and cervical cancer by a substantial number of years. The epidemiology and the dynamics of HPV infection in populations satisfy previous observations that related cervical cancer to a sexually transmitted disease”.
Biological gradient	“Biological gradient refers to the presence of a dose–response curve. If the response is taken as an epidemiological measure of effect, measured as a function of comparative disease incidence, then this condition will ordinarily be met”	“The risk of cervical cancer may be related to estimates of viral load. The technology to estimate viral load is being developed and compliance with the biological gradient requirement needs to be further validated”.
Plausibility	“Biological plausibility of the hypothesis, an important concern but one that may be difficult to judge”	“The association of HPV DNA in cervical specimens and cervical cancer is plausible and coherent with previous knowledge. This includes in vitro experiments, animal experiments, and observations in humans. Novel criteria of causality are being proposed and tested as molecular technology develops and is introduced into epidemiological research protocols”.
Coherence	Taken from the Surgeon General’s report on Smoking and Heath (1964) “The term coherence implies that a cause and effect interpretation for an association does not conflict with what is known of the natural history and biology of the disease.”	“The natural history of HPV infection and its relation to cancer development is being described by molecular technology. These investigations indicate that the induction of cancer by HPV is mediated by viral interference with essential regulatory mechanisms of cellular growth, DNA repair, and immunological escape. The alternative hypothesis of HPV being an opportunistic passenger in the tumoral tissue is no longer tenable”.
Experimental evidence	“Such evidence is seldom available for human populations. In human data, the experimental criterion takes the form of preventive interventions and explores whether there is evidence that a reduction in exposure to the agent is associated with a reduction in risk”.	“Experimental evidence shows that species specific papillomaviruses induce papillomas and cancers in the susceptible host”.
Analogy	“The insight derived from analogy seems to be handicapped by the inventive imagination of scientists, who can find analogies everywhere. Nevertheless, the simple analogies that Hill offers—if one drug can cause birth defects, perhaps	“The HPV and cervical cancer model is analogous to many other examples of PV induced papillomas and carcinomas and cancers caused by other viruses”.

	another can also—could conceivably enhance the credibility that an association is causal”.
--	--

Table 18 Criteria to determinate causality
Source: Bosch et al. 2002: 246

These criteria try to solve a critical problem for epidemiology and medical statistics in the attribution of causality: the differentiation between statistical correlations and causality in the absence of laboratory experimentation. STS scholars have extensively described the ways in which causality is a sociotechnical assemblage produced in the laboratory by chains of translations between objects (Latour, 1994) or entanglements between phenomenon and apparatus (Barad, 2007). These assemblages produce the reality that experiments claim to describe. In the case of epidemiological and clinical research the disentanglement and the reordering of such objects seems a harder task. Not only are there ethical and legal restrictions regarding experimentation with populations and people, practical problems in relation to the classification and translation of bodies into data make the production of facts in medical research and in particular in epidemiology a more distributed task. Bosch and colleagues in their paper summarize different studies: epidemiological, clinical and laboratory studies, gathered and classified to ‘infer’ the causality between HPV infection and development of cervical cancer. These studies were realised in different locations around the world at different times (from 1980 to 2000) and with different methodologies from randomized controlled trials, epidemiological surveys to molecular experimentation in laboratories.

Alongside the development of the different criteria, the most determinant aspect in the establishment of causality is the strength of association between HPV infection and cervical cancer. Bosch and colleagues determine such strength through the systematic review of the literature produced by case controls and cohort studies. Following EBM guidelines, these studies are ordered in relation to the statistical association (in terms of their odds ratio) they report between HPV and cancerous cervical lesions in a box plot (Bosch et al. 2002: 252). The authors argue that the strength of the association between HPV and cervical cancer is possibly the strongest found between an exposure to an agent and the development of cancer by scientific research. Figure 15 shows a comparison between rates of association expressed in odds ratio for different agents and the development of particular types of cancer. The baseline is defined by the association between cigarette smoking and lung cancer. This link that was much contested when it was first established by epidemiological research during the 1970s, is nowadays considered a fact and the basis of anti-tobacco regulation around the world. This comparison not only emphasises the strength of

association between HPV and cervical cancer, it also is a claim for strong public health strategies. In the context of pharmaceuticalisation it is a claim for vaccines.

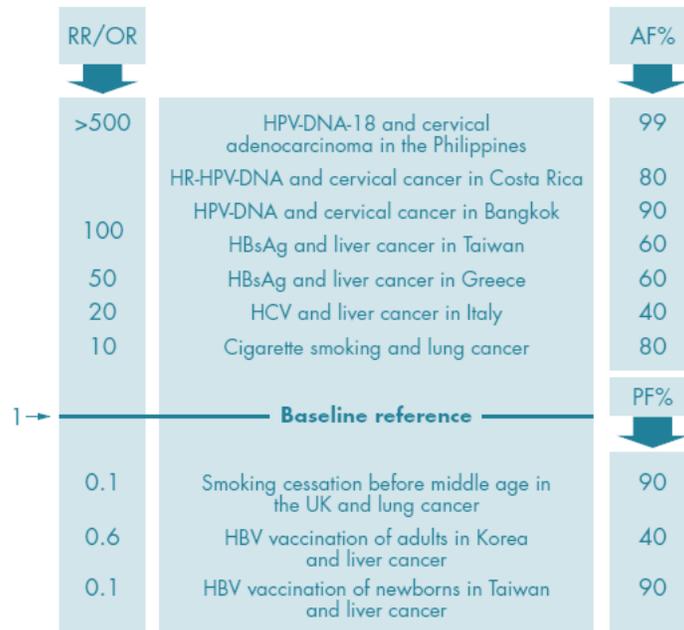


Figure 15 Selected examples of the strength of the associations (RR/OR) between risk factors and human cancer.⁷⁹ Estimates of the attributable fraction (AF%) and of the protective fraction (PF%). Refs: the Philippines, Costa Rica, Bangkok, Taiwan, Greece, Italy, UK, Korea, and Taiwan. Source: Bosch et al. 2002

Systematic reviews like this one mediate between a simplified and molecularised image of the development of cervical cancer and the diversity, messiness and heterogeneity of epidemiological research. As I noted earlier, systematic reviews are calculative spaces that disentangle different entities that are reordered and re-entangled in new sets of relations. In the case of reviews about the natural history of cervical cancer, data from different epidemiological and clinical studies are re-enacted in order to produce a coherent and linear account of the relation between HPV and cervical cancer. Many elements are left outside this assemblage; most of them related to contradictions and contingencies that do not fit into the general narrative. For instance, the natural history of cervical cancer heavily relies on data and studies about HPV type 16. It is one of the most oncogenic types of HPV but it is just one of the almost

⁷⁹ Relative Risk (RR) and Odd Ratio (OR) “In statistics and mathematical epidemiology, relative risk (RR) is the ratio of the probability of an event occurring (for example, developing a disease, being injured) in an exposed group to the probability of the event occurring in a comparison, non-exposed group. Relative risk includes two important features. One, a comparison of risk between two "exposures" puts risks in context, and, two, "exposure" is ensured by having proper denominators for each group representing the exposure” (Wikipedia: Relative Risk).

10 types of high risk virus. Moreover, HPV 16 is globally only the cause 19.7% of cases of cervical cancer (Clifford et al., 2005: 1).

Causality is an assemblage, the result of intensive work of ordering and re-entanglement of objects and relations. Nevertheless, at the end of this process, causality itself becomes icon (see Chapter Two). Although these reviews point out that the “nature” of causality is complex, what travels from the reviews to other documents and arenas is an idea of simple causality that supports a linear connection between HPV and cervical cancer.

This natural history will be the basis to define the plot that will recreate the Markov chain simulation. Markov chain modelling is an attempt to enact a ‘local’ version of the disease, recreating this process in a *hypothetical cohort* of Colombian women. Some accounts of uncertainty and contingency that were left behind in the general narrative about natural history of cervical cancer are reintroduced in this process; for instance, the diversity in the prevalence of HPV types, or the low probability of developing cervical cancer from HPV infection. Markov chain modelling renders visible HPV as a necessary but not a sufficient cause for the development of cervical cancer.

However Markov chain—as any calculation and standardisation practice—produces messiness through its orderings, exclusion in its attempts of inclusion (Law, 2004). Despite this, modelling generates a reflexive account of the uncertainty in the natural history of cervical cancer; it reinforces the homogenisation of the population through the simulation of cohorts (Bauer, 2008). This cohort enacts an undifferentiated image of Colombian women. Elements of differentiation such as race and class, which are key elements in the development of HPV vaccination as public health strategy, are rendered invisible in the modelling. Such reduction is important not only because the simulated cohort is the base to calculate the economic costs of the vaccination programme and its cost-effectiveness, but also because it enacts the HPV vaccination as the right strategy for the local and national features of Colombian population. In contrast, researchers and advisors of the Expanded Programme of Immunisations in Colombia have noted the role of difference in the production of these data. Not only are marginalised groups defined as populations in risk, they (their bodies) are in most of the studies the main source of information underpinning epidemiological surveys, cohort studies and clinical trials.

Below I introduce Markov chain modelling as a device of calculation and describe the ways in which this tool has been used in Colombia to simulate the natural history of cervical cancer based on “national” demographic and epidemiological data. This modelling is what underpins the base of the definition of

scenarios of cost-effectiveness and of the estimation of the costs to compare vaccines, cervical screening programme and clinical treatments.

Markov chain simulation, probability and the tame of uncertainty

Markov chain model is a probabilistic method, named after the Russian mathematician Andrey Markov, used to describe the ways in which objects and systems change over a particular time. They are commonly used to represent random processes that change over time, known in statistics as stochastic processes (Bonacich and Lu. 2012: 149). This kind of modelling has had a huge impact in medical decision analysis. Markov chains have been extensively used to simulate the development and the progression of chronic diseases. As Briggs and Sculpher have noted, Markov chain suits the dynamics of diseases that change by states. “The disease in question is divided into distinct states and transition probabilities are assigned for movement between these states over a discrete time period known as the Markov circle” (Briggs and Sculpher, 1998: 399).

Although Markov chains have a long history as probabilistic technique, it was in the 1980s that it became a tool integrated in medical decision making. The increasing use of the technique is linked with the rise of information technologies in healthcare institutions, with the digitalisation of clinical and administrative data and with the development of software that has facilitated statistical and different mathematical operations. Such software has allowed Markov models to be constructed and evaluated more easily (Sonnenberg and Beck, 1993: 222).

Modelling has had an important role in the contemporary governance of healthcare (Bauer, 2008; Mansnerus, 2013; Mackenzie, 2013; 2014). Such models have allowed healthcare managers to calculate risks and enact detailed descriptions of future scenarios. These scenarios interfere with the current practices of management of healthcare and with the distribution of economic and symbolic resources. Decisions about procedures and actual interventions are done based on calculation about their sustainability and the impact in future budgets. On the other hand, models have provided a way of synthesising, extrapolating and harmonising data from different sources producing coherent and sound versions of medical objects. And even more importantly, modelling is one of the practices of calculation that have made economic valuation of health technologies by public institutions and pharmaceutical companies possible. For instance, pharmaceutical companies use this kind of analysis “prior to large investment in phase II and III trials in order to begin to understand the likelihood of a new drug being cost-effective at particular price levels” (Briggs and Sculpher, 1998: 401).

In this context, Markov models have contributed to medical decisions and analysis about chronic diseases that involve an ongoing risk over time. Markov chains modelling assumes that the agent (patient, population) is always in one of a finite number of possible health states, these stages are known as Markov states (A and E in the Figure 16). For each state a utility is assigned; the contribution of this utility to the complete process depends on the length of time spent in such state (Sonnenberg and Beck, 1993: 224). A utility or a rate in this case is “an instantaneous likelihood of transition at any point in time, whereas a probability is the proportion of a population at risk that makes a transition over a specific period of time” (Briggs and Sculpher, 1998: 402). Markov chains’ modelling is a process without memory, which means that the probability of each stage is independent of other stages’ probabilities. This requirement is known as the Markov assumption. In the case of Markov chains there are at least two strategies of simulation⁸⁰: Cohort and Monte Carlo. Both strategies run the model through many cycles to define a “profile” of how many patients are in each state of the model over time (Briggs and Sculpher, 1998: 402).

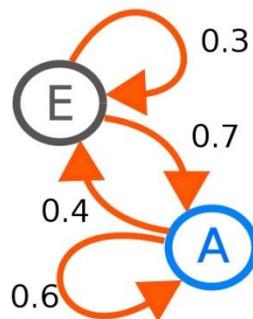


Figure 16 Example of a two-state Markov Chain
Source: Decoding Science, 2014⁸¹

In a cohort simulation, populations are the units of analysis. A cohort of individuals moves through different stages of the model following a set of probabilities or utilities of transition. The objective of this modelling is to determine exactly what proportion of the cohort is in which state at a given time (or model cycle). In contrast, in the Monte Carlo simulation, rather than simulate the dynamics of a whole cohort of

⁸⁰ It is important to be precise –at this point- about the difference between modelling and simulation. Although modelling and simulation are hardly distinguished in practice, they can be understood as stages in the process of virtual constitution of entities. The Wikipedia entry about Modelling and Simulation (M&S) offers a clear definition. “Modelling is understood as the purposeful abstraction of reality, resulting in the formal specification of a conceptualization and underlying assumptions and constraints. M&S is in particular interested in models that are used to support the implementation of an executable version on a computer. The execution of a model over time is understood as the simulation”.

⁸¹ <http://www.decodedscience.com/cancer-research-applies-a-markov-chain-monte-carlo-approach/27675>

patients through the model together, a large number of individuals or patients are followed through the model individually. Both cohort and Monte Carlo simulation involve the same probabilities of transition. However, as Briggs and Sculpher have noted the main difference between these methods is that in the Monte Carlo simulation “an individual patient can only be in 1 stage at a given time, they may or not transit between stages in any given cycle” (Briggs and Sculpher, 1998: 407).

Cohort and Monte Carlo⁸² simulations enact different epidemiological objects; such objects are embedded into political narratives about disease, risk and population control. Cohort simulations are used to produce demographic units which generally correspond to political classifications such as cities, departments and countries (Bauer, 2008). In contrast, as Adrian Mackenzie has noted, the increasing use of Markov chain Monte Carlo (MCMC) simulation is related with the post-demographic power attributed to data by information experts, politicians and policymakers, in which individuals rather than populations or sub-populations are the main objects of interest (Mackenzie, 2013: 2). Simulations have rendered computers “as substitutes for events in the world, and they render that world more manipulable by knowing subjects” (Mackenzie, 2013:14).

Markov chain modelling of cervical cancer: virtual trials and the taming of clinical complexity

Although randomised trials are regarded by evidence based medicine as the ideal vehicle of data collection, modelling has an important role in producing evidence when due to ethical, economic restrictions or lack of data it is not possible to run clinical trials. In the case of the introduction of HPV vaccines in Colombia, the different studies of cost-effectiveness and burden of disease relied on data and epidemiological scenarios produced by a simulation of the natural history of cervical cancer in a cohort of Colombian women. Using a Markov model, the natural history of cervical cancer and genital warts in a hypothetical cohort of 430.859 Colombian women was simulated. The parameters were defined from a literature review of national and international studies (UNAL, 2011). At the same time this model was used to estimate the costs of treatment at different stages of development of the disease. Such costs were defined through micro-costing methods and were validated by experts. Most of these experts were members of the committee of immunisation practices. Moreover, the effects of different treatments were simulated. The simulation offered a comparison of the effect in the reduction of the burden of cervical cancer and genital warts between cervical screening programmes (1-1-3 years per test), bivalent HPV vaccine and tetravalent HPV vaccine (UNAL, 2011:2). The model was the main source of information to

⁸² MCMC technique is a key technique in Bayesian statistics. As Mackenzie has noted: “In short, MCMC allows, at least in principle, every number to be treated as a probability. This a key shift in the probability practice, and one that opens the way to post-demographic conceptions of individuation” (Mackenzie, 2013: 5).

determine the cost-effectiveness of the different competing alternatives by their Incremental Cost-Effectiveness Ratios (ICER, see Chapter Four).

In principle, a Markov model fits in the ways in which medical science traditionally has represented the development of cervical cancer. This malady has been understood as a disease whose stages are clearly identified. The first international classification of cervical cancer development was done by the Radiological Subcommittee of the Cancer Commission of the Health Organisation of the League of Nations in 1928. The commission generated a classification system for grouping carcinoma of the uterine cervix into four stages according to the extent of the growth. “Since then, seven changes have been made to the staging system for cervical cancer, the most recent being in 1994. Almost all of these changes were made to Stage I cervical cancer” (Benedet and Pettersson, 2003: 1).

These different stages will define the Markov states of the model. In the different technical reports (UNAL, 2009; UNAL, 2011) the Model is represented through a flow diagram which describes the transitions between states and the different paths that the cohort may follow. The model recreates *in silico* the dynamics that a cohort would follow *in vivo* during a clinical trial. As I have noted, the advisory team from Universidad Nacional developed two studies of cost-effectiveness; both were supported on Markov simulations. The first study (UNAL, 2009) simulated the development of cervical cancer and the impact of the national cervical screening programme and the bivalent vaccine. The second study (UNAL, 2011) introduced genital warts and a comparison between tetravalent vaccine and bivalent into the model.

Both models share the intention of recreating the development of the disease according to the specificities of the Colombian epidemiological profile. Such specificity relies on the origin of input data, the location of data and other technical sources. As noted in the 2011 study: “The parameters of incidence, prevalence and mortality by cervical cancer were defined through a review of Colombian literature, governmental and clinical databases, such as DANE⁸³, Cali Cancer Demographic Register, Colombian National Cancer Institute and IARC” (UNAL, 2011: 25).

Nevertheless, in the moment of assembling the model the limitations of gathering and using “Colombian” data as the main source of evidence becomes clear. Who designs the model identifies problems and ‘bias’ in the register the information. These issues are *solved* through the use of algorithms. For instance, mortality databases were assessed and corrected using Bennett-Horiuchi method: “In order to correct bias by wrong classification of deaths by cervical cancer this algorithm was used: Deaths by cervical cancer:

⁸³ Colombian National Department of Statistics, DANE, in spanish Departamento Nacional de Estadística.

deaths registered by cervical cancer + α *deaths by cervical cancer not specified + β * deaths by corpus uteri cancer: $\alpha= 0.9$ and $\beta= 0.3$ ” (UNAL, 2011: 25).

However, the main limitation is the lack of data. These reports (UNAL, 2009; 2011) note the lack of national information about the prevalence of cervical cancer and HPV infection. The ‘National epidemiological profile’ is rendered an extension of the data provided by the Cancer Register of Cali and the Cohort Study of Bogotá. Even more importantly in some cases there are not any national data about the disease in the model. As it is noted by one of the experts in charge of the modelling:

In all these studies because of the lack of epidemiological data there is a long and careful process to construct scenarios of morbidity, mortality and loss of life years by disability (DALY) using local data but also international data of close countries. This is a delicate process because for some things there are no data. For example, in the HPV case, mortality and incidence data of cervical cancer are more or less robust but for other cancers are not. Even less regarding the role of HPV in other cancers and warts, there is no data about incidence, nor data about national prevalence. Therefore, one has to use data from other sources and make simulations to see what sounds reasonable **Epidemiologist Sr. 1 NCIP.**

The political and ‘clinical’ interest in genital warts contrasts with the lack of studies and epidemiological data about their incidence, costs and treatment in Colombia. This is not an exclusive problem of Colombia; information about incidence, prevalence and treatment costs of genital warts is relatively scarce compared to cancers and other maladies associated with HPV infection⁸⁴. Even the paper used as ‘evidence’ to define the parameters of the model in relation to genital warts (Hillemanns et al., 2008; see Appendix 1) notes the difficulties of gathering information about genital warts in Germany, where the study was conducted. This research team decides to calculate incidence and costs of genital warts in Germany through the analysis of a statically representative sample.

The management of uncertainty⁸⁵ is one of the elements that define the boundaries between calculative spaces, decision making and public arenas. From the perspective of EBM, uncertainty is the starting point of health decision making, however, “uncertain knowledge should not be translated into the realm of

⁸⁴ For instance, in PubMed it is possible to find just 109 papers about genital warts incidence, costs of treatments and cost-effectiveness of HPV vaccination as prevention strategy from 1995 to 2013. Most of this literature is associated with the possibility of extending HPV vaccination to boys.

⁸⁵ In health economics, uncertainty is distinguished from variability and heterogeneity. Variability is understood as the “natural variation” between patients in their response to treatments and the costs associated. “Heterogeneity refers to differences between patients in terms of identifiable characteristics such as age, gender and the severity of the disease” (Griffin and Claxton, 2011: 769).

decision making” (Moreira, 2012b: 80). Data harmonisation is very important in the management of uncertainty; it encompasses strategies such as sensitivity analysis and choosing the most “conservative” rates and data about the interventions. Conservative in this case means the lowest estimation. As it is noted by the experts that designed the epidemiological modelling:

“We found a German study that had very conservative estimations, even the reported incidence was very low compared with other countries, that was the source for the analysis of costs and with that study we did the simulation, and the sensitivity analysis (...) it was putting something, taking something else... Anyway genital warts have an effect and we had to find the ways of estimating it. We thought that such study (Hillemanns et al., 2008) really underestimates the effect of the economic burden produced by genital warts. In spite of such underestimation, those data have an important role in the cost-effectiveness”

Epidemiologist Sr. 1 NCIP.

These limitations make explicit the contingency of modelling. The assemblage of a coherent and complete history of genital warts and cervical cancer in Colombia is only possible because of the gathering of heterogeneous elements that are connected by uncertain relations expressed in terms of probability. As Hacking has noted, probability tames change, constituting a reflexive account to manage contingency and uncertainty. “The whole point of probability is that we may not be able to establish a proposition with certainty; we can at best measure the extent to which data warrant our inferences” (Hacking: 1975: 90). Probability makes uncertainty a matter of calculation that can be quantified, identified and therefore controlled.

Statisticians, health economists and epidemiologists have understood uncertainty as a function of the availability of information (Moreira, 2012b: 80; Griffin and Claxton, 2011: 759). In principle uncertainty means weakness of the knowledge and the evidence in a particular issue. Moreover, uncertainty is itself a matter of opportunity cost. In particular from the perspective of health economists, at some point to act and to make decisions is justified under uncertainty instead of waiting for additional evidence in a particular issue and delaying action (Griffin and Claxton, 2011: 759). This same logic operates in the Markov chain modelling; the uncertainty and the lack of evidence in a particular subject can be controlled through its expression in terms of probability. Furthermore, a holistic reading of the model can overcome blind spots and lack of evidence.

Nevertheless, the main instrument to tame uncertainty in modelling and in cost-effectiveness analysis has been sensitivity analysis, in particular probabilistic sensitivity analysis (PSA) (Andronis, et al. 2009; Griffin and Claxton, 2011: 759). PSA is a form of sensitivity analysis “in which probability distributions

are applied to the ranges for a model's input parameters, and samples from these distributions are drawn at random to generate an empirical distribution of the relevant measure of cost-effectiveness" (Andronis, et al. 2009: 3). Andronis and colleagues make a systematic review of the use of PSA within the appraisals that are conducted to assess the inclusion of technologies and procedures into NHS. The importance of the technique relies on its promise of rendering uncertainty visible and defining an interval of confidence that integrates the uncertainties of the different parameters simulated in the model.

In their analysis, statisticians Andronis and colleagues define a set of types of uncertainty in cost-effectiveness modelling that can be useful in understanding the role of this tool in the production of evidence. They distinguish between methodological uncertainty, that is the disagreement about the right method of evaluation; parameter uncertainty, which is the uncertainty in the estimated values of the model's parameters; structural or modelling uncertainty which refers uncertainty on the nature of the model as the appropriate tool for combining the input parameters and generalizability, the extent to which model results can be applied to another setting (Andronis, et al. 2009). For them PSA is a tool that facilitates dealing with parameter uncertainty. From statisticians' perspective, Andronis and colleagues note the main problem of NHS appraisals is the confusion between types of uncertainty and the generalization of PSA beyond its scope of use. They, moreover, point out that in relation to PSA calculation "the variability in the form of distribution used for similar parameters is surprising, and it is concerning that the justification for such choices is rarely given" (Andronis, et al. 2009: 24).

Beyond this critique, PSA is increasingly used as the standard of presentation of Markov modelling results in order to define the cost-effectiveness of treatments within the parameters' uncertainty. Most PSA are conducted using Monte Carlo (MCMC) simulation; Monte Carlo shows for each set of randomly drawn parameter values, the treatment that should provide bigger benefits. "By plotting the proportion of times each treatment the maximum net benefit across the whole simulation on the y axis, and the threshold value used to calculate net benefits of x-axis, a cost-effectiveness acceptability curve is produced" (Griffin and Claxton, 2011: 778). That is the case of Figure 17, which compares the performance of HPV vaccines and cervical screening programmes in relation to their cost-effectiveness. These alternatives are rendered in a plane which contrasts willingness to pay and the proportion in which the strategy can be considered cost-effective (UNAL, 2009).

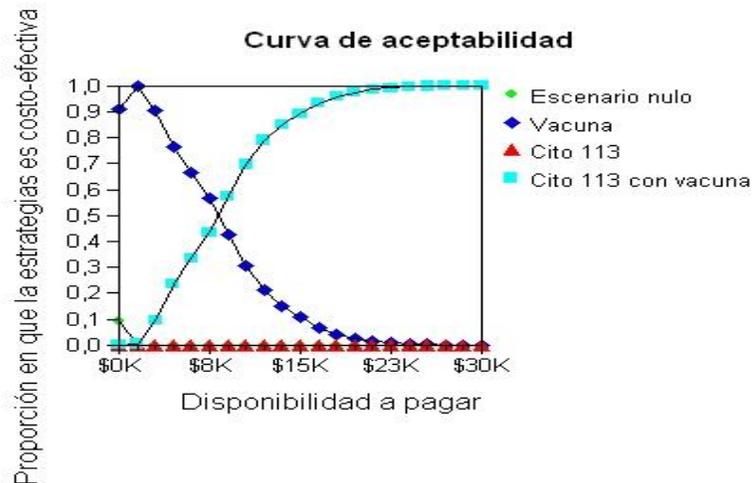


Figure 17 Acceptability curves and Monte Carlo PSA for the evaluation of HPV vaccines' cost-effectiveness to prevent cervical cancer in Colombia.

X axis: Willingness to pay. Y axis: Proportion in which is cost-effective the strategy. Source (UNAL, 2011: 19)

PSA is often visualised by means of scatter plots. Scatter plots render data as independent points located within a Cartesian plane; eventually through their concentration these points can render emerging relations between them. Scatter plots are used to present correlations and regressions, but also they are one of the privileged ways of presenting the results of Monte Carlo simulations. Andronis and colleagues recommend their use in cost effectiveness analysis. They argue that scatter plotting “can facilitate understanding of the results of probabilistic analyses and the extent of uncertainty for decision-makers” (Andronis, et al. 2009: 40).

Adrian Mackenzie (2013, 2014) has noted that Bayesian statistics and simulation techniques such as Monte Carlo Markov chain are transforming the understanding of probability and therefore our representation of uncertainty, chance and change. “Certain shifts in the role played by probability change the meaning and value of data as such, and hence, everything that depends on data’ (Mackenzie, 2013: 20). I agree: the use of these devices of calculation is extending the perception of control over uncertainty, and it is increasing the trust in the realities enacted *in silico*. The increasing use of these virtual trials to support decision making shows part of the impact of these practices of calculation in the reshaping of healthcare governance. On the other hand, PSA and its technologies of visualisation have a very important role in making these calculations objective; they are part of the process of creating a black box of figures and numbers that will make invisible contingency and uncertainty once these objects are moved from calculative spaces to policy and public arenas.

In this regard, Andronis and colleagues (2009) in their review are concerned about the gaps and difficulties of communication between analysts and policymakers in relation to uncertainty management and in particular the meaning of PSA. “It is evident that some cost-effectiveness work, especially around the sensitivity analysis components, represents a challenge to become accessible to those making decisions” (Andronis, et al. 2009: 47). They note that in technical literature about sensitivity analysis there is a debate in relation to the best ways of presenting PSA, some are “in favour of scatter diagrams and intervals around incremental net benefits, and others arguing for cost-effectiveness acceptability curves and frontiers, especially in the case of more than two treatment options” (Andronis, et al. 2009: 47).

In Colombia both graphic presentations were used in the different cost-effectiveness analysis. However, PSA is an object which remains in the calculative space of the reports and modelling software but that does not travel to other spaces and more public arenas. In minutes of the National Committee of Immunisations PSA is just an acronym to point out a technique that made the analysis of data robust. The uncertainties and contingencies that the technique entails become invisible.

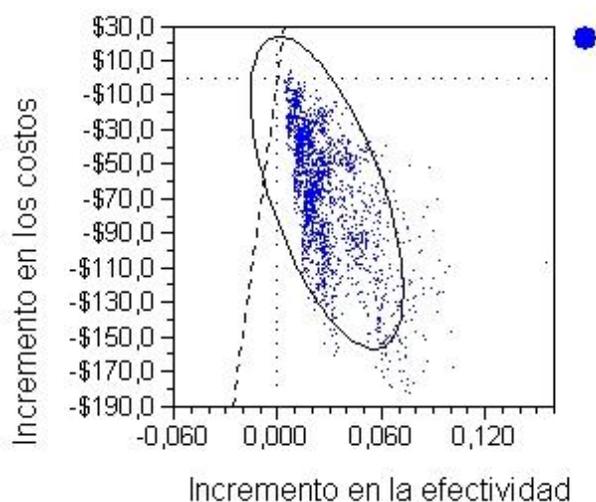


Figure 18 Scatter plotter Monte Carlo PSA for the evaluation of HPV vaccines' cost-effectiveness to prevent cervical cancer in Colombia. Source (UNAL, 2011: 19)

In the last section of this chapter I discuss two issues: Firstly, which enactments are produced by this model and secondly, what objects, problems and people are excluded and rendered invisible by these practices. These are far from being simple questions. To some extent I have partially answered the first question in this analysis of the ways in which modelling assembles causality and uncertainty. However, in

what follows I want to focus on the ways in which population, nation and risk are enacted in the Markov modelling. At the same time, I would like to explore the elements that are left out of Markov modelling. I have presented Markov chain modelling as a machine of producing actual and future realities of population and disease. Accordingly, the exclusion of objects, people and entities from the analysis has important consequences in rendering invisible or marginal those objects.

Enacting the women of the nation: Statistical reflexivity and homogenization

The Markov chain modelling can be understood as a systematic review in movement. Its parameters are selected from an evaluation of technical and scientific literature. Such review does not correspond necessarily with the standards of evidence based medicine for systematic reviews but in principle it is assumed that it should follow the ‘best’ available evidence. Papers contribute data about demographical composition of the cohort that is simulated; moreover they provide information about incidence and prevalence of HPV infection, cervical lesions, genital warts and cancer. Finally the literature contributes information about the probabilities of transitions between states in the development or healing of the disease. Such probabilities connect the data and the rates defined as parameters and make the model dynamic.

Figure 19 is a graphical representation of the Markov model used by Universidad Nacional in the cost-effectiveness study of 2011. This diagram is organized in three levels: firstly at the top the sequence of possible states in which the individuals of the cohort can be: normality, contagion without lesion, reversible lesion, pre-cancer, cancer and healing/death. Below this level, different stages of development of the diseases are rendered. For instance the infection with low risk HPV types can lead to genital warts, whilst infection with high risk HPV lead down a path in which cancer is a possible ending point. During the different stages death is a possibility. In low risk stages the probability of death is the same as that of the general population; in stages in which the risk is higher the probability of death increases. The third level, at the bottom of the diagram, encompasses different stages of detection and treatment and their effect in the transits of the simulated cohort on the possible paths.

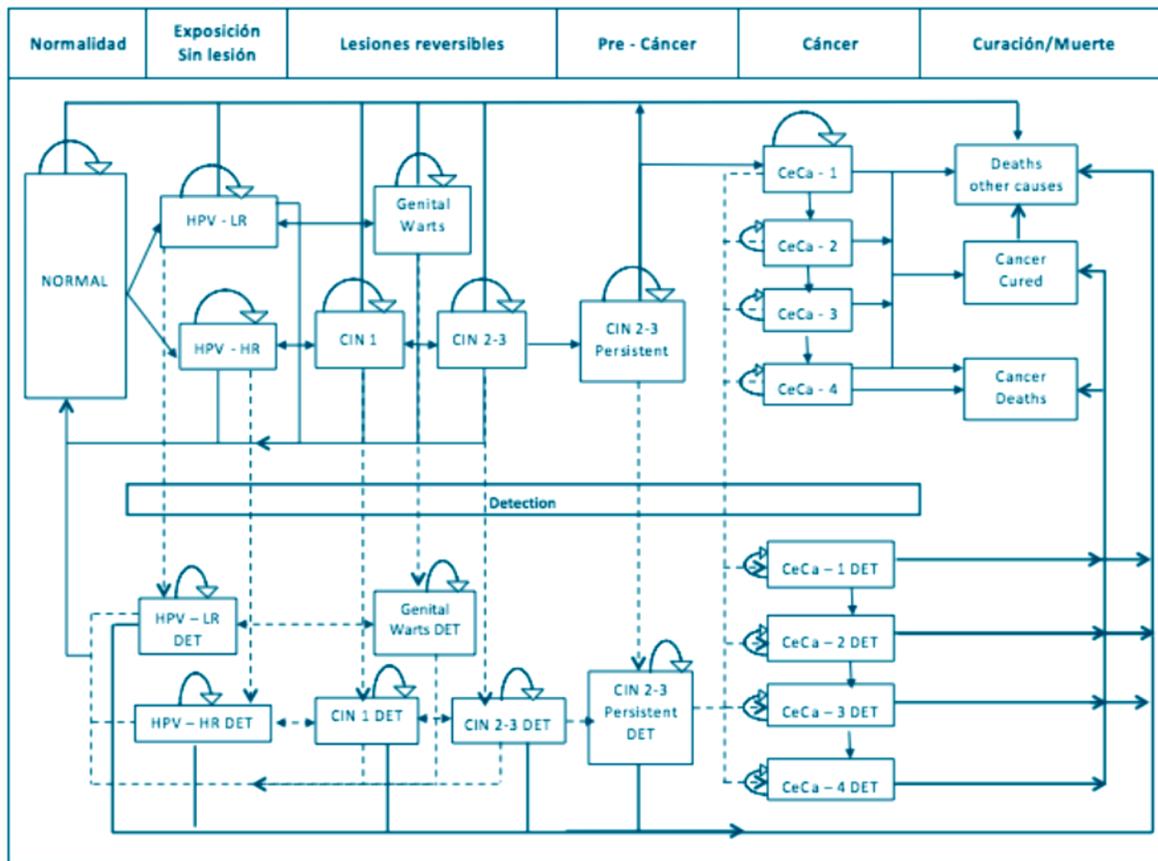


Figure 19 Markov chains model for the evaluation of HPV vaccines' cost-effectiveness to prevent cervical cancer in Colombia.

Source (UNAL, 2011: 19)

For each one of these stages and transitions, a set of parameters is defined; these parameters constitute the assumptions of the model. Appendix 1 shows the parameters of the Markov modelling (UNAL, 2011), for each parameter a confidence interval (sensitivity analysis range) is defined and the used source (paper) noted. The model is designed based on at least 20 papers, which can be organised in the following sets: national studies or international research with data about Colombia (32, 33, 34 see Appendix 1⁸⁶); methodological studies and mathematical models (35, 36), international data [studies about other countries] (31, 37); pharmaceutical RCT (39, 40, 41, 42); HTA and economic evaluation about treatments' costs (43, 44, 45, 46, 47, 48, 49, 50, 51).

As Bauer (2009) has noted epidemiological data from biobanks, registries and cohort studies are constantly re-used and re-assembled to construct new objects. Despite the papers that support the model

⁸⁶ This numeration corresponds with the used in the study from Universidad Nacional (2011). In Appendix 1 you can find the complete bibliography.

showing a diversity of sources, these different papers are the result of a reduced number of studies and share the same socio-material origins. For instance, the papers about HPV and cervical cancer in Colombia are the result of the Bogotá's Cohort study developed between 1997 and 2007; the articles on bivalent vaccine are the result of the clinical trial PATRICIA (GSK) and on tetravalent vaccine from the RCT FUTURE (Merck). These entanglements are stronger, we take into account the role of pharmaceutical companies funding to sponsor some local studies and the recruitment of local populations in the development of big international clinical trials for drug licensing⁸⁷. For instance, according to INC researchers, the same women that participated in the Bogotá were enrolled in the phase III and IV of FUTURE. The populations recruited have developed a particular relation with the researchers, who are perceived as healthcare providers. At the same time the researchers have used their connection with these groups as an asset in their negotiation with pharmaceutical companies in relation to funding and participation in bigger studies and trials.

This heterogeneous assemblage of papers, figures and institutions have an important role in the representation of populations and in the shaping of governance. A detailed reading of the assumptions of the model shows the ways in which it makes different accounts and distributions of multiplicity/homogeneity, visible/invisible risk and inclusion/exclusion. The main assumptions of the model which are expressed in its parameters (See Appendix 1) can be summarized in the following:

- i. Starting point: Cohort of adolescents (10 years old) without infection by HPV. The following finishes at 85 years old.
- ii. Cervical screening programme starts at 20 years old
- iii. All the cases of cervical cancer are caused by high risk HPV types. It is assumed that low risk HPV infections do not progress to cancer.
- iv. Probabilities of infection and its progression to CIN and cervical cancer depend on women's age and HPV type.

⁸⁷ The same can be said in relation to medical professionals and the experts involved in the modelling and gathering of evidence in Colombia. That is the case of policies about cervical cancer and HPV vaccines, at least in Colombia, researchers have had an important role in the promotion of this disease as a public health problem and in the debate about the inclusion of technologies into healthcare system for its treatment. National Cancer Institute in Colombia has had an important role in that regard, its researchers were involved in two studies: the Bogotá Cohort study (1997-2007), which was the basis for the development of the trials FUTURE III and IV in Colombia; and the creation of the Cancer Population Register of Cali. The last is one of the most complete cancer register in Latin America and the world; it has been a keeping register of different kinds of cancer during the last 40 years. This is the local point of cancer data gathering for a centre of calculation, the IARC in Lyon, proving data to Globocan for calculating the Global Burden of Cancer.

- v. HPV 16 and 18 are the cause of 37% high risk infections, 35% of LSIL, 40% of HSIL and 63% of cervical cancer.
- vi. After 5 years of treatment the probability of death is the same of the general population
- vii. Coverage of cervical screening: 50% and HPV vaccination 60%. Cervical screening is understood as the probability of having a Pap test in the last year.
- viii. Cost of HPV vaccine (three doses) is \$25 (International dollars) in 2009 and \$44 (Bivalent) and \$49 (Tetravalent)
- ix. HPV vaccines efficacy to prevent cervical cancer associated to HPV 16-18 is 97% (Bivalent) and 98% (Tetravalent).
- x. Calculated reduction in the probability of infection for high risk HPV: 63.9% (Bivalent) and 67.86% (Tetravalent).

The model's parameters show the effort to differentiate viruses, stages and paths of development of the disease whilst women and female populations are homogenized. In contrast to the unified portrayal of HPV presented in vaccination campaigns and public arenas, the model makes explicit the diversity of HPV types and its consequence in the development of different disease alternatives. The model produces a modest account of the incidence, probability of contagion and probability of developing cervical cancer from HPV infection. These parameters affect the ways in which HPV vaccines' efficiency and its protection are enacted in the model.

Figure 20 illustrates this point. This figure encompasses a set of pie charts that show the incidence of HPV infections by type of virus organized by geographical regions. The charts show that HPV 16 and 18 constitute just 12% of infection by HPV in Sub-Saharan Africa, 19% in Asia, 20% in Latin America and 26% in Europe. This narrative contrasts strongly with the public discourses about HPV vaccines where the contagion of HPV is presented as undifferentiated and universal. Moreover, as medical anthropology has noted in the case of other pharmaceuticals (Petrina, 2006; Lakoff, 2005), the diversity of HPV types and incidence of infection around the world suggest that in the design and development of pharmaceutical interventions such as HPV vaccines the priority is to attend the necessities of "markets" in Europe and U.S. which later are promoted as universal and pertinent for other populations and "markets" around the world.

Although the Markov model's account of the diversity of HPV is simplified compared to the version presented in journal articles; it still presents the limitation of attributing a direct association between HPV infection and the potential development of cervical cancer. The modelling distinguishes high risk and low risk HPV types. The range of high risk virus is wide and contrasts with the focus of vaccine

advertisements on HPV 16 and 18. Forty percent of cervical cancer cases simulated in the model can be attributed to other high risk types (HPV 31, 33, 52, 56, 58, 59). This account of the contingency and diversity involved in the design of the modelling and in the gathering of data can be called statistical reflexivity. Numbers and quantified expressions have the capacity to show contingency; they are not exclusively elements to enact objectivity.

Another aspect that is not emphasised in public discourses about cervical cancer and HPV vaccines but is relatively clear in the narrative of the Markov model is that cervical lesions are a very rare consequence of HPV infection. The model using as reference a study of Bogotá's Cohort (Muñoz et al., 2004: 2078) describes that incidence of HPV16 is 5.0 (Incidence rate per 100); HPV 18, 1.0 and HPV 31, 1.0. Even if the infection of these hypothetical cases progress to further stages, the individual risk of having cervical cancer is low, because it should be added to the probability of contagion with a high risk type, the different probabilities of transition to CIN and eventually to cervical cancer.

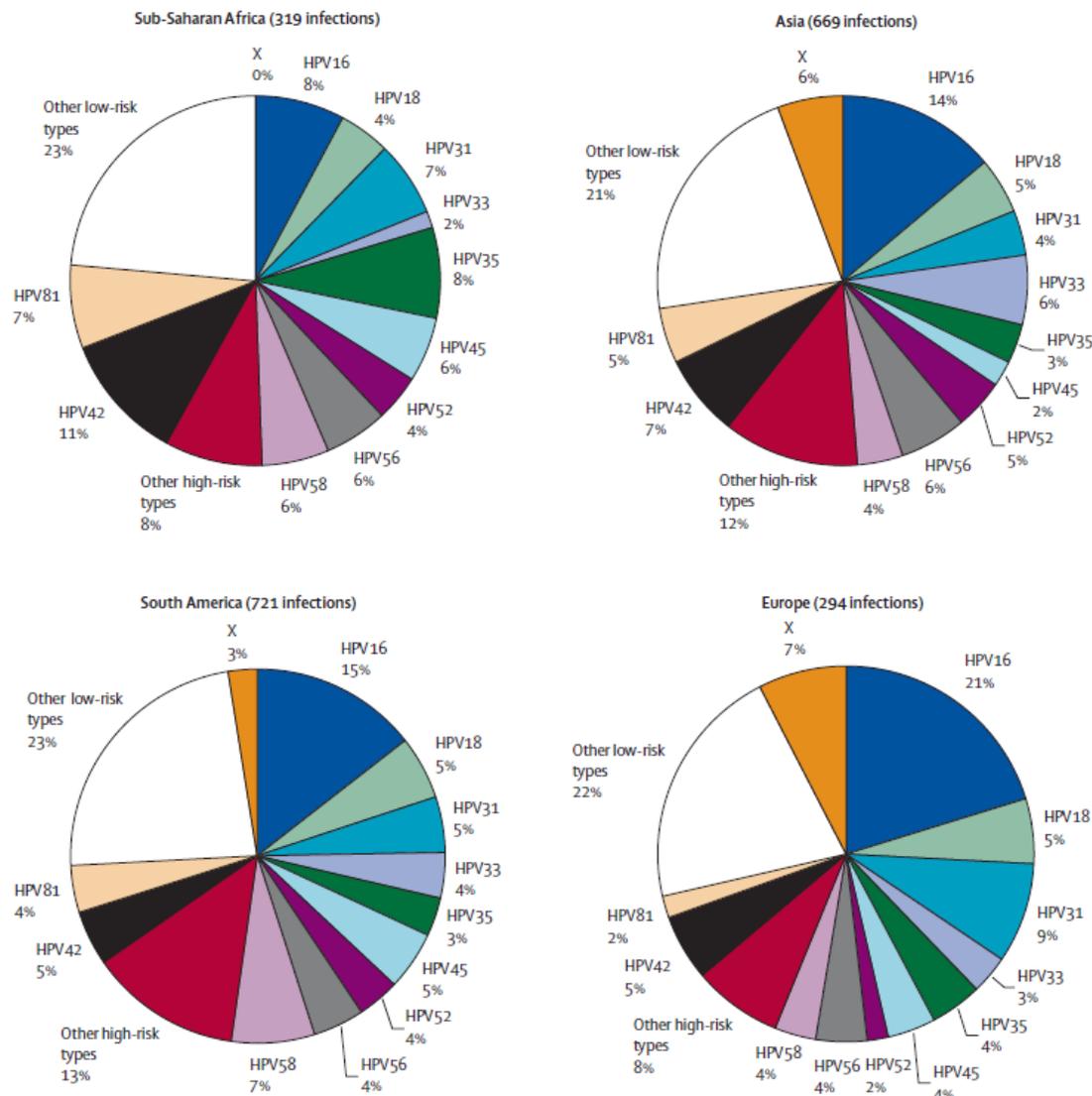


Figure 20 Infections by HPV type and region
 Source (Clifford et al., 2005: 4)

Nevertheless, this is a model of big numbers and the modelling is not based on individuals (Monte Carlo) but in a cohort simulation. Accordingly, risk is enacted and distributed in terms of populations, not in terms of individual perceptions and gambling. The different calculations done through the Markov chains model constitute a detailed portrayal of a collective entity, the population, which is the enactment that fits better into the state governance practices (Mackenzie 2014: 189).

Although the probabilities of transition from HPV infection to cervical lesions and cervical cancer are very small, they become important in terms of population and from an economic perspective. The results

of the modelling expressed in deaths avoided and DALYS avoided have important consequences in decision making and it is the kind of information that will travel from the model to public arenas as evidence. In this case, because of the aggregation of small probabilities and effects, small matters have important consequences in the constitution of the population as object of governance. In this framework, individual risk is reshaped and redistributed from the perspective of the population. The risk is not understood as a matter of individual chances but as an issue that affects the society as whole and therefore represents a threat for individual safety because the individual is part of the group. The population becomes the framework to understand the individual perception of risk.

However, not all the risks are rendered visible. Other risks remain absent in the modelling and in the experts and public narratives. Possibly the most dramatic case is the estimation of adverse effects from HPV vaccination. Although this is a contested issue and a matter of concern addressed by different publics, it is completely absent in the modelling and in the discussion about cost-effectiveness of HPV vaccines in Colombia. Whilst low probabilities and small numbers of disease progression are rendered visible, the probabilities of adverse effects are not taken into consideration in the simulated cohort. The intended invisibility of risks is a recurrent problem in the design of trials in the South (Sunder Rajan, 2007) an issue that became particularly visible in the controversy about deaths associated to HPV vaccines trials in India (Mattheij et al., 2012).

In that regard, analysts and health authorities have argued that adverse effects have such small probabilities that everyday risks represent a bigger threat. For them, any reference to adverse effect in numbers could undermine the trust in the vaccine. Paradoxically, legal and ethical requirements such as informed consent assume that adolescents and parents understand the risks and the benefits of vaccination and they can make a trade-off. Adverse effects' discussion seems proscribed from technical and policy making arenas, and it is even statistically and numerically absent. In the conclusion of this thesis, I reflect about these exclusions from calculation and about the possibility of thinking other ways of calculation, of caring with numbers (Haraway, 1997).

Exclusion: disentangling difference in calculation, re-enacting difference in the policy arena

The objective of modelling and simulating a cohort is to enact a consistent and trustworthy image of a population. In this simulation in particular, it means a representation of Colombian women. Modelling, by definition, implies simplification. The messiness, heterogeneity and diversity of the individuals constituting the entity known as the population are organised into categories and parameters. In this process of homogenisation, some features are rendered visible and constitute the elements that define the “identity” of this entity. Epstein (2007) has described the importance of these standards in the design of

medical and clinical research, in the licensing of medicaments and in healthcare regulation. Epstein argues that in the U.S. in the last 20 years a transformation of these standards has happened from a homogeneous human standard toward one that includes racial and gender diversity. He describes that change as a transformation in the inclusion paradigm (Epstein, 2007: 277).

The relation between the public discourses about HPV vaccination and the cohort modelled in technical reports shows a tension between these ‘paradigms’. As I presented in Chapter One, vaccination campaigns and public speeches about healthcare in Colombia are deeply framed in the recognition of multi-cultural and racial diversity that constitutes the ‘contemporary political identity of the country. In contrast, the cohort simulated in the Markov model is homogenous; it is just differentiated in terms of age. Other aspects such as geographic differences, socio-economic background and ethnicity/race are not taken into account in the modelling. Ageing classification is very important in the definition of parameters in the modelling—based on research data—probabilities of infection, transition and regression are assigned to specific age groups. The omission of other classification parameters has important consequences in the representativeness of the model. The problem of the dependance on one regional source to produce estimations on the whole country has been noted before by Colombian National Cancer Institute (INC) in relation to the calculation of national cancer incidence reported by Globocan and the Cali Register.

Because of the enormous geographical and socio-cultural heterogeneity of Colombia, the data from Cali’s Cancer Population Register are not representative of the country. This has generated the creation of new registers in other cities, which do not provide reliable and continuous information yet. In absence of data about incidence, the estimation from mortality figures has been recommended. This is the methodology used by the IARC and is published in Globocan. In spite of the quality and utility of the information of Globocan, this aggregation is very limited. It just presents information at national level, moreover it lacks specificity (INC, 2005: 7).

In the case of cost-effective analysis and Markov modelling, data and parameters depend heavily on Bogotá’s Cohort study (1997-2007). This was a longitudinal study developed by Colombian National Cancer Institute in Bogotá from 1997-2007. This research followed a cohort of 2.000 women during 10 years in order to detect incidence and prevalence of HPV infection, the types of virus involved and the transitions toward cervical lesions and cervical cancer. This study was supported by the IARC and constituted one of the local cases used in the assembling of a global epidemiological characterization of the relation HPV-cervical cancer. The last years of development of the Cohort study, were funded by Merck: the data and in particular the population recruited were part of stages III and IV of the RCT FUTURE (2008-2012).

This epidemiological research has contributed detailed information about the development of HPV infection to cervical cancer. Details about the recruited population are omitted in the journal articles that have communicated the results of the study. The cohort is enacted as an average aggregation of women which is representative of a general population. Nevertheless, in practice the recruited individuals come from very particular backgrounds, most of them are poor or marginalized women. As it is noted by one of the researchers of the Cohort study:

Initially, the study wanted to have people from different socio-economic backgrounds (strata) but at the end most women came from low socio-economical settings. The base group included 2.000 women (...) they were polled with a highly structured questionnaire about different factors: smoking habits, contraception, sexual behavior, nutritional habits, among others. The questionnaire was very structured because we wanted to treat with specificity factors associated with cervical cancer. Contraceptives were the emphasis **(Sr. researcher 3 INC)**.

As I presented in Chapter One, cervical cancer and social class have had a long relationship. Social difference has been considered as a risk factor or as an element that clusters other risks associated with the development of the disease. The risk factors traced by the questionnaire: smoking habits, contraception, sexual behavior and nutritional habits have been perceived as unhealthy in marginalized populations. However these risk factors gradually disappear from narratives and calculations of cervical cancer. HPV becomes the key factor to understand the development of the disease, erasing other factors, other relations. To the extent that risk factors were not a matter of concern, the cohort became more homogeneous in the Markov modelling and social difference disentangled from the calculation.

Paradoxically, the production of clinical trials and epidemiological studies in the Global south has depended on the recruitment of populations marked by poverty and exclusion. Clinical trials and cohort studies have constituted promises of healthcare for the populations whose bodies are the input in the production of data. Despite the claim that studies and clinical trials such as Bogotá Cohort and FUTURE (Females United to Unilaterally Reduce Endo/Ectocervical Disease) that the recruitment of population is based on raised consciousness and altruism; in practice data production is heavily supported by the promises of healthcare. In that regard one of the researchers from Bogotá's cohort points out:

May I be very clear: I think they never really understood the benefits of the vaccination, many of the participants really needed and wanted a doctor. The health system did not provide one, so we became the

doctors for them. We were their physician for everything... if I have an allergy, [family] planning... (**Sr. researcher 3 INC**).

Although risk factors are strongly entangled with difference, with many kinds of embodied and material difference, once the cohort is enacted, these issues are assumed to be secondary. The social entanglements that make possible the production of these data are perceived as mere accidents. For instance, the connections between the Bogotá Cohort and the trial FUTURE were the result of affective and familiar involvements between researchers and patients. The cohort study lasted 10 years, in which the recruitment was promoted from mothers to daughters. In an attempt to reach a more heterogeneous population, even researchers' and doctors' daughters participated in these studies:

In the institute we do not have access to high strata, except the daughters of the doctors, so we have in the study from stratum 1 to 6, we have daughters from colleagues that study in “Los Andes⁸⁸” and girls stratum 1, daughters or relatives of women from the original cohort. We know absolutely the socio-economical background of our patients because we need to know which kind of healthcare coverage they have. But it was not important for the recruitment (**Sr. researcher 2 INC**)

This effort to disentangle and make invisible social difference in calculation and modelling of cervical cancer and HPV infection in Colombia contrasts heavily with the public discourses about cervical cancer and vaccines. As I presented in Chapter One, HPV vaccines have been promoted as an intervention of equity; the government argues that the main benefits of vaccination will be felt by marginalized women in the future. Campaign materials such as videos and posters present a multiracial and diverse country of girls who are democratically protected by the vaccine. Moreover, pilot vaccination was developed in public schools in poor neighbourhoods in Bogotá.

However, beyond this contrast, public narratives and technical modelling are manifestations of a new regime of public health and healthcare governance in which pharmaceuticals are promoted as the privileged strategy of intervention. Despite the experts and policymakers perception about the connections between material conditions of living and the development of the disease, pharmaceutical technologies promise an immediate, simple and cost-effective solution to control maladies. Such policy disjuncture is nicely described by one of the advisors of the Ministry of Health involved in the Bogotá cohort epidemiological design:

⁸⁸ Universidad de los Andes is a private university in Colombia. Traditionally it has been perceived as an elite institution.

Personally, I have strongly argued that mortality for cervical cancer is an indicator of inequity in social and economic development. Countries with bigger social and economic inequity have a bigger mortality of cervical cancer. So when one introduces a technology such as vaccination, you will vaccinate the indigenous people, poor women... one will reduce the problem of cervical cancer, in 30 years we will see such reduction. I would prefer that the reduction of this indicator, I mean cervical cancer, were effectively done by improving the quality of life of women, the vaccine does not solve inequity. Probably many women will have just primary education, many will never finish...

(...) but if we vaccinate almost 100% of the population, as it has happened with other vaccines, we will eradicate the disease” (Sr. researcher 1 INC).

Conclusion

This chapter explored the implications of understanding natural history of cervical cancer as an assemblage. In this exploration I described many versions of this narrative that are present in scientific literature and technical studies about burden of the disease and cost-effectiveness of HPV vaccines. Moreover, I have completed this narrative by means of interviews with researchers involved in the production of these studies. As I have noted before, this group has been actively involved in the introduction of HPV vaccines in Colombia as advisors to the government.

First, I presented a molecularised narrative of this process which has been structured around the idea of causality, the recognition of HPV as the necessary cause of cervical cancer. In this part, I explored the ways in which causality is understood in technical and scientific literature and the role of systematic reviews in assembling causality. This narrative is the basis of the production of models and simulations on the development of the disease in the context of cost-effectiveness analysis.

Second, I introduced the Markov chains modelling as a calculation device. This statistical method is the tool that has made calculable and quantified the different stages of development of cervical cancer drawn in the natural history of the disease. Markov chains reshape the causal relation between HPV and cervical cancer introducing uncertainty expressed in terms of probability. As Hacking (1975) has noted, probability is Janus-faced. This means that probability at same time has been used to express the strength of beliefs and to note the “occurrence” of states in the world. The use of Markov chains in healthcare decision making shows both dimensions of probability. On the one hand, probability presents the uncertainty and the contingency in the development of the disease: HPV and cervical cancer are not connected by a mechanical link; the movement from infection to cancer depends on chance. The knowledge about this is highly uncertain. On the other hand, probability makes it possible to measure and to quantify such uncertainty. In that sense probability and probabilistic methods perform objectivity.

Third, these different elements were traced in the modelling of cost-effectiveness studies of the introduction of HPV vaccines in Colombia. Models and simulation have an important role in the production of scenarios for medical decision making. In this particular case, the simulation is regarded by experts and policymakers as a virtual trial, which produces evidence about the impact of different treatments in the prevention of cervical cancer. Many characteristics of systematic reviews (see Chapter Three) as devices of calculation are shared by the Markov modelling. In fact, modelling can be considered a systematic review reenacted in a temporal horizon. Markov chains simulation produces an “ideal” cohort of Colombian women. Such portrayal is an assemblage of data and parameters from different studies. These elements are harmonised through statistical methods to enact a coherent and sound representation of the women of the nation. The presentation of HPV vaccines as the ‘right tool’ (Clarke and Fujimura, 1992; Casper and Clarke, 1998) for preventing cervical cancer depends on the enactment of the cohort as representative of the epidemiological specificity of Colombian women.

STS has noted the ways in which standards produce realities and through such enactments generate difference and exclusion (Star and Bowker, 1999). Modelling enacts a homogeneous representation of Colombian women’s epidemiological profile which is socially undifferentiated. Such enactment contrasts heavily with the socio-material conditions of production of the data entangled and ordered through calculation. Social difference has been a key element in the generation of data about cervical cancer. Risk factors and criteria of selection of population have identified marginalised groups as special targets of research and policy intervention. The connections between research and healthcare services have encouraged the recruitment of populations with unmet healthcare needs.

Policymakers and analysts recognize the material and discursive connection between risk of developing cervical cancer and social exclusion. However, these considerations are excluded from calculations because they are seen as very complex to control and tame through quantification. Moreover, to disentangle social difference from disease produces the right scenario for introducing pharmaceuticals—in this case, vaccines—as the best healthcare alternative. Such disentanglement is supported by ‘practical’ considerations on the Colombian healthcare system and its limitations. As one of the INC experts noted: “it is easier to prevent cancer than to change inequity”.

After this analysis, the question about the possibility of doing other calculations, more humble and reflexive but still operative and useful for decision making, remains open. To some extent the Markov modelling developed by Universidad Nacional provides a illuminating account of contingencies and

complexities in the understanding of the relations between HPV, cervical cancer and vaccines that are taken for granted in policy and public arena. On the other hand, social difference can be reintroduced in this calculative space, even with the current limitation of data. For instance, in the model developed by Universidad Nacional (2011) a more open account of social difference could be generated without changing the current parameters and probabilities of transition for HPV infection. This calculation can be re-enacted by including differentiated rates of access to treatments by socio-economic background and region. This could have important changes in the estimations and make modelling more sensible to difference.

Chapter Six

Finding the right price for prevention

The price of pricelessness, HPV vaccines as commodities and gifts in Colombia

What is a cynic? A man who knows the price of everything and the value of nothing. Lord Darlington, Act III, Oscar Wilde, *Lady Windermere's Fan* (1892)

Introduction

Up to this point I have presented different devices of calculation integrated in the technical and political justification of HPV vaccines in Colombia. I have presented the role of systematic reviews in enacting evidence, of cost-effectiveness analysis and DALYs in enacting efficiency and the ways in which Markov modelling has enacted a homogenised portrayal of Colombian women. In this analysis, I have understood calculation as a process of constant disentanglement and re-entanglement of diverse objects and agents. Particular rules, spaces and devices are defined in calculation practices. Such configurations organise these elements and present them in the form of results. The primary objective of calculation is to produce results. As I have shown, what is considered a result can have different forms such as figures, maps, quantities, charts, diagrams, numbers and rates. These objects also become get involved in new entanglements and new practices of calculation.

The separation of practices and objects in modes of calculation is an analytic strategy; in reality such elements are deeply intertwined. Modelling, literature reviews, the calculation of burden of disease in DALYs, sensitivity analysis and micro-costing are different elements embedded in a wider process of demonstrating the value of HPV vaccines. As I have noted, I understand value in a pragmatist perspective (Dewey, 1939; Kjellberg and Mallard, 2013), in which what matters is the process of valuation, the practices defining a particular entity having as worth. All the technical and political narratives, public and media presentations, committee discussions and technical reports are part of the effort to make the value of HPV vaccines as public health strategy visible.

As valuation studies have pointed out, the relations between price and value are very important to understand the ways in which economic valuation interacts with other ways of enacting value (Kjellberg and Mallard, 2013). In the realm of healthcare practice and policymaking, this relation allows us to follow the ways in which some values such as health, wellbeing and care are enacted in contexts where financial sustainability and profit-making are required. The previous chapters have presented the practical limitations of using conventional prices to estimate the value of health, the quality of life and the costs of disease and death. Health currencies such as QALYs and DALYs and the ranges defined by probabilistic sensitivity analysis are attempts to produce metrics of value different to money. However, as I present in this chapter, such disentanglement of monetary units from other metrics is partial and momentary. Prices are constantly entangled in these calculations and constitute the privileged way of communicating to the ‘public’ the value of health interventions.

Calculations and interactions based on prices are the best known characteristic of markets. Partially as result of different political reforms, as described in Chapter One, policymakers have developed an understanding of healthcare based on the market. The market offers a repertoire of concepts and practices of calculation to define healthcare in terms of goods and services. Different attempts to establish healthcare as a market and the emphasis in user choice have been described by various scholars (Armstrong and Caldwell, 2004; Mol, 2008; Moreira, 2012a) as its marketization. This chapter is an exploration of the performativity of prices and pricing practices. In other words, I want to explore the nature of pricing as a practice of calculation, the entanglements that are entailed and pricing’s role in the configuration of particular socio-technical relations around vaccines and healthcare.

In this chapter I present an analysis of this process in Colombia through following the constitution of HPV vaccines as a good. In the previous chapters I have presented a set of practices of calculation around HPV vaccines in which they are considered primarily as a healthcare technology and a public health intervention. The agent that has developed such practices of calculation and valuation is the Colombian State, which is a multiple and heterogeneous actor that encompasses a blurry set of institutions and actors: technical committees, consultants and decision makers among others. In the case of pricing the calculative agents are pharmaceutical companies. This chapter is an attempt to constitute pharmaceutical companies as agents. As I show in this chapter, such characterisation has not been an easy task.

Pharmaceutical companies are not very transparent in relation to the practices that they use to define the price of their products. Indeed, in 2014 there was great controversy about the price of pharmaceuticals in

Colombia. The Colombian Ministry of Health introduced price control for priority medicines after comparing international prices and finding that prices in Colombia are substantially higher than in other countries of the region, even higher than in developed countries. For instance, some drugs such as Ciprofloxacin cost 4 times more than in China (Perspectiva, 6th August 2013). In 2012-2014 I tried to establish contact with technical staff from Merck and Glaxo Smith Kline to ask about practices of pricing of HPV vaccines in Colombia. However, it was not possible. I was constantly remitted to communications and external relations departments which provided general information about the vaccine and the relationship with the Colombian government. Accordingly I have reconstituted pricing practices through other sources such as scientific conferences (HPV International Conference, San Juan, Puerto Rico 2012; ISPOR Conference), literature reviews (*Nature reviews*), pharmaceutical business magazines (e.g. *Forbes*, *Pharmainnovation*, *Fierce Vaccines*, *The New Street Journal*), company websites and interviews with the National Committee of Immunisation Practices (NCIP).

In what follows I analyse the ways in which pharmaceutical companies have enacted relations between price and value in the case of HPV vaccines in Colombia. Firstly I present the use of pharmacoeconomics in the calculation of prices of pharmaceuticals. In particular I describe the negotiation and practices involved in the definition of vaccines' prices. Price has been presented as a key element in the movement of vaccines across countries and regions, as well as a factor that produces health gaps and exclusion. As Çalışkan and Callon have noted. "prices are estimated quantifications and therefore imply the mobilization of calculation tools. As such, they are at the heart of agents' struggles to produce asymmetries in the distribution of value" (2010: 17). Debates and practices of pricing offer a unique opportunity to trace the role of quantification and calculation in the demonstrations of value that different agents undertake.

Secondly, I explore the role of price in enacting the value of HPV vaccines. Although primarily used as a measurement of economic value, HPV vaccines' price becomes a visible manifestation of other values beyond economic valuation, such as parental care and social distribution. It becomes a comparison unit to estimate the compromise and engagement of parents with their daughters and of the State with its female citizens. I present the role of advertisements in communicating and producing the values of HPV vaccines. Pharmaceutical companies' explicit presence in public and policy arenas has been done through "awareness" campaigns and advertising. Pharmaceutical companies have developed information campaigns to raise awareness of particular diseases, encouraging the public to search for information about particular 'cures' (Dumit, 2012). In this chapter I describe such campaigns and explore the ways in which these narratives are entangled with public decision making in Colombia. In awareness campaigns

within healthcare markets, vaccines are enacted both as consumption goods (commodities) and gifts. An analysis of gift economies allows us to understand the ways in which vaccines are enacted as affirmative interventions of the State and proofs of parental care.

Prices, valorimeters, calculation and the constitution of markets

Contemporary healthcare governance has been shaped by models of organisation inspired in the market (Moreira, 2012a, Mol, 2008). However, at least in STS literature, market influence has been understood in a variety of ways. Some authors such as Moreira (2012a), Epstein (2007) and Armstrong and Caldwell (2004) have emphasised the role of quantification and calculation practices from Management Science in the shaping of healthcare decision making. On the other hand, authors as Mol (2008), Timmermans and Berg (2003) have associated the market with the rise of the logic of choice; that is with a model of healthcare based on the understanding of the patient as a rational and informed actor that should choose the best care alternative according to a diverse and competitive supply of goods and services. Although these are all fundamental elements in understanding the interference of market narratives and practices in the contemporary configurations of healthcare governance, it is also important to characterise the concrete practices and narratives that correspond with the establishment of markets, in terms of their interactions and material settings.

The anthropology of markets—an extension of STS approaches to study economies, finance and markets—has developed a set of concepts that help to characterise markets and more importantly to identify the process of a market's constitution (Çalışkan and Callon, 2009; 2010). Çalışkan and Callon (2009) propose a set of problems and concepts to understand the ways in which markets are configured as socio-technical assemblages. These elements are: 1. pacifying goods; 2. marketizing agencies; 3. market encounters; 4. price-setting; and 5. market design and maintenance (Çalışkan and Callon, 2009: 5). These elements, they argue, provide a set of empirical problems and concepts to trace the complexities of markets' interactions.

Some interventions of the State can be considered marketised processes. Particular processes involved in the introduction of HPV vaccines could be an example: cost-effectiveness analysis, committee meetings, and Panamerican Health Organisation consultations can be thought as parts of the process of buying a particular good (in this case: HPV vaccines). To the extent that health technologies are considered a good, the calculation practices and exchanges between agents can be characterised as a market. As Çalışkan and Callon have noted, “markets are not possible without generating and then reproducing a stark distinction between the ‘things’ to be valued and the ‘agencies’ capable of valuing them. Two basic types of entities

result: “entities with pacified agency that can be transferred as property, and entities that are able to engage in operations of calculation and judgment” (Çalışkan and Callon, 2009: 6).

Prices and price settings are important elements in the definition of markets that have usually been taken for granted in the analysis of healthcare practices and governance. Çalışkan and Callon (2009) have noted that “The existence of a market implies that the valuations, and the calculations that produce them, come out in the form of prices” (2009:17). Prices and costs⁸⁹ are very important elements in the calculations and valuations that the committee of immunisations—on behalf of the Colombian government—and pharmaceuticals do. In the case of the pharmaceutical industry, strategies to enact value through price can be traced to the discipline of pharmaco-economics. On the other hand, as I have previously shown, cost-effectiveness analysis is a good example of calculations and valuations made by the Colombian state.

Çalışkan and Callon (2009) have suggested the term valorimeters to denote “tools, procedures, machines, instruments or, more generally, devices effecting this controversial translation of values into figures and, more precisely, into monetary amounts” (Çalışkan and Callon, 2010: 17). Devices such as DALYs, CEA, Markov chain simulation, and micro-costing can be understood as valorimeters. These entangle different objects in order to enact evidence, effectiveness and statistical representativeness and they present such enactments as numbers, figures and monetary amounts. Valorimeters also work in the opposite direction; not only translating monetary amounts and prices into quality of life and efficiency metrics but also as issues of emotions and moral economy. Nevertheless, as committee minutes, regulations and official documents show, monetary amounts are the privileged way of presenting the result of these calculations and therefore the most common form of communicating value.

⁸⁹ Regarding the difference between price and cost, these ideas can be useful. “Cost is simply what it takes, in terms of dollars or resources, to produce a particular product or service. So let's say we're looking at a restaurant meal. You look at the cost of the food that goes into that restaurant meal, the labour, maybe some piece of the building and the kitchen equipment and so forth, so basically, what the costs of the inputs are that go into making that restaurant meal. Now, price, on the other hand, some would say, 'Well, price should be the same as cost.' But not necessarily, price is simply what someone is willing to pay for that product or service. So price is really more of a demand or consumer phenomenon, whereas cost comes from the supplier. And so, for example, the price of that restaurant meal would be the price that the owner thinks that he or she can sell it at and is posted on the menu, and the owner will see if that's the right price by how many people are willing to come into the restaurant and pay for it. Now, usually price is greater than cost. That's what gives a business a profit. But it's not always the case. Sometimes price is less than cost, and we're seeing that right now in our down economy, for example. Some real estate is selling at a much lower price than what the cost of that real estate is, and that's a signal to the business to change things, to get out of that business or perhaps try to become more efficient and produce things at a lower cost” (Walden, 2008).

The value expressed in these entanglements is much more complex than that considered by neoclassical economics when it understands the relation price-value as willingness to pay and equilibrium between demand and supply. Economic anthropology (Mauss, 1954; Douglas, 1992; Parry and Bloch, 1989; Abolafia, 1998; Zelizer, 1998, Hénaff, 2010) has shown the ways in which price and price setting are attached to moral dynamics and mediate political and symbolic relations deeply entangled within “economic” exchanges. Although this research has focused on ‘traditional’ and indigenous communities, it is possible to follow such entanglements in more contemporary and “rationalised” settings (Çalışkan and Callon, 2009). For instance, the problem of price opens up discussion about the distinction between (public or common) Good and goods. That is the differentiation between things that are individually consumed (goods) and things that enact the society’s benefit (Good), and between commodities (things with prices) and gifts (altruistic objects) (Waldby and Mitchell, 2006).

HPV vaccines are goods whose inclusion in public healthcare programmes has involved their enactment as public Good. The modes of calculation that I have presented in previous chapters are part of the different socio-technical arrangements that make possible such “transformation”. The definition of prices for HPV vaccines is one of these arrangements for producing them as matters of concern. On the other hand, pricing in the context of public policy and state interventions renders visible the boundaries and the problems that a radical distinction between market and public sector entails. From the perspective of pharmaceutical companies, the public sector is characterised as a market and different strategies of marketing and production-communication of value are developed for these companies to address the particularities that the public sector market involves. Furthermore, prices are performative; they affect the practices and considerations of the agents that are engaged in producing them. Prices, moreover, can be addressed as quantified qualifications of different values; however, such character is performed in practice, in the particular and local settings in which valuations happen.

In what follows I describe some problems that the pricing of HPV vaccines opens up in relation to the valuation and shaping of healthcare markets. As Sjögren and Helgesson have noted, in markets pricing is a central activity in which the qualities of goods are settled and who should pay which price for what is decided (Sjögren and Helgesson, 2007: 215). Following Çalışkan and Callon’s (2010) suggestions to understand marketization,⁹⁰ I will present some elements that allow the identification of the interactions between pharmaceutical companies and governments as a market performance.

⁹⁰ Although Çalışkan and Callon have titled their installment of two papers *Economisation* (2009, 2010), they present a set of concepts to understand the production of markets. *Marketisation* can be addressed as a process of “economisation”, that is as a process in which practices and narratives from economics is used to enact a particular representation of social and natural reality. Markets are a particular set of practice within such universe.

In this chapter, pharmaceutical companies are the protagonists. I describe the ways in which they interfere in the process of introducing HPV vaccines in Colombia, mainly through the definition of prices and the production of information about their products. This part is focused on the pricing methodology, the role of pharmaco-economics as a practice of calculation in the strategic appropriation of evidence based medicine (narratives and practices) that pharmaceutical companies have undertaken to enhance the value of their products. In the second part of this chapter, I explore the performative effects of pricing in the multiple enactments of HPV vaccines as a public Good, commodities and gifts. I will present the consequences of these entanglements in the reconstitution of the State, parents, girls, doctors and companies as calculative agents engaged in markets.

Market, exchange and the constitution of agencies

There are at least two kinds of entities that are able “to engage in operations of calculation and judgment” (Çalışkan and Callon, 2010: 6): producers and buyers. Both develop their own dynamics of valuation of the goods in question. The producers in this case are the pharmaceutical companies (Merck and GSK); in contrast, the set of buyers is more diverse: individual consumers (families), health organisations and national healthcare authorities. HPV vaccines once licensed have been marketed for individual consumption; they can be bought in some countries through healthcare providers and pharmacies. For example, in Colombia Gardasil was advertised as the best “gift” that parents could give their teenage daughters. However, the main buyers of HPV vaccines are the different national healthcare authorities. Different countries have considered the introduction of these vaccines into their healthcare plans of services or into their programmes of immunisation. All these different agents have to develop calculation and valuation strategies in order to make and legitimate decisions about vaccines’ worth.

In general, the analysis of cost-effectiveness of healthcare interventions—such as vaccines—is done from ‘a societal perspective’ or ‘third-party payer’; this means that such interventions are considered valuable from the perspective of the *society* as an actor. However, as I have presented previously, the society is a very general and abstract actor to be capable of operating. The voice of the society is assumed by the State and—within its multiplicity—by technical organisations, in the UK, for instance, by the Joint Committee on Vaccination and Immunisation (JCVI), which is part of the Department of Health. In Colombia such decisions are delegated to the National Committee of Immunisation practices (NCIP) by the Ministry of Health.

In contrast, constituting the pharmaceutical industry as an agent in the production of value and in the enactment of markets has been a much harder task. Big pharma are multinational companies with

complex governance and a highly segmented division of labour. It is hard to determine the degree of autonomy between local and national branches regarding international headquarters decisions (Mirowski, 2011, Abraham, 2008). Furthermore, most of pharmaceutical companies' interactions with governments and regulatory authorities are highly mediated by other organisations such as independent laboratories, universities, hospitals and consultant companies. For instance, although clinical trials are funded by pharmaceutical companies, their development is done by universities, hospitals, research centres and smaller companies. As organisations, pharmaceutical companies can act beyond their "organisational" boundaries through trials, scientific papers, professional associations, conferences and even patients' organisations (Moreira, 2012b). This extended network allows them to present and promote their estimation of value as the result of the work of independent agents.

In my research, reconstituting pharmaceuticals as agents has been a challenge that had involved assembling different objects, texts and actors. The traditional method of interviewing the social actors "behind" these interactions has not been possible. First, at least in Colombia, there is some lack of trust; pharmaceuticals' staff suspect that social researchers are looking for mistakes and "bad" practices. That situation has made arranging face-to-face interviews very difficult. On the other hand, the interaction of Big Pharma with government agencies is so diverse, complex, mediated and dispersed that the account of pharmaceutical staff is just one of the different voices that can tell stories about these practices of valuation.

Çalışkan and Callon have noted that market encounters are the material spaces where exchange and interchange between agencies happen. In the market, valuation is a dialogue, a dialectic dynamic between different calculations and estimations. In the case of government valuation and acquisition of particular goods such encounters are highly mediated and fragmented among many actors and spaces. For different reasons (many of them legal) direct interactions between governments and pharmaceutical companies to negotiate and define the value of medicines and healthcare technologies are very rare. Often such interactions are mediated by international organisations, scientific institutions and political lobbying.

In Latin America, for instance, vaccines are acquired through the technical and bureaucratic support of PAHO (Pan-American Health Organisation). A mechanism called the PAHO Revolving Fund consolidates all the purchases of vaccines and syringes from the member states. Through the Revolving Fund, PAHO issues an Invitation to Bid (ITB) consolidating demand from the participating Member States. The ITB specifies quantities of vaccines, syringes, and related supplies and gives directions about quality characteristics, presentations, and conditions required by PAHO. The ITB is sent to producers, inviting

them to submit a bid that meets the estimated demand. Following the deadline for the close of bidding, the bids are opened and disclosed in the presence of the participating bidders. Based on, among other things, the lowest price, the quantity offered, and the producer's quality and service record, producers are selected to cover the estimated demand that has been calculated. To guarantee the supply, PAHO assigns at least two producers, whenever possible, to cover the demand calculated for each product (PAHO, 2013: 4)

ITB is the end stage of a complex and long process of decision making and valuation of the acquired good, in this case vaccines. When a government makes an official request to the Revolving Fund, the decision to introduce the vaccines has already been made. Price, quantities and a line item in the national budget for the procurement of this good have already been defined. The encounters between the main agents involved in this valuation process (governments and pharma) are distributed in material spaces such as committee meetings, international summits (e.g. GAVI Alliance and pharmaceutical industry meetings), informative presentations, media advertising, academic conferences and political lobbying.

As I have presented in Chapter Three, the committee of immunisations at different moments discussed the possibility of introducing these vaccines into the Expanded Programme of Immunisation (PAI). Committee members had participated in different international conferences where these technologies were presented by pharmaceutical researchers and staff. Some of them had even been speakers for pharmaceutical companies presenting technical information to practitioners and healthcare professionals. The speakers are well-known researchers and practitioners who are hired by pharmaceutical companies to present technical information about particular diseases, showing new drugs and treatments related to the supply of the company.

Committee members have noted in interviews that speakers are key actors in making cervical cancer visible as a public concern and in presenting HPV vaccines as an effective solution. Particularly for regional healthcare authorities, pharmaceutical companies are the most direct source of technical information. Some of them, noted that speakers have met politicians' wives to promote a wider awareness among decision makers about the importance of cervical cancer and the urgency of introducing new vaccines. As one of the members of NCIP states:

Well, we made a study with Dr. X and Dr Y to evaluate the activities for the control of cervical cancer. The study started in 2005; at that time nobody talked about the vaccine yet. When we talked with local and departmental decision makers, cervical cancer was not a public health priority for them. It was considered

below the importance of maternal mortality and adolescent pregnancy. Even HIV was considered more important than cervical cancer. After, we made other study—I think it was around 2009—and we interviewed decision makers again. Then we found that cervical cancer was considered a priority. Local health authorities had decided to buy vaccines; they started to invest money in immunization. Obviously, because of the high cost of the vaccine they decided to immunize populations at risk. For us such strategy was not the most appropriate; we thought it was a misunderstanding of the idea of being at risk. For instance, they considered the daughters of prostitutes as a population at risk. Such program not only stigmatized these girls, it also did not guarantee its sustainability or equity.

(...) So through that work, we realized that the pharmaceutical industry was the most direct influence in local decision making⁹¹. Pharmaceuticals contacted the wives of decision makers who adopted vaccination as their political “battle flag” and to that extent more money and resources were invested. We were very concerned about the use of resources in such a limited vaccination program. Pharmaceutical industry has had a key role in the development of these programmes (**NCIP Committee member 8**).

In what follows I describe pricing and calculation strategies developed by pharmaceuticals to interact with their “customers”: government and patients. In interacting with governments and public agencies, pharmaceutical companies have appropriated the language and practices of evidence based medicine. They argue that pricing is turning toward evidence and value. Pharma-economics is providing a set of methods to understand the ways in which “payers” value therapeutic advances, and what evidence they require to demonstrate those advances (Gregson et al., 2005: 126).

Pricing and calculation strategies: Pharmaco-economics and value based pricing

An emphasis on HPV vaccines as promising medicines and anticipated treatments has rendered invisible their character as manufactured products, designed goods for particular markets and objects that should generate profits. Vaccines’ molecular technology was developed to produce immune response against HPV types predominant in the most attractive markets: Western Europe and North America. As I presented in the previous chapter, HPV 16 and 18 are the most prevalent high risk HPV types in these regions (Clifford et al., 2005: 4).

⁹¹ In relation to informative campaigns, “speakers” are very important actors. Usually, they are well recognised doctors and researchers that are hired by the companies for presenting to medical associations, patients’ organisations, and policymakers, among others information about particular diseases and “innovations” for their treatment. Finally, big companies usually have communication departments that are the “voice” of the company. There are official spokespersons whose mission is to deal with press, NGO’s and organisations that want to know about the company. Big pharma have been the target of critique by different organisations and in general pharmaceutical development has become a very controversial issue, thus communications management has become highly controlled in many companies.

Both vaccines were produced around cervical cancer prevention. Nevertheless, whilst Cervarix only protects against HPV 16 and 18, Gardasil was designed to prevent infection of HPV 16, 18, 6 and 11. Gardasil claims to produce protection against cervical cancer and genital warts. This strategy of differentiation has had important consequences in the rise of genital warts as a public health concern. In one magazine about pharmaceutical innovation, Merck is praised for the design of Gardasil: its design has had an important impact in its appreciation expressed in cost-effectiveness and in its competitiveness against alternatives on the market.

The solution was a to develop a quadrivalent vaccine—literally, four vaccines in one—that targeted four dangerous or nasty HPV strains: HPV 16 and 18, which cause 70 percent of all cervical cancers, and HPV 6 and 11, which cause 90 percent of all genital warts. A vaccine against the former, it was believed, would greatly enhance the vaccine’s appeal to the public and, thus, the take-up rate. Genital warts are a painful and an especially embarrassing condition that is quite common. Nor are they inconspicuous to partners. There was also an unintended consequence: the choice of a quadrivalent vaccine also enhanced its cost-effectiveness, since the cost of treating genital warts, which often requires three or four treatments, is very high⁹² (Innovation, 2009⁹³).

Price has been presented by policymakers and global health scholars as a key element in the movement of healthcare technologies—in particular vaccines—across countries and regions, as well as a factor that produces access gaps and social exclusion. Within this framework price is enacted as a tension between demand and supply; the point of view of the consumer and the point of view of the producer. The pricing of medicines summarizes the process of attributing value of pharmaceutical products. It is a complex task which entails gathering different types of data and, more importantly, representing the expectancies of potential customers.

In that regard, considerations about health and medicine as a public good and the interest of the industry in producing profits have often clashed. As I have noted in Chapter Three, the rise of evidence based medicine has been linked to the promise of providing calculative tools to defend public interest from the profit interest of companies. In response, pharmaceutical companies have assimilated the language and

⁹² Although, in principle the interest of healthcare authorities and governments in these vaccines was based in their promise of prevention against cervical cancer and genital warts were considered in the most cases as a bonus; genital warts became a decisive factor in the selection of Gardasil as vaccine for national vaccination programmes. For instance, in 2012 the Department of Health (United Kingdom) changed from Cervarix to Gardasil, after a discussion about the burden of genital warts and its costs of treatment (Department of Health, Reference: 16896). In the Colombian case, as I have shown in previous chapters, genital warts were a key element in the choice and justification of Gardasil as public health tool. All these elements are taken into account in the calculation of introduction prices made by pharmaceutical companies.

⁹³ http://www.innovation.org/index.cfm/StoriesofInnovation/InnovatorStories/The_Story_of_Gardasil

the practices of calculation of EBM as a reaction to its use by governments and healthcare authorities. Pharmaco-economics can be understood as a response of the pharmaceutical industry to changes in healthcare decision making; in particular regarding the introduction of cost-effectiveness and price control. As noted by one of the members of Committee of Immunisations in Colombia:

The industry has developed many studies in the field of economical evaluation on cancer medicines (...) One often sees these works in congresses and conferences, those are cost-effectiveness analysis of cancer treatments. The companies intensively use health economics to support their valuation of medicines in negotiations with the government (**NCIP Committee member 4**).

A good example of the adaptation of pharmaceutical companies to EBM is presented in a special issue of *Nature Reviews* devoted to Drug Discovery (Vol 4, No 2; February 2005). This issue gathers different ways in which pharmaceutical industry faces changes in regulation, intellectual property, safety control, innovation economics, media perception and evidence based policy. One of these papers (Gregson et al., 2005) offers a synthesis of pharmaco-economics' approaches to pricing, which the authors call value-based pricing. For them, the pricing of health technologies is moving from cost-based pricing to value-based approaches. From a market perspective, value (V) is equal to reference price (R) plus/minus differential value (D):

$$V=R+/-D$$

As is noted by Gregson and colleagues (2005), "the appeal of this simple framework is that it intuitively fits with how we, as consumers and 'purchase decision-makers', evaluate price as part of purchase decisions, whether consciously or subconsciously" (Gregson et al., 2005: 122). They argue that the fundamental pricing question has shifted from 'What price do we need to charge to cover our costs and make a good return?' to 'Given market perceptions of value, which products can we profitably produce?' (Gregson et al., 2005: 122).

Reference price and commensurability

This pricing equation simplifies a complex assemblage in which each element can be opened up and also understood as an assemblage. The starting point of the calculation strategy depicted by Gregson and colleagues is to define reference price. They argue the reference product is generally the present standard of care. In principle this supposes a perception of technological progress between drugs. Product X is better than Product Y in dealing with a particular condition. The price of Y is the reference price to define

the price of X. However, most often such comparisons are not so direct; many medicines claim to be pioneers in the treatment of particular diseases and therefore there is not a previous technology of reference. More importantly through the definition of standards of care medical technologies produce the disease and the populations that they target (Dumit, 2012).

In the case of HPV vaccines, Gardasil and Cervarix were developed almost at the same time and have been considered as reference good defining each other. On the other hand, both have offered a different solution to HPV infection treatment and cervical cancer prevention. In relation to cervical cancer the standard of care encompasses a heterogeneous set of treatments and technologies such as national cervical screening programmes (CSP), radiation, surgery and chemotherapy depending on the stage of the disease. HPV vaccines promise a simplified new standard of care based on immunisation and control of HPV infection.

HPV vaccines fundamentally change the frames of cervical cancer prevention and care. From the perspective of CSP, cervical cancer prevention's success depends on following each woman as a particular case. In contrast, vaccines shape prevention in terms of populations and epidemiological concepts; Cervical cancer is understood in terms of the impact that the disease has on a population's dynamic described in morbidity, mortality and burden of disease. These are key elements in the definition of a reference price. As is noted by a Merck spokesperson in an interview in the popular science publication *Discovery Magazine* (2007):

We based the price on a number of factors, most importantly the value Gardasil brings to individuals and society," says Jennifer Allen, a spokesperson for Merck. "HPV-related diseases cost the U.S. health care system about \$5 billion every year, and we took that into consideration (Discovery Magazine, 2007).

In the case of Gardasil, Merck calculated the price based on the money the vaccine could save the entire health-care system. Merck's spokesperson points out that price enacts value, understood in this case as the contribution of this technology to society. These are the same calculations that are done by technical committees and government agencies in order to define the cost-effectiveness of this healthcare intervention. Nevertheless, reference value is just one the factors used to define vaccine price. In the case of the Colombian Committee of Immunisation's decision, the cost-effectiveness analysis made by Universidad Nacional (2009-2011) is based on estimation of cervical cancer treatments costs in Latin America developed by PAHO and the Sabin Institute (PAHO, 2008). PAHO study gathers data about the costs of surgeries, cervical screening programmes and medicines in Argentina, Brazil, Chile, Colombia,

Mexico, and Peru. This study constitutes the only source to estimate the cost of treatments in the region. It translates the different costs linked to cervical cancer detection and treatment into international dollars (I\$), an analytic currency recommended by WHO to establish international comparison between healthcare procedures.

Based on available data for six countries, the total direct medical cost per case for screening ranged from I\$10 to I\$81 per woman and from I\$534 to I\$1,402 per woman for treatment of precancerous lesions. Highest screening costs occurred in Argentina, and highest treatment costs occurred in Brazil. These costs were mainly attributed to the cost of specialist consultation (in the case of screening) and hospital stay (in the case of treating precancerous lesions). The cost of cervical cancer treatment was much higher than precancerous lesion treatment and ranged from I\$3,745 (Peru) to I\$14,438 (Argentina) per woman, with highest costs for more advanced stages of cervical cancer. The majority of this treatment cost was attributed to the costs of hospital stay and palliative care (PAHO, 2008: 9).

The other factor in the definition of prices is the differential value. Such value is estimated through a mixture of data which justify clinical, economic and quality-of-life “improvements”. The finality of such calculations is to demonstrate the additional value that the new technology entails. Within evidence based medicine, clinical trials (particularly Phase III pivotal trials) are the primary means of demonstrating such differential value (Gregson et al., 2005: 125).

Pharmaco-economics has provided pharmaceutical companies with a methodological framework to quantify and legitimise the economic value of a new product compared to other therapies and healthcare standards. Gregson and colleagues argue that pharmaco-economics, properly applied, is a tool that incorporates value-based pricing and provides a reference point for quantifying the differential value of a new pharmaceutical (Gregson et al., 2005: 125). As I have noted earlier, this approach incorporates “evidence based” practices and narratives in order to define the value of a healthcare technology. “For a drug-value analysis, changes in health outcomes are most commonly measured in changes of quality-adjusted life years (QALYs), which are computed on the basis of the level of well-being in alternative health states and the duration of time in each alternative health state, both with and without the new drug” (Gregson et al., 2005: 125).

In the case of HPV vaccines the differential value has been based on estimations about the cost of innovation, the saving that vaccines represent to society (money, lives and quality of life) and the added value of prevention in relation to cure (it is better prevent cancer than cure it). In the case of Gardasil, for instance, Merck spokespersons have pointed out that Gardasil took more than 20 years to develop and the

molecular technology: the virus-like particle (VLP) is an innovation from the perspective of vaccines' development. According to Allen, Merck's spokesperson, the company calculated the price based on both the cost of R&D and what the vaccine could save in HPV-related treatment costs, which she estimated at \$5 billion per year for the four strains targeted by the vaccine (McGee, 2007).

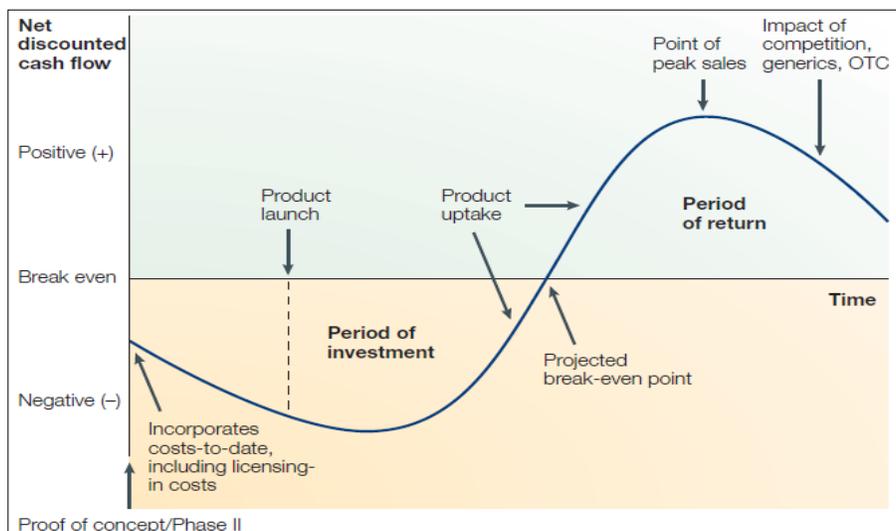


Figure 21 A hypothetical cash-flow curve for a pharmaceutical product (Gregson et al., 2005: 127).

As Gregson and colleagues have noted, “in parallel with the identification-production of the ‘social’ value of the healthcare technology and its translation in price (money); the pharmaceutical company has its own claims regarding the minimum price in relation to Research and Development costs and profit” (Gregson et al., 2005: 127). Pharmaceutical companies calculate the cost of development adding a set of investments and expenditures such as preclinical costs, clinical development costs, stability testing and manufacturing scale-up costs, the costs of goods produced and marketing costs (Fisher and Ronald, 2010). The companies emphasise that in general, “for every 5,000 molecules that are tested in the laboratory, only 5 reach Phase I and only 1 will actually be marketed” (Gregson et al., 2005: 127). These considerations around pricing from the perspective of company costs, investments and profits are rendered as a cash-flow curve (Figure 21). “A long initial period of negative cash flow is typical, a high gross margin is required to recoup, and provide a return on, this investment, OTC, over the counter” (Gregson et al., 2005: 127).

The impact of evidence based medicine devices of calculation in marketing and R&D of pharmaceutical companies can be traced in the rise of consultant companies such as Pricerspective⁹⁴ and ICON⁹⁵ which

⁹⁴ <http://pricespective.com/>

specialise in the development of cost-effectiveness analysis as a source to determine the price of drugs for regional and national markets. These companies argue that pharmaco-economics analysis is a decisive factor in the success of pharmaceuticals within the contemporary framework of healthcare governance⁹⁶.

Price fairness

Possibly the most interesting case to follow the ways in which these calculation are performed is the debate about the fair price of medicines. In recent times the pricing of medicines has become one of the most debated topics in different countries around the world; the pharmaceutical industry profits have been the main target of this controversy (Danzon et al., 2011: 532). In Colombia, the current Minister of Health Alejandro Gaviria has argued for better control and regulation of prices of pharmaceuticals in the country. In 2013 the government introduced a system of control of prices for 334 medicines and created a technical commission to define and follow their introduction⁹⁷. In the case of vaccines, according to the vaccines' news portal *Fierce Vaccines*, over the past 10 years the cost that countries should pay to buy the main recommended vaccines grew from less than \$1.50 to nearly \$40. Rotavirus and pneumococcal vaccines make up 74% of the total cost to vaccinate a child (*Fierce Vaccines*, 2013).

In the case of HPV vaccines the price of introduction defined by the pharmaceutical companies was highly contested. This controversy developed mainly around Gardasil, in part because it was the first HPV vaccine that entered the market. This vaccine requires three doses, and the private market price was initially US\$ 120 per dose (Nguyen et al., 2011: 2). In an article published in the popular science magazine *The Scientist*, the journalist Gleen McGee discussed the difference between the costs attributed to Gardasil's R&D and the sales and profits of Merck during the first year:

Merck dedicated more than 20 years to Gardasil, and a 1998 report estimated that companies spend \$250 million developing a vaccine. Merck sold \$365 million worth of the vaccine in the first quarter of 2007, and that's before some states have mandated it for all young girls, something many are considering. To that end, Merck lobbies the offices of governors and other legislators, arguing that Gardasil saves regions money by reducing the long-term cost of treating HPV-related illnesses. In short, pay now, save later (McGee, 2007).

⁹⁵ <http://www.iconplc.com/services/late-phase/>

⁹⁶ For instance, in a paper presented in the ISPOR 16th Annual International Meeting by a group of consultant of Pricespective London (Oshinowo, Ng-Haing and Grosvenor, 2011), they attribute the success of HPV vaccines to the capacity of companies to translate the value of the vaccine into the priorities of decision makers. For them, cost-effectiveness is not enough to guarantee the success of a medicine, such cost-effectiveness should be translated in value for the society (e.g. herd immunity) and it should be supported by the lobby of stakeholders.

⁹⁷ <http://www.minsalud.gov.co/salud/Paginas/sistema-informacion-precios-medicamentos.aspx>

As Çalışkan and Callon have noted, “the actors themselves directly link the question of the fairness of prices to the content and construction of formulas serving to calculate them: it is not the prices that are fair or unfair, but their modalities of calculation, i.e. their formulas” (Çalışkan and Callon, 2010:18). In this particular case, the journalist shows that the difference between the costs of 20 year R&D and the sum of just one year of sales does not reflect the pricing curve symmetry between costs and profits. Other element that is present in this controversy is the clash of valuation perspectives regarding the same goods: at the same time HPV vaccines are presented as a public good (in terms of population health) and as an investment. A good that should generate profits for the company and investors. The encounter between these different valuations makes medicines and drugs price a contested issue. This asymmetry and tension is noted by the McGee, when he points out:

Does Merck really need to charge \$360 per dose to earn back what they've spent on developing it? The company estimates its net income for 2006 at nearly \$4.5 billion. If they sold Gardasil for 1/10th its current price, assuming the number of units sold stays relatively steady, the company would have \$36.5 million in sales each quarter, or \$146 million each year, from that product alone. A few more months, and they could recoup their development cost, and start making up for the funds wasted on researching vaccines that didn't make it to market (McGee, 2007).

This claim heavily contrasts with an article published by Forbes (23rd April 2012) in which the journalist Matthew Herper criticises the engagement of politics in public health, in particular the controversy in the U.S. on parent consent, promiscuity and HPV vaccines. The consequence, he notes, was a drop in the sales of Gardasil.

Launched in 2006, Gardasil sales immediately shot to \$1.5 billion in 2007 before the poisonous politics clipped it back. By 2010 sales fell to nearly \$1 billion. Last year sales crawled back a bit, to \$1.2 billion. But 2011 was still a very bad year for Gardasil (Forbes, 23rd April 2012).

The discussion about the fair price of HPV vaccines shows that the boundaries between between healthcare as a market and as a public service are in constant negotiation. Pharmaceutical companies attempt to demonstrate that their estimations of value reflect a delicate equilibrium between business profit and society's common Good. For them, such balance can be reached only by an autonomous market, independent of 'poisonous politics'.

Price segmentation and the enactment of market geopolitics

Another contested issue in relation to drug pricing is their national differentiation. Prices of vaccines, for instance, change among countries because each one is treated as a particular and different market. At the same time these differences are understood as local expressions of global price interdependency. Companies keep a global perspective to define market segments and to make decisions about the “right” price. National HPV vaccine prices are the result of health technologies’ geopolitics. National prices are based on economic development and marginal calculation on scale production. Within global health narratives, price is perceived, in the beginning, as a barrier for the mobility of vaccines from developed to developing countries. However, a set of differentiated prices is subsequently produced attending to differences of social and economic development. In the last decade, global health organisations have centred their actions in mediating international pricing of vaccines and medicaments, for instance, the GAVI Alliance.

The GAVI Alliance is a public-private partnership focused on promoting access to immunisation in poor countries; this organisation is supported by multilateral institutions such as WHO, UN, World Bank and philanthropic organisations such as the Bill and Melinda Gates Foundation. The GAVI Alliance has been a very important agent in the process of negotiation of prices of HPV vaccines for poor countries, through the promotion of differential or “tiering” pricing. The Alliance has defined a threshold to define which countries can afford vaccines at the lowest price, which is \$1.520 GDP per capita.

This can be seen in the case of HPV vaccines’ price evolution. Nguyen and colleagues (2011) describe such process from 2007 to 2012:

Merck licensed its vaccine in the US in 2006. The vaccine requires three doses, and the private market price was initially US\$ 120 per dose. In 2007, the US public market price was US\$ 97 per dose, making it the most expensive publicly funded vaccine at the time. GSK’s first licence for its three-dose HPV vaccine was obtained in 2007. The price of the vaccine was initially in line with Merck’s, but then rapidly decreased. For example, in late 2008 GSK announced a 60% price reduction in the Philippines to approximately \$48 per dose. In South Africa, a 36% price decrease brought the price down to \$44 per dose. Overall, HPV vaccine prices varied widely from 2007 to 2011. In industrialised countries the price ranged from US\$ 100 to US\$ 233 per dose and in developing countries from US\$ 30 to US\$ 100 per dose, and were mainly available through the private sector.

The two licensed HPV vaccines produced by Merck and GSK were prequalified by WHO in 2009, opening the door for purchase by UN organisations. The price offered to the Pan American Health Organization (PAHO) Revolving Fund decreased from US\$ 32 per dose in January 2010 to US\$ 14.00 per dose in April 2011 for the GSK vaccine. The Merck vaccine was offered to PAHO within the same price range. GAVI's preliminary work with vaccine manufacturers has resulted in a further price reduction. Merck's recent offer to provide its HPV vaccine at US\$ 5 per dose to GAVI, marks the first-ever public offer of a price for HPV vaccines for low-income countries. In November 2011, the GAVI Board will decide whether to invite countries to apply for funding for HPV vaccines. Once a funding window is approved, GAVI, through its procurement partners, will issue a formal tender to ensure that it achieves the lowest sustainable price for GAVI countries. The prices offered need to translate into a cost-effective and affordable proposition for GAVI and its eligible countries (Nguyen et al., 2011: 2).

This brief history of HPV vaccine price shows the ways in which prices are organised following a political pattern; the distinction between countries and markets according to classifications based on countries income is clear. HPV vaccine price is higher in high income countries such as United States, Canada and European countries, middle income countries such as South Africa, Mexico, Argentina and Colombia have to pay prices between 35 USD to 14 USD. Finally, HPV vaccines in poor countries are priced with the mediation of the GAVI Alliance and are in the range of 10-5 USD.

The GAVI Alliance calls this as “pro-active market shaping strategy”, it recognises that “too often market forces alone do not ensure the most favourable conditions for low income countries” (GAVI, 2013). For them the production of vaccines demands greater time and investment in R&D than generic medicines. As a consequence, there are fewer producers, high barriers for new entrants, poor supply reliability and slow price decreases (GAVI, 2013).

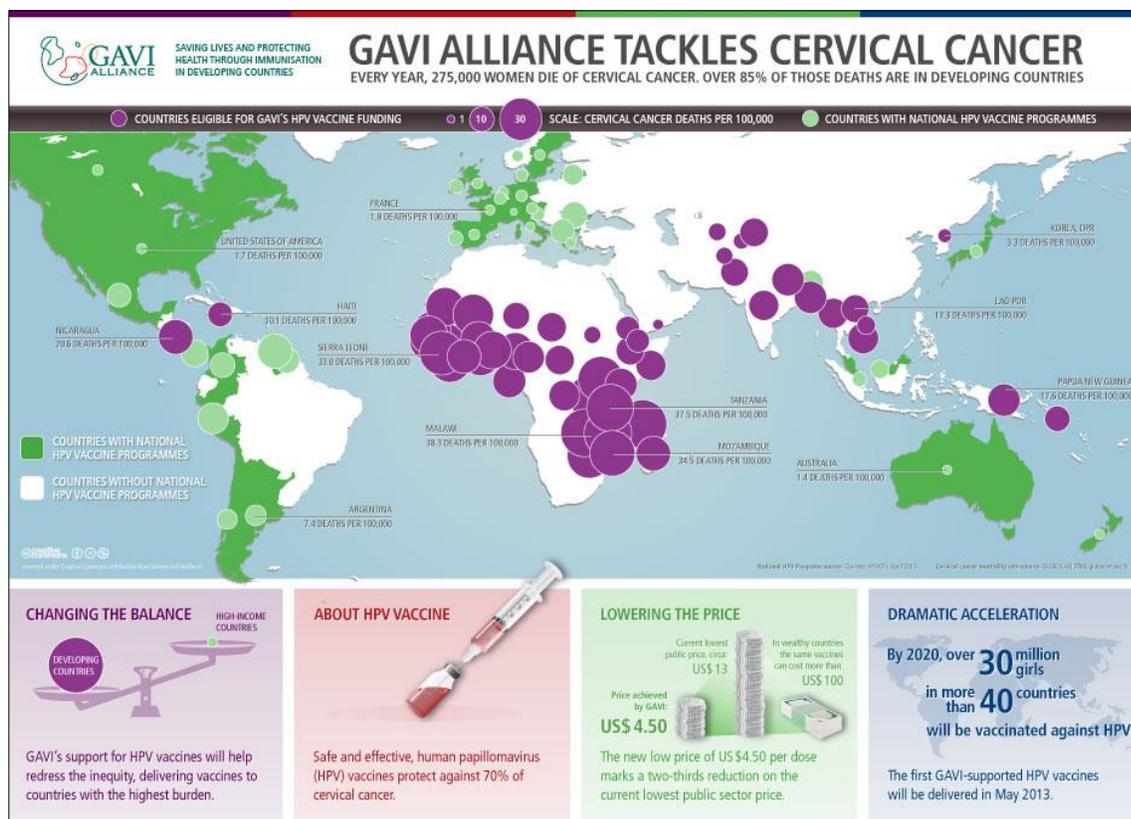
This strategy is embedded into the framework of global price interdependency. The GAVI Alliance attempts to deal with market failures for vaccines by aggregating volume, increasing certainty of demand, stimulating competition where possible and ensuring that a sufficient quantity of appropriate quality vaccines is available through a diverse manufacturer base at affordable and sustainable prices (GAVI Briefcase, 2013). As is noted by GAVI Alliance:

The idea behind differential pricing is to reduce financial barriers to vaccine access for low-income countries while providing manufacturers with a profitable market in richer markets so that they will have an incentive to invest in sufficient production capacity and new product research and development (GAVI Briefcase, 2013: 2).

Calculations about cost-effectiveness and affordability have an important role in the definition of prices for poor countries. WHO has produced several models that indicate HPV vaccination in low-income and middle-income countries in which quality screening is not widespread may be cost-effective if the cost per vaccinated girl (including 3 doses of vaccine and programmatic costs) is less than US\$10-25 (GAVI, 2011: 4). WHO has provided ‘evidence-based guidance’ to developing countries on how ‘best’ to introduce such vaccines (WHO, 2013). These studies have shaped the discussion and the negotiation with pharmaceutical companies in the definition of prices.

Map 5, taken from a poster produced by the GAVI Alliance, offers a visual enactment of the relation between pricing, political geography and value. It presents the countries that have included the HPV vaccines into national programmes and the countries that have not. It also presents the morbidity of cervical cancer (deaths per 100.000) in different countries. This contrast between national programmes and cervical cancer morbidity enacts differences in HPV vaccines’ value. Paradoxically in the countries in which they have a higher price HPV vaccines are less valuable (in terms of number of deaths avoided) than in countries where, through GAVI mediation, lower prices have been reached. The GAVI Alliance and the WHO are interested in making visible the gap between developing and developed countries in relation to the access to HPV vaccines, as well as in presenting that vaccines are not distributed in the regions where they may be better appreciated.⁹⁸

⁹⁸ As is noted by the WHO Immunisation Committee: “HPV vaccine is a critical development for low-income countries. Not only does it contribute to reducing the burden of cervical cancer, it also creates a new opportunity to routinely deliver messages on health services and health promotion to adolescents (ages between 9 and 13 years) , offering an entry point to delivering preventive health care to girls and adolescents” (WHO, 2013).



Map 5 GAVI Alliance, International Price negotiations

Price and value, re-entangling money in calculation

This presentation of the elements entangled in the calculation of prices shows the ways in which evidence based medicine is shaping practices and languages to legitimate particular estimations of value that are confronted in markets. Pharmaceutical companies have appropriated the devices of calculation used by public agencies to enhance their own valuations. Prices are material-semiotic elements with an important role in the configuration of entanglements between institutions, technologies and bodies. Price and price setting render visible hierarchies and classifications of political objects such as countries and constitute a way of quantifying claims of impact and social value. A closer examination of these practices contributes to the understanding of quantification and quantified entities in the shaping of contemporary healthcare governance.

Nevertheless, the perception of prices' role in health decision making is ambiguous. On the one hand, price is acknowledged by policymakers and analysts as key element in the definition of the policy and is perceived as material manifestation of companies' interest and search of profits. On the other hand, price is naturalised. In spite of the high regulation of pharmaceutical markets, prices are understood as

relatively unproblematic results of the equilibrium and tension between demand and supply. Other elements such as direct engagements with decision makers are considered a more decisive element in the introduction of vaccines into national markets. As is noted by one of the executive directors of Merck:

The price part was perhaps the least significant in this process of engagement with the government of Colombia, local health experts and patient groups, in order to establish the policy environment in which the vaccine could be introduced in the country (Executive Director, Public Policy - Latin America Merck, email communication 20th June 2013).

Additionally as I have previously noted, prices and monetary measurements do not seem to be the right language to talk about human life and its quality. But at the same time, monetary measurements and prices seems the most direct and clear way of communicating the ‘value’ of a particular entity. In public arenas prices, costs, investments and savings of money are privileged enactments to communicate the value of HPV vaccines and the considerations of the State.

In the final section of this chapter I explore the ways in which prices and monetary estimations are entangled with other metrics, narratives and emotions in order to perform the value of HPV vaccines as healthcare entities. These entanglements show the difficulty of establishing a clear separation between vaccines as commodities and as gifts, between their individual consumption and their perception as common good, between economic value and the values of pricelessness. HPV vaccines have been advertised and presented to the public in a way that constantly integrates their presentation as gifts and commodities. These elements are deeply intertwined in the valuation of HPV vaccines as an act of care and a public right. As noted by the Merck representative, prices operate insofar as they are entangled with other agents. What they have called the ‘policy environment’ is an exercise of socio-technical engineering to produce favourable entanglements.

Through analysing the advertising of Gardasil and the public presentation of the HPV vaccination programme in Colombia, I describe the role of pricing in the configuration of affective modes of calculation on vaccines’ value. Prices are attached to the calculations that pharmaceutical companies and the government offer to different publics, in particular women and parents. The numerical enactment of prices has an important role in the communication of value. However, the role of pricing—as quantification—in the constitution of moral and affective economies on prevention shows a different aspect of governance and trust in numbers. Numbers are powerful not only because their ‘objectivity’ and ‘impersonality’ (Porter, 1995), their power in this case, relies on their capacity to re-entangle themselves

in heterogeneous settings and affective trade-offs. Advertisements and public portrayals of HPV vaccines invoke prices as an element of calculation that render visible dimension of values that are precisely priceless.

Price, gift and the priceless

The price of bio-objects has been used to define its character as commodities or gifts (Waldby and Mitchell, 2007). The dichotomy between gift and commodity has had an important impact in healthcare organisation, shaping distribution systems, policies and regulation around human tissue. Richard Titmuss' classic study *The Gift Relationship: From Human Blood to Social Policy* (1971) offers a useful portrayal of this dichotomy. Blood donation has been analysed in relation to communalization of health and risk and there is a disjunctive in the way in which this human bio-tissue is conceived. On one hand it can be considered as a gift, result of selfless, voluntary and altruistic behaviour. On the other hand, bio-materials can be conceived as commodity and thus, are enacted as objects whose distribution depends on interests and profit communicated through price. This dichotomy, moreover, counters public delivery and market as alternatives of healthcare distribution and governance. Although this framework has been developed to understand primarily bio-tissue, it also has shaped many narratives of healthcare objects (medicines, procedures, treatments) in a more general sense. Gift systems and commodity systems are often understood in this way, as mutually exclusive and morally incompatible social forms (Waldby and Mitchell, 2007: 9).

Nevertheless, in practice such separation between gifts and commodities is not clear. Price and cost cannot be used as element of distinction between commodities and goods. As Marcel Mauss (1954:9) has argued there is no free gift. For him, the gift is entangled in a system of relation of solidarity and reciprocity. "A gift that does nothing to enhance solidarity is a contradiction" (Douglas, 1992: 9). As different authors (Callon, 1998, Appadurai, 1986; Frow, 1997, Waldby and Mitchell, 2007) have suggested there is neither pure gift nor pure commodity. "Gifts and commodities are always intertwined in various hybrid configurations and present a range of alternative possibilities for the use of objects. Gift and commodity are not mutually exclusive modes of transaction, since they tend to have common certain ways of calculation, strategy and motivation" (Frow, 1997: 124).

The same can be said in relation to goods, commodities and market settings. There are not discrete realms or spheres of social and economic life. Markets are not autonomous and separated spaces limited by non market regulatory institutions and social life. In that sense, "gift relationships cannot function free of

market calculation or considerations of exchange value” (Callon, 1998: 8), neither can marketised relations without emotional and affective connection.

Medicines and pharmaceuticals but particularly vaccines are a good object to follow this intertwining. As I have previously presented, HPV vaccines are considered commodities by different agents involved in the calculation of their value. On the other hand, to the extent that they are understood as medicines to prevent a serious disease; they have been surrounded by narratives about protection, care and gifts/gifting.

Direct-to-consumer advertising (DTC) of drugs is allowed only in United States, New Zealand and Sweden, in the rest of the world the promotion of drugs is highly regulated and limited to informing about diseases and technologies available, avoiding direct references to particular brands or products. Nevertheless, the boundaries distinguishing DTC from educational campaigns are not clear. The contents of the informative campaigns promoted by the pharmaceutical industry to raise awareness about medical conditions and DTC messages do not differ substantially. Both are understood as information for decision making. As Beverly J. Lybrand, General Manager for Gardasil in Merck notes in a pharmaceutical business magazine:

After discovering the tremendously low awareness, communicating the link between HPV and cervical cancer became the primary focus of the campaign. It required tailoring the message to each particular audience: for physicians, the focus was obviously the medical impact along with physicians’ role in helping patients become better informed; for mothers, it was the emotional call to protect their daughters; and for young women, it was the notion of empowerment from taking control of their own health (Next Generation Pharmaceuticals, 2007).

This communication strategy has assembled a narrative in which parents and women are enacted as calculative agents (Linden, 2013: 90). For instance, testimonial-style footages presents confident and expressive women relaying their concerns and decisions on vaccination in relation to HPV and cervical cancer statistics. On the other hand, these narratives render visible the tensions between globalised discursive repertoires about health, risk and gender and their local (national) translations. Female empowerment through awareness and action is a highly globalised plot promoted by governments and companies. The U.S. Gardasil campaign “One less⁹⁹” (Mamo et al., 2010; Fernandez, 2012, Vardeman-Winter, 2012; Stöckl, 2010; Haas et al., 2009), the promotion of Gardasil in Sweden (Linden, 2013) and

⁹⁹ <http://www.gardasil.com/> (Accessed 16th March 2013).

the campaign “Haría lo que fuera¹⁰⁰” en Colombia have appropriated feminist discourses to assimilate vaccination as empowerment (Image 7). On the other hand, pharmaceutical companies produce nationally situated narratives that are the result of their own perceptions about cultural and political characteristics of locally segmented markets. In Sweden, for instance, the HPV vaccination campaign has focused on autonomy and freedom of adolescents in relation to their own sexuality and health and on their responsibility in the management of risk (Linden, 2013). Although the same narrative is present in Colombian Gardasil advertising, the emphasis shifts from adolescents to parents, in particular to mothers (Image 6).

The campaign *Haría lo que fuera* ‘Everything I can’ offers mothers a scenario of calculation in which benefits and costs of protecting their daughters health should be evaluated. The campaign entangles data about cervical cancer risk and HPV infection, testimonial footage about women’s future plans and “dreams” and mothers’ care and responsibility. The suggested trade-off is between daughters’ health and lives and the potential (economic) costs to guarantee their protection. Although an explicit price is absent in the campaign, the value of HPV vaccines is enacted in relation to the pricelessness of health and the moral duty of affording HPV vaccines despite their price. One member of Colombian committee of immunisation notes the moral burden of such calculation:

The campaign of the industry, “Haría lo que fuera” sets out the problem between the devil and the deep blue sea. Such advertisement was very criticized by us because it suggested a hard trade-off for the parents. The message was that as I save money and pay loans to organize a “quiceañera” party, I should to save money to pay the HPV vaccine. Because, the vaccine guarantees my daughter her life, I would do anything (haría lo que fuera) for her dreams. So if I do not let her to be vaccinated I am sinning” (**NCIP Committee member 8**).

¹⁰⁰ <http://www.harialoquefuera.com.co/disease/harialoquefueracomco/co.html> (Accessed 16th March 2013).



Image 6 Webpage Merck's informative campaign "Haría lo que fuera" in Colombia
 In the poster: "What would I do to keep my daughter healthy? (...) Everything I can!"

Gardasil's promotion framework has been reproduced by private healthcare providers in the country. The targets of these campaigns are women (25-40 years old) and girls who are not vaccinated through public programmes. Private healthcare companies have developed DTC adverts (see image 7) to promote the consumption of these vaccines. Those messages have focused on middle class and professional women who can afford the vaccines. The price (for 3 doses) oscillates between 374.000 COP to 750.000 COP, 115 GBP to 231 GBP.



Image 7 Promotional poster HPV vaccine (Bogotá, Colombia 2012).

Da tu brazo a torcer (Let twist your arm). This 7th and 8th March, special offer in the first dose of the vaccine against HPV, main cause of cervical cancer and other related diseases. Get the vaccine, no excuses. *Conditions apply. For women between 20-45 years old.

HPV vaccines are not only portrayed as gifts and as priceless goods in relation to market consumption and parenting. The delivery of these medicines by the Colombian State has been shaped by narratives and practices in which vaccines are enacted as a right, a gift and a coercive manifestation of the State. In these entanglements, prices as a quantified measure of value have an important role in the constitution of calculative spaces to estimate other forms of value than economic valuation.

The Right, the Gift and the price of State paternalism

Vaccines and political institutions have had a long-standing relation (Allen, 2007; Colgrove, 2006; Colgrove et al., 2010). As I have noted previously vaccination entails practices of population governance which make it an object of primary interest for governments and politicians. Vaccines connect materially the most global and the most intimate and personal worlds (Leach and Fairhead, 2008). Such material connection has produced deep narrative and semiotic entanglements between political governance and embodied subjectivity. Price plays an important role in these entanglements because it put economic valuation at the heart of the discussion about State responsibility and the way in which vaccines materialise it.

The inclusion of HPV vaccines in the national expanded programme of immunisation is the result of practices of valuation that legitimate them as objects of public interest. In Colombia such estimations have been embedded in narratives and networks of regulations that have supported a constitutional view of Health as a fundamental right. Colombian High Courts have extended such framework to medicines and pharmaceuticals. These objects are portrayed by regulators as material manifestation of a political right. Such valuation has been very controversial because it has imposed on the State the duty of sometimes affording medicaments regardless of their price. This is the conundrum in the debate about healthcare sustainability between economic technocrats and High Courts. In this case, the price of pharmaceuticals has been an important element in the discussion about exclusion, health and State responsibility.

For instance, the Council of State in its ruling about the introduction of HPV vaccines perceives that the market price of these medicines constitutes a barrier of access for the poorest populations. In 2011, the price of market of HPV vaccines oscillated between 680.000 and 861.000 COP; this price was higher than the minimum wage in Colombia for that year 535.000 COP. Such perception of cost enhances the presentation of the HPV vaccination programme as a redistributive policy.

Public speeches at opening campaigns have presented HPV vaccines as one of the many ways in which the Colombian State promotes equity. President Santos in his speech in Sincelejo (August 2011) included HPV vaccination as one of the policies to fight poverty, close social gaps and promoting equity. Such narratives have been reproduced by other agents involved with HPV vaccination within the Colombian State. For instance, the Colombian Congress in the debates to approve the Act 1626 [2013] (that guarantees vaccination funding) addressed these vaccines as a policy to promote social equity. The Colombian Congress assumed risk factors of cervical cancer as indicators of the association of this disease with social disadvantages. On the other hand, HPV vaccines have been framed into a long-standing tradition presenting vaccination as one few material manifestations of the Colombian State that have a national extent. Such paternalism has portrayed vaccination not only as a right but also as gift¹⁰¹.

¹⁰¹ The blurriness between gifts and political rights is one of the main characteristics of clientelism. Clientelism is characterized by a conception of the State based on the combination of particularistic targeting and contingency-based exchange. “This method of contingent exchange thrives in both autocracies and democracies. It exists in a large variety of cultural contexts. There is a connection between clientelism and a variety of political and economic outcomes, including democratic accountability, corruption, and public goods provision” (Hicken, 2011: 288). In Colombian historiography of the State, this is a ‘classic’ subject, in particular in relation to political parties history and elites (Safford and Palacios, 2002).

I would like to close this reflection with a political advertisement produced by MIRA, one of the political parties involved in the promotion of the Act 1626 [2013] through the Colombian Congress. This advertising was produced for the election of Congress in 2014 (Image 8). It is a video that summarizes many elements shaping the discourse of politicians and the government about HPV vaccines, including anticipation and citizen rights. In the commercial two references are used to enhance the value of vaccination. One is a girl writing ‘dreams’ in her diary. Professional and personal success (becoming a doctor and getting married) are complemented by an expectation of good health, in this case being free of cervical cancer. Then the message is directed to parents: they should consent vaccination in order to protect their daughters’ dreams.



Image 8 Screenshot from, political video from MIRA, about the Act 1626 of 2013

1. *At 25 years old I want to be a doctor ** At 30, I want to get married and***I never want to have cervical cancer.
2. Do not allow the dreams of your daughters to disappear. 3. The 3 doses would cost you \$800.000. Act 1626 of 2013. 4. MIRA, Political movement

The other reference is the price of the vaccine expressed as the amount of money saved by the families through the State’s intervention. The saved amount is 800.000 COP for 3 doses; this figure is presented with a reference to the Act 1626 [2013]. Finally, the video finishes with the logo of the MIRA party. The figure 800.000 COP is particular meaningful in a context in which minimum wage is 616.000 COP (approx. £200 per month) and measurements of poverty are based on individual income. According to the Colombian National Department of Statistics (DANE) the poverty threshold for 2012 was 202.083

COP¹⁰². In some regions, up to 68% of the population is considered poor (Chocó 68,0%; Cauca 62,1%; Córdoba 60,2%, La Guajira 58,4%). In contrast in Bogotá less than 11,59% are poor, according to this methodology. This context highlights the role of pricing in the enhancement of the value of public vaccination. Through the explicit reference to the market price of the vaccine, politicians are not only connecting economic value to care and parental protection; they also are locating themselves as the gatekeepers in the distribution of goods and gifts by the State.

Conclusions

Prices are highly naturalised measurements of economic value. They have been taken for granted in the social and political analysis on healthcare governance and the shaping of health as a market. This chapter presented the complexities and contingencies that are attached to price setting and the ways in which prices are entangled in different modes of calculation around HPV vaccines. As I have argued the price of HPV vaccines has been a mechanism to enhance the value of this technology in relation to health, wellbeing and care. This interaction is full of tensions between financial sustainability, profit and claims of care.

The repertoires of evidence based medicine have shaped the strategies of pricing of pharmaceutical companies. EBM has provided practices and languages to legitimate particular estimations of value that are confronted in markets. Pharmaceutical companies have appropriated devices of calculation used by public agencies to enhance their own valuations and to translate economic interest into public health governance narratives. Prices can be considered material-semiotic elements that mediate between institutions, technologies and bodies.

Furthermore, prices are performative; they produce hierarchies and classifications of political objects such as countries and they constitute a way of quantifying their public value. On the other hand, price setting has been a way of constituting pharmaceutical companies as actors in the development of the HPV vaccination programme. Price setting has involved the communication of value through the presentation of technical information and the development of emotional narratives about healthcare and responsibility.

¹⁰² These thresholds define minimum incomes to afford a set of foods to cover the minimum intake of energy (calories) in the case of the poverty line and to afford food and other basic needs such as transportation, accommodation, health and education in the case of poverty threshold. Within this framework, a person is considered “technically” poor if his or her monthly income is less than \$202.083 and extremely poor if his or her income is less than \$87.000. These methodologies to measure poverty and inequity have been extremely contested because they underestimate the complexity of inequality and limit poverty to income; but they still provide an interesting picture of the income inequity in Colombia and the gaps between regions.

The analysis of pricing in the context of public policy and state interventions makes visible the boundaries and the problems that the distinction between market and public sector entails. From the perspective of pharmaceutical companies, the public sector is characterised as a market and different strategies of marketing and production-communication of value are developed for these companies to address the particularities that “public sector” markets involve.

Pricing practices and narratives render visible the ways in which public goods and consumption goods are intertwined. HPV vaccines are goods whose inclusion into public healthcare programmes has involved their enactment as public goods. On the other hand, they have been extensively presented as personalised protection against risk. The same happens with the distinction between commodity and gift. Advertising and public campaigns about HPV vaccines have entangled narratives about reciprocity, price, pricelessness and care. Price has operated as an element to enhance and highlight the responsibility of parents with to daughters, healthcare providers to their patients and governments to its citizens. From the perspective of public vaccination programmes, vaccines are perceived as interventions of the State. These narratives have reproduced practices of government in which rights are understood as gifts, such style of governing has characterised many actions of the Colombian State (Safford and Palacios, 2002). Vaccines are perceived by politicians and decision makers as a ‘Good’ for Colombian society; a good that they manage because its political value is understood. Through vaccination campaigns a paternalist State is enacted; consequently in this account the risks, uncertainties and anxieties about the vaccine are absent.

Conclusion

Numbers that matter:
Evidence, responsibility and caring with numbers

Sometimes, with the best intentions, scientists and public officials and others involved in working for the benefit of us all, forget that people are people (...) They concentrate so totally on plans and programs, experiments, statistics –on abstractions- that people become objects, symbols on paper, figures in a mathematical formula, or ‘impersonal’ subjects in a scientific study

Atlanta Constitution cited by Jones, 1993

Summing up

This thesis started with the story of outbreak in Carmen de Bolívar of adverse effects related to HPV vaccination. As I noted in the introduction, this event began to reveal a set of narratives and calculation practices that legitimised the introduction of HPV vaccines as the right tool against cervical cancer according to the particularities of Colombian female population and the economic capability of the State. The set of objects that constitute what is presented by technical committees and decision makers as evidence, most of the time remains invisible to ‘non expert’ audiences. However, once an event such as this where hundreds of girls were hospitalised happens and reaches public arenas, different actors demand evidence from the state and the technical and political organisations that operate on its behalf.

The Carmen de Bolívar controversy was a springboard for showing the critical place that evidence has reached in contemporary healthcare policy and the important consequences that dry, seemingly ‘impersonal’ calculations have on the lives of large populations. This thesis rendered visible the contingency of the production of evidence and the enactment of efficiency in the introduction of HPV vaccines in Colombia. The different chapters showed the ways in which a repertoire of evidence based medicine tools has been locally appropriated and reshaped in order to legitimize this intervention. In this process, I have shown that contingency is not a destabilizing element in the production and use of

evidence, on the contrary, the flexibility and the limits in the application of rules and calculative principles contributes to the operability of such practices.

In Chapter One, I drew attention to how HPV vaccines incorporate many tensions that have made vaccines a contested medical intervention. They invoke tensions between individual risk and social protection, actual risk and anticipated futures. These vaccines have established material and semiotic connections with the world of cervical cancer, assimilating and reshaping its dynamics of distribution of risk and production of difference. This thesis critically presented the re-enactment of these elements in the process of calculation and decision making undertaken by technical committees in Colombia.

Evidence is the result of different calculation practices, which constitute a mode of ordering heterogeneous sets of objects, data and people. Such ordering constitutes evidence based medicine as a mode of calculation. By means of the analysis of technical documentation, scientific literature and news; interviews with decision makers and technical advisors, and the re-enactment of calculation practices; I presented the ways in which calculation devices such systematic reviews, cost-effective analysis, statistical modelling and pharmaco-economics operate in the enactment of legitimacy by technical committees and decision makers. In consequence, certain kinds of knowledge are considered proper evidence whilst others remain as mere information. Within such devices quantification and numerical operations have provided a way of performing objectivity and impersonality, whilst also presenting the contingency and the uncertainty of HPV vaccine's protection.

Chapter Two presented conceptual and methodological tools to trace the ways in which these devices produce different results that travel through institutional paths and several scenarios, such as media, national congress, High Courts among others. Finally, these calculations involve different ways of ordering and quantifying heterogeneous sets of objects to produce justifications for policymaking. Methods of valuation and devices of calculation materialise normative claims of evidence and efficiency. From a theoretical perspective, this thesis explored the character of numbers as material-semiotic objects and their role in contemporary health governance, showing the transformation of quantified and statistical expressions in icons and closed objects.

The introduction of HPV vaccines provided an opportunity to analyse the 'reception' of evidence-based policy repertoires in Colombia, and their use by policymakers and pharmaceutical companies, presenting the local enactments of globally depicted tensions, related to risk, anxiety and anticipation. This thesis has offered an empirical and detailed analysis of the relations between calculation and governance. It

presented the role of systematic reviews in enacting proper ‘evidence’, of cost-effectiveness analysis and DALYs in enacting ‘efficiency’; the ways in which Markov modelling has enacted a homogenised portrayal of Colombian women, and the role of pricing in enacting ‘fairness’, ‘distribution’ and the commitment of State and parents with their citizens and daughters.

Despite evidence based medicine’s claims that the formalization of searching practices guarantees the objectivity of systematic reviews, Chapter Three demonstrated systematic reviews are not isolated from the interests and concerns of those who design them. In the case of HPV vaccines in Colombia, systematic reviews are key instruments in the identification of legitimate sources of knowledge, rendering visible Colombian scientific communities and local technical organisations within the international production of evidence. Additionally, systematic reviews have been integrated in the strategies to transform particular diseases and medical objects in matters of public interest for health policymakers. That is the case of the surge of genital warts as a public health concern for the Colombian Government and their role in the selection of Gardasil as the official vaccine of the Expanded Programme of Immunisations.

The movement of data and the reshaping of evidence within technical committees is an important element in the production of the boundaries between experts and decision makers, and citizens and lay people. This process of division frames some data as ‘evidence’ especially from the perspective of the experts and others as information that will circulate around lay and public arenas. Accordingly, strategies of calculation are strategies of production of value. This analysis has highlighted the fragility of evidence in relation to other interests beyond public health. In particular, pharmaceutical companies have appropriated these devices of calculation to enhance their own estimation of vaccines’ value.

These claims of evidence have been complemented by an obsession with efficiency and cost-effectiveness. Cost-effectiveness analysis has been particularly important in contemporary decision making for its capacity to transform a political process of selection of alternatives of healthcare into an ‘objective’ calculation. In relation to the selection of Gardasil in Colombia, Chapter Four showed how cost-effectiveness analysis and its measurement units (DALY) are designed in a way that privileges pharmaceuticals as medical technologies over other approaches to public health. In terms of cost-effectiveness these metrics increased the value of vaccines over screening programmes. On the other hand, they have an important role in creating some diseases as public health concerns; such as is the case of genital warts and its expression in DALYS.

In the different institutional pathways and scenarios, cost-effectiveness has been the key tool to justify the inclusions and the exclusions that HPV vaccines entail, such as the selection of Gardasil as official vaccine and the exclusion of boys from the public vaccination programme. Although cost-effectiveness was invoked as the main framework to understand the social and economic value of HPV vaccines in decision making scenarios, the metrics that rendered visible such value did not travel through these different institutional settings. Whilst the calculation of DALYS played a decisive role in the demonstration of Gardasil's value over Cervarix and cervical screening, these units of measurement were not used beyond technical reports. Despite quality of life metrics being limited to technical arenas, they act to redefine the notion of human health in policy, in favour of a concept based on opportunity cost and marginality. Such concept is one of the cornerstones in the economisation of healthcare.

These metrics, moreover, are segmented geopolitically. Standards and practices of calculation reproduce international classifications based on attributions of social and economic development. In relation to measurement units based on health-adjusted life years, there is a clear division of national groups between QALY and DALY. Because of the associated costs and the technical infrastructure that QALY implementation demands, their use has been very limited in developing countries. In contrast, global health specialists and advisors have strongly promoted the use of DALYs in this region by means of the measurement of the Global Burden of Disease. DALYS have been perceived by local experts in the introduction of HPV vaccines as the metrics that fit better to the features of Colombian healthcare system and that provide a clearer alternative to pharmaceutical companies' estimation of value.

In this process of calculation, Chapter Five showed that modelling and simulation have constituted an interface between the sources identified by systematic reviews and the generation of objects and numbers for cost-effectiveness analysis. In the analysed case, Markov chain modelling produces a material and semiotic connection between individual body and the population as social body, intertwining individual and social histories of the disease. Markov chain simulation as calculative device produces "ideal" cohorts of populations, diverse in an epidemiological and statistical sense but socially undifferentiated. Colombian data about cervical cancer rely heavily on the recruitment of poor women as research subjects. Markov chain modelling makes invisible the social origins of these data and transforms them into sources for the production of a socially homogenised and statistically representative portrayal of Colombian female population. This is the object that better suits vaccination as public health strategy.

At the same time, this model is a device of reflexivity. Markov chain modelling provides a space in which contingency and the limitations of the data are explicit. For instance, the probabilities of transition

between states show the contingency of the different paths an individual can follow in relation to cervical cancer development. This plot contrasts with the portrayals of the causal relation between HPV infection and cervical cancer that circulate amongst public arenas. However, once the simulated objects travel to other spaces beyond technical reports and software, they lose their indexicality and become icons. The estimated data about cervical cancer's incidence produced by Markov chain modelling are received by politicians and decision makers as real and anticipated scenarios that justify the current vaccination programme and its potential risks.

The reconstruction and analysis of these devices of calculation has shown some of the multiple configurations and organisational settings of the Colombian State. It is a multiple and heterogeneous actor that encompasses a blurry set of institutions and actors: technical committees, consultants, decision makers among others. These different actors do not act always in a coordinated way, despite being part of the Colombian State, they have their own rules to deal with what they consider important public matters. They have different valuation frameworks that often clash. However, once decisions are enacted, consensus rhetoric is performed.

Finally this thesis explored the practices of pricing by which pharmaceutical companies enhance the value of their products in the negotiation and interactions with governments and public agencies. Chapter Six showed how although price is primarily used as a measurement of economic value, in the case of HPV vaccines it becomes a measurement of other values beyond economic valuation. It becomes a comparison unit to estimate the compromise and engagement of parents with their daughters and of the state with its women citizens. Prices and price settings are important elements in the definition of markets that usually are taken for granted in the social analysis of healthcare governance. Evidence based medicine has shaped the practices and languages used by pharmaceutical companies and public decision makers to legitimate particular estimations of value that are confronted in markets. Pharmaceutical companies have strategically appropriated devices and practices of calculation from the repertoire of evidence based medicine to enhance their own valuations.

Price setting and its quantified expressions are key elements in the construction of parents and girls as calculative agents. Adverts for HPV vaccines in Colombia have presented the decision to vaccinate as a moral calculation in which are entangled emotions, data about risk and monetary amounts. These narratives have had a global reach, however in comparison with other international campaigns, in Colombia this message has been aimed particularly at mothers. The price of HPV vaccines is portrayed as a small price if the protection of girls' lives is taken into consideration. Something similar happens in the

promotion of the public vaccination programme. Campaigns and politicians' speeches have emphasised the pricelessness of the HPV vaccine, its character as gift. In the political context of Colombia, vaccines have represented one of the most consistent and extended interventions of the state on the Colombian territory and its population. The HPV vaccination programme has been a tool for enacting the Colombian state. Vaccination has been promoted by politicians and health authorities more as a state gift than a citizen Right. Furthermore, politicians have depicted themselves as the gatekeepers of these goods.

Thinking HPV vaccines in the South and other contributions

This thesis has contributed empirically to the study of HPV vaccines in the South from a material-semiotic perspective. As I have noted in the introduction, these technologies have generated an important set of academic analysis about gender, anticipation and sexuality. However, most of these works have been centred in the experience of Europe, Australia and North America. In this regard, this research constitutes one of the first works about HPV vaccines in the South, concretely in Latin America. Despite the global character of many of these technologies and calculation devices, STS has shown that global is always locally produced. The study of the Colombian experience has shown the persistence of concerns about development and modernisation and their impact in the reception and reshaping of technologies and calculation devices. The analysis of the introduction of HPV vaccines in Colombia contributes to the study of the reception of evidence based medicine in the South, particularly in middle income countries.

The justification of Gardasil as the right vaccine for the Colombian vaccination programme was one of the first processes in which health authorities explicitly invoked the repertoire of evidence based medicine to legitimate their decisions. With the establishment of the Institute for Health Technology Assessment (IETS) in Colombia in 2013, evidence based medicine and its calculation devices are reaching an important position in the discussions about inclusion of treatments and health technologies in the country. Currently, the Minister of Health Alejandro Gaviria is promoting a reform of the National Healthcare System in which clinical guidelines, health technology assessments and cost-effectiveness analysis promise to guarantee its sustainability. Evidence promises efficiency. The problems that are addressed in this thesis should be extended to other health technologies and other locations in the South in order to depict a more diverse image of the contemporary transformations of health care.

In terms of methodology, this thesis is an effort to make the most of the sources that constitute a policy. I have tried to assume radically the material-semiotic character of policy, within the limits of access to information that I have had. This meant paying close attention to the ways in which institutions enact themselves through documents and the material transit of information between organisations. I have

considered these documents as repositories of content and objects that travel between different scenarios. Following Verran's approach to the material semiotics of numbers (2012a, 2012b) I have analysed the production and circulation of technical documents in relation to practices of calculation. Despite the concept of calculation not being restricted to quantification, I have had a particular interest in showing the role of numbers and quantified expressions in policy. This thesis has emphasised some elements such as figures, graphs and formulae which are not often taken into consideration in more conventional content and discursive analysis of documents.

In the case of the relationship between technical calculation and policy making I have shown how numbers and data appear as closed and disentangled objects in public and decision making arenas. This thesis has traced the movements of information and results between documents, emphasising their transformation, their disentanglement from the calculation spaces in which they were produced and their re-entanglement in new texts by new institutions. I have shown how the movement of data and the reshaping of evidence within technical committees is an important element in the production of the boundaries between experts and decision makers, and citizens and lay people. Evidence is black-boxed and presented as a set of icons: numbers, papers, figures, statistics, and maps, among others. Once decisions are made, contingency is just recognised as an attribute of the 'lay' attributions made by people's reports of adverse effects of vaccination.

The study of evidence production and use contributes to the analysis of contemporary policy making, in particular by showing the practices and devices involved in the production of synthesis for decision making. Information technologies have increased the reproduction and circulation of technical and scientific information that is used by different actors to support their own claims. In the last 20 years Western Europe and North America have experienced the rise of activism based on evidence, in which many social groups have moved from a critical position regarding EBM (Harrison et al., 1997; Barnes et al., 1996; Barnes et al., 1999; Glasby and Beresford, 2006) to appropriate this repertoire as a political tool in their interaction with governments and pharmaceutical companies (Rabeharisoa et al., 2014; Akrich et al., 2014). In Latin America, patients' and users' associations are still in process of organisation, however some of these groups are turning themselves to evidence based medicine as a strategy to enhance their own political position.

Learning from Moreira (2012b), this thesis has integrated different analytical perspectives in order to account for the complexity of contemporary health governance. These frameworks are: material semiotics (Law, 2004; Suchman, 2012; Haraway, 1997, Verran, 2012a, 2012b, Mackenzie, 2013, 2014),

anthropology of economy (Çalışkan and Callon, 2009; 2010; Boltanski and Thevenot, 2006), valuation studies (Mallard and Kjellberg, 2013) and co-production (Jasanoff, 2004; Epstein, 1997, 2009, Frickel and Moore, 2006). Despite the risks that such syncretism entails, this thesis was mainly empirically oriented. This repertoire of theoretical tools contributed, I hope, a more complex and interesting account of contingency of public decision making, providing concepts to analyse the entanglements between governance, healthcare, calculation and moral economies in the introduction of HPV vaccines in Colombia.

Evidence, humility and caring with numbers: in defence of evidence based medicine

As I was finishing this text, around February 2015, the controversy and the public concern generated by the Carmen de Bolívar outbreak seemed to be over. Media and politicians have become silent about this event. Their interest has moved to new concerns, such as the fall of oil prices, the rise of the dollar, a new Colombian Miss Universe, amongst others. One of the last news items about this issue in the national media was related to a report of the Colombian National Institute of Health (El Tiempo, 6th January 2015, El Colombiano 22nd January 2015). This report states that the vaccine was not the cause of the adverse effects and that the outbreak was a psychosomatic disease. Although the report is not yet published, the Institute's press statement was widely reproduced by newspapers and television. After the momentary hesitation of some journalists and politicians about vaccination risks and adverse effects, the black box seems closed again.

Despite evidence based medicine providing a critical starting point against direct claims to scientific authority in policy, what travels from reviews and technical reports to other documents and arenas is a closed idea of scientific knowledge. This is particularly visible in relation to risk. For instance, whilst simulations enacted and distributed risk in terms of populations, in public arenas such risk is presented in terms of individual gambling. Originally, the risk of death from cervical cancer was calculated in terms of cohort, not in relation to individual risk and probabilities of individual exposition. On the other hand, not all the risks are rendered visible. Other risks remain absent in the modelling and in the experts' and public narratives. Possibly the most dramatic case is the estimation of adverse effects from HPV vaccination. Although this is a contested issue and a matter of concern addressed by different publics around the world, it is completely absent in the modelling and in the experts' and committees' calculation about HPV vaccines in Colombia.

After this analysis of evidence, the ways in which is produced, its absences and limitations, what is 'evidence' worth?

Despite my critical approach to the practices of calculation and the use of evidence based medicine by health authorities in the introduction of HPV vaccines; it was not my intention underestimate the potential value of this movement in the production of better policies in terms of social justice and human dignity. I consider that the discussion about evidence in policymaking opens up the production of policy and makes explicit concerns about responsibility, accountability and the contingency of technical knowledge.

One of the basic assumptions of evidence based medicine is that scientific production is not homogeneous in terms of quality and pertinence. This is for me a critical starting point that is different from technocratic approaches to healthcare in which science is undifferentiated and completely trustworthy. Evidence based medicine and policy aims to render visible decision making, producing practices and devices to make it accountable. The rise of evidence based medicine has been linked to a promise of providing calculative tools to defend public interest from the profit orientation of companies. This is an important goal particularly in middle income countries, whose economies have attracted the interest of pharmaceutical companies motivated to make the most of growing incomes, expanding markets and precarious governance.

However, as this thesis has shown, the normative principles that define evidence based medicine can hardly go beyond the initial calculations. In practice, evidence works more as a formalisation of bias and assumptions rather than a device of accountability. The ways in which evidence based medicine is performed have little effect in developing better policies in terms of social justice and defence of the public interest. As I noted before pharmaceutical companies have appropriated this repertoire to enhance the value of their products. In the Colombian case, moreover, these calculations have replicated assumptions and dynamics of the Colombian State's relation with its citizens.

On the other hand, as Timmermans and Berg (2003) have noted, one of the biggest problems of evidence based medicine is the narrowness of its definition of evidence. The evidence pyramid is its clearest enactment. It not only privileges randomized controlled trials as the gold standard in spite of their limitations and the conflict of interests that involves their production and funding. By defining objectivity and rigour in strictly statistic terms, this hierarchy explicitly excludes other kinds of rigorous knowledge such as history and social sciences.

Such limitations should be taken into consideration in order to reshape evidence based medicine. Only a wider and flexible normative definition of evidence can enable the production of more responsible and socially sensitive health policies. I close with two elements that can contribute to thinking about the

production of health policies in an alternative way. Briefly, I would like to draw attention on the concepts ‘technologies of humility’ and ‘ethics of quantification’.

Technologies of humility is a concept developed by Sheila Jasanoff (2003; 2007) to describe strategies to promote more reflexive and less arrogant perceptions of the role of science and technology in the shaping of contemporary politics. The starting point of her reflection is that public matters entail different layers of ignorance and uncertainty that cannot be addressed by scientific knowledge despite its pretensions. She claims it is necessary humility in policy making, “about both the limits of scientific knowledge and about when to stop turning to science to solve problems. Policy-makers need to focus on when it is best to look beyond science for ethical solutions. And science advisers need to admit that other sorts of analyses must also inform political decisions” (Jasanoff, 2007:33).

What is interesting in Jasanoff’s proposal is the use of the word technology. Rather than promoting humility as an abstract value, she is pointing out the necessity of creating methods to deal with an over-dependence on fact-finding in contemporary policy. Technologies of humility are methods “to accommodate the partiality of scientific knowledge and to act under irredeemable uncertainty” (Jasanoff, 2007:33). At least in their foundations, this sounds quite similar to the basic principles of evidence based medicine. The transformation of evidence making into a technology of humility demands a close work between different academic traditions and social groups. Social science and in particular STS should have an important role in the assemblage of different methods for more responsible policymaking.

The second issue could be called ethics of calculation. I am not sure about the use of the term ethics, in particular because STS has been suspicious of its use to tame some debates and to soften their political nature. Nevertheless, I want to express with this concept a set of concerns about the importance of quantification in relation to the consequences that has in peoples’ lives.

Different voices have warned about the perverse effects of policies when people become just numbers. For instance, recently *The Guardian* reported the tragedy of a person that suffered from diabetes and who died after his benefits were cut. His sister in an interview in the newspaper said:

‘I don't think anyone should die like that in this country, alone, hungry and penniless,’ she says. ‘They must know that sanctioning people with diabetes is very dangerous. I am upset with the system; they are treating everyone as statistics and numbers’ (Guardian 3rd August 2014)

Verran (2012b) and Espeland and Stevens (2009) have expressed the importance of thinking about the ethics of numbers and quantification. Information technologies and the proliferation of data (Big Data) are encouraging the use of algorithms and formulae in different realms of policy and social life. To the extent that numbers and data are becoming more ubiquitous, more important things will depend on their calculation.

As I have presented in this thesis, calculations and numbers by themselves do not involve a reduction of the complexity and the dehumanisation of the policies. The problems come from the arrangements that are produced around these devices by those that use them exclusively as mechanisms to perform objectivity and authority. In that regard, social studies of calculation and quantification offer conceptual and methodological tools to critically trace and estimate the consequences of quantification.

As I have noted, numbers are powerful not only because of their “objectivity” and “impersonality” (Porter, 1995), but also because their capacity to re-entangle themselves in heterogeneous settings and affective trade-offs. Quantified objects and calculation practices have a very important role in the constitution of moral and affective economies. In the case of HPV vaccines in Colombia, I have shown how affective calculations have been appropriated as marketing strategy. Advertising and public campaigns about HPV vaccines have entangled narratives about reciprocity, price, pricelessness and care; using commitments of care to enhance the value of particular products. This analysis has made explicit the entanglements between cultural representations of risk and its rationally calculated enactments based on probability and cost-benefit analysis.

However, numbers and quantified objects—as any language—have the capacity to express reflexivity or produce black boxes. Some statistical enactments can make explicit the uncertainties, the contingencies and the limits of particular objects. The black-boxing of these objects is not a direct consequence of quantification but it depends on the extended socio-material arrangements in which they are integrated. As Haraway (1997) has noted, numbers, statistics and quantified objects are “specula”, tools to produce new states in the World. “Feminists have high stakes in the speculum of statistical knowledge for opening up otherwise invisible, singular experience to reconfigure public, widely lived reality” (Haraway, 1997: 199). Numbers and calculation devices are key elements in the constitution of political objects. Any emancipatory policy needs to integrate devices of calculation in order to be operative. The study of calculation is part of the effort that should be made in order to understand numbers and quantification in their diversity and complexity, understanding the things that can and cannot be expressed with them.

Further research about evidence, quantification and healthcare governance should start in the paper worlds of policy, but should move forward, following calculation as an embodied experience. In future work I would like to extend the analysis of calculation in healthcare to citizens, families and practitioners' experience, tracing and highlighting their practical trade-offs and understandings of risk, chance and probability, to contrast these with the imaginaries and calculations from policy. This kind of analysis could be the basis to develop an empirically oriented discussion of the relationship between responsibility and calculation in healthcare.

References

- Abadia, C. and Oviedo, D. (2009). Bureaucratic Itineraries in Colombia. A theoretical and methodological tool to assess managed-care health care systems. *Social Science & Medicine* 68 (2009) 1153–1160
- Abolafia, M. (1998). Markets as cultures: an ethnographic approach. *Sociological Review Monograph Series: The Laws of the Markets*, 46 (1): 69-85.
- Abraham, J. (2008). Sociology of pharmaceuticals development and regulation: a realist empirical research programme. *Sociology of Health and Illness* 30(6): 869-885.
- Adams, V., Murphy, M. and Clarke, A. (2009). Anticipation: Technoscience, life, affect, temporality. *Subjectivity* 28: 246-265.
- Admon-Rick, G. (2014). Impaired Encoding: Calculating, Ordering and the 'disability percentages' Classification System. *Science Technology and Human Values*, 39(1): 154-179.
- Akrich, M., Leaneb, M., Roberts, C. and Arriscado, J. (2014). Practising childbirth activism: A politics of evidence. *BioSocieties* 9 (2): 129–152
- Allen, A. (2007). *Vaccine: the controversial story of medicine's greatest lifesaver*. New York; London:W.W. Norton.
- Anand, S. and Hasson, K. (1997). Disability-adjusted life years: a critical review. *Journal of Health Economics* 16(6): 685-702.
- Andronis, L., Barton, P. and Bryan, S. (2009). Sensitivity analysis in economic evaluation: an audit of NICE, current practice and a review of its use and value in decision-making. *Health Technology Assessment* 13(29).
- Appadurai, A. (1986). *The Social Life of Things: Commodities in Cultural Perspective*. Cambridge: Cambridge University Press.
- Armstrong, D. and Caldwell, D. (2004). Origins of the Concept of Quality of Life in Health Care: A Rhetorical Solution to a Political Problem. *Social Theory & Health* 2(4): 361-371.
- Aronowitz, R. (2010). Gardasil, a Vaccine against the Cancer and a Drug to Reduce Risk. In: *Three Shots at Prevention. The HPV Vaccine and the Politics of Medicine's Simple Solutions*. K. Wailoo, J. Livingston, S. Epstein and R. Aronowitz (eds). Baltimore: Johns Hopkins University Press.

- Arrow, K. (1963). *Social Choice and Individual Values*. New Haven: Yale University Press.
- Asdal, K. and Moser, I. (2012). Experiments in Context and Contexting. *Science, Technology, & Human Values* 37(4):291-306
- Ashmore, M., Mulkey, M. and Pinch, T. (1989). *Health and efficiency. A sociology of health economics*. Portsmouth: Open University Press.
- Atun, De Andrade, Almeida, Cotlear, Dmytraczenko, Frenz, Garcia, Gómez-Dantés, Knaul, Muntaner, De Paula, Rígoli, Serrate, and Wagstaff. (2015). Health-system reform and universal health coverage in Latin America. *The Lancet*, 385(9974), 1230-1247.
- Austin, J.L. (1955). *How to do Things with Words: The William James Lectures delivered at Harvard University in 1955*. Oxford: Clarendon Press.
- Azimont, F. & Araujo, L M. (2010). Reconnecting Marketing to Markets. In: *Reconnecting Marketing to Markets*. Araujo, L., Finch, J. & Kjellberg, H. (eds.). Oxford: Oxford University Press. 78-96.
- Barad, K. (2007). *Meeting the universe halfway. Quantum physics and the entanglement of matter and meaning*. Durham: Duke University Press.
- Barad, K. (2012). Intra-active entanglements (Interview). *Kvinder, Køn & Forskning* 10 NR. 1-2: 10-25.
- Barnes, M, Harrison, S, Mort, M & Shardlow, P. (1999). *Unequal Partners: User Groups and Community Care*. Bristol: The Policy Press.
- Barnes, M, Harrison, S, Mort, M, Shardlow, P & Wistow, G. (1996). Users, Officials and Citizens in Health and Social Care. *Local Government Policymaking* 22(4): 9-17.
- Bauch CT, Li M, Chapman G, Galvani AP. (2010). Adherence to cervical screening in the era of human papillomavirus vaccination: how low is too low? *Lancet Infectious Diseases* 10: 133-137.
- Bauer, S. (2008). Mining data, gathering variables and recombining information: the flexible architecture of epidemiological studies. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences* 39: 415-428.
- Bazerman, C. & Prior, P. (2004). *What writing does and how it does it: an introduction to analyzing texts and textual practices*. London: Lawrence Erlbaum.
- Bazerman, C. (2009). How does science come to speak in the courts? Citations, intertexts, expert witnesses, consequential facts, and reasoning. *Law and Contemporary Problems* 72(1): 91.
- Bazerman, C. (2012). Genre as social action. In: *The Routledge handbook of discourse analysis*. J. P. Gee & M. Handford (eds). London: Routledge.

- Benedet, J. L. and Pettersson, F. (2003). History of the Annual report. *International Journal of Gynecology & Obstetrics* 83(1): 1-3.
- Blume, S. (1992). *Insight and industry: on the dynamics of technological change in medicine*. Cambridge, Mass.: MIT Press.
- Blume, S. (2009). Assessing health technologies in a changing world. *International journal of technology assessment in health care* 25(1): 276.
- Blume, S. and Tump, J. (2010). Evidence and policymaking: The introduction of MMR vaccine in the Netherlands. *Social Science & Medicine* 71(6): 1049-1055.
- Blume, S. and Zanders, M. (2006). Vaccine independence, local competences and globalisation: Lessons from the history of pertussis vaccines. *Social Science & Medicine* 63(7): 1825-1835.
- Boltanski, L. and Thévenot, L. (2006). *On justification: Economies of worth*. Princeton: Princeton University Press.
- Bonacich, P. and Lu, P. (2012). *Introduction to Mathematical Sociology*. Princeton: Princeton University Press.
- Bonneux, L and Birnie, E. (2001). The discount rate in the economic evaluation of prevention: a thought experiment. *J Epidemiol Community Health* 55:123-125.
- Bosch, F. X., Lorincz, A., Munoz, N., Meijer, C. and Shah, K. V. (2002). The causal relation between human papillomavirus and cervical cancer. *Journal of Clinical Pathology* 55(4): 244-265.
- Bowker, G. and Star, S. L. (1999). *Sorting things out: classification and its consequences*. Cambridge, Mass.: MIT Press.
- Braun, B. (2007). Biopolitics and the molecularization of life. *Cultural Geographies* 14: 6-28.
- Briggs, A. and Sculpher, M. (1998). An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics* 13(4): 397-409.
- Brown, T., Craddock, S. and Ingram, A. (2012). Critical interventions in Global Health: Governmentality, Risk, and Assemblage. *Annals of the Association of American Geographers* 102 (5): 1182-1189.
- Çalışkan, K. (2007). Price as a Market Device: Cotton Trading in Izmir Mercantile Exchange. In: *Market Devices*. M. Callon, Y. Millo and F. Muniesa (eds.) London: Blackwell Publishing. pp. 241-262.
- Çalışkan, K. and Callon, M. (2009). Economization, part 1: shifting attention from the economy towards processes of economization. *Economy and Society* 38(3): 369-398.

- Çalışkan, K. and Callon, M. (2010). Economization, part 2: a research programme for the study of markets. *Economy and Society* 39 (1), 1-32
- Callon M. and Law, J. (2005). On qualculation, agency, and otherness. *Environment and Planning D: Society and Space* 23(5) 717 -733.
- Callon, M. (2007). An essay on the growing contribution of economic markets to the proliferation of the social. *Theory, Culture and Society* 24 (7-8): 139-163.
- Callon, M. (1998). An Essay on Framing and Overflowing: Economic Externalities Revisited by Sociology. In: *The Laws of the Markets*. M. Callon (ed.) Oxford and Keele, Blackwell and the Sociological Review: 244-269.
- Cambrosio, A., Keating, P., Schlich, T. and Weisz, G. (2006). Regulatory objectivity and the generation and management of evidence in medicine. *Social Science and Medicine* 63(1):189-99.
- Carpenter, L. and Casper, M. (2009). A tale of two technologies: HPV Vaccination, Male Circumcision and Sexual Health. *Gender & Society* 23(6): 790-816.
- Carpenter, L. and Casper, M. (2010). Global intimacies: innovating the HPV vaccine for women's health. (human papillomavirus). *Women's Studies Quarterly* 37: 80-100.
- Casper, M. and Carpenter, L. (2008). Sex, drugs, and politics: the HPV vaccine for cervical cancer. *Sociology of health & illness* 30(6): 886-899.
- Casper, M. and Clarke, A. E. (1998). Making the Pap smear into the right tool for the job. *Social studies of science* 28(2): 255.
- Cellini, S. and Kee, J. (2010). Cost-Effectiveness and Cost-Benefit Analysis. In: *Handbook of Practical Program Evaluation*, Third Edition. J. Wholey, H. Hatry, and K. Newcomer (eds). San Francisco: Jossey-Bass.
- Center for Disease Control (CDC). (2013). Cost-effectiveness, definitions and calculation tools. <http://www.cdc.gov/owcd/eet/costeffect2/fixed/4.html> (Accessed 20th December 2013).
- Center for Disease Control (CDC). (2014). Current Vaccine Price list, Price in the United States, 2013-2014. <http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/> (Accessed 7th February 2012).
- Christley, R. M., Mort, M., Wynne, B., Wastling, J. M., Heathwaite, A. L., Pickup, R., Austin, Z. and Latham, S. M. (2013). Wrong, but Useful: Negotiating Uncertainty in Infectious Disease Modelling. *PLOS ONE* 8(10).
- Clark, A. M. (2005). New Civic Epistemologies of Quantification: Making Sense of Local and Global Indicators of Sustainability. *Science, Technology & Human Values* 30(3): 403-432.

- Clarke, A. (2010). *Biomedicalization technoscience, health, and illness in the U.S.* Durham, NC: Duke University Press.
- Clarke, A. and Fujimura, J. (1992). *The Right Tools for the Job: At Work in Twentieth Century Life Sciences.* Princeton: Princeton University Press.
- Clifford, G. M., Gallus, S., Herrero, R., Munoz, N., Snijders, P. J. F., Vaccarella, S., Anh, P. T. H., Ferreccio, C., Hieu, N. T., Matos, E., Molano, M., Rajkumar, R., Ronco, G., de Sanjose, S., Shin, H. R., Sukvirach, S., Thomas, J. O., Tunsakul, S., Meijer, C., Franceschi, S. and Study, I. H. P. S. (2005). Worldwide distribution of human papillomavirus types in cytologically normal women in the international Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. *The Lancet* 366(9490): 991-998.
- Cochrane, A. (1971). *Effectiveness and Efficiency: Random Reflections on Health Services.* London: Nuffield Provincial Hospitals Trust.
- Colgrove, J. (2006). *State of Immunity: The Politics of Vaccination in Twentieth-Century America.* Los Angeles: University of California Press.
- Colgrove, J., Abiola, S. and Mello, M. M. (2010). HPV Vaccination Mandates-Lawmaking amid Political and Scientific Controversy. *The New England Journal of Medicine* 363(8): 785-791.
- Connell, E. and Hunt, A. (2010). The HPV vaccination campaign: a project of moral regulation in an era of biopolitics. *Canadian Journal of Sociology-Cahiers Canadiens De Sociologie* 35(1): 63-82.
- Cooren, F. (2004). Textual agency: How texts do things in organizational settings. *Organization* 11(3): 373-393.
- Crane, D. (1972). *Invisible colleges: diffusion of knowledge in scientific communities.* Chicago: University of Chicago Press.
- Cressey, D. (2009). Health economics: Life in the balance. *Nature* 461(7262): 336.
- Danzon, P., Mulcahy, A. and Towse, A. (2011). Pharmaceutical pricing in emerging markets: Effects of income, competition and procurement. Working Paper 17174 <http://www.nber.org/papers/w17174>
- Dargent, E. H. (2015). *Technocracy and Democracy in Latin America: The Experts Running Government.* Cambridge: Cambridge University Press.
- De Solla Price, D. J. (1965). Networks of Scientific Papers. *Science* 149 (3683): 510-515.
- Desrosières, A. (1998). *The politics of large numbers: a History of statistical reasoning,* Cambridge, Mass.: Cambridge, Mass.: Harvard University Press.

- Dewey, J. (1939). *Theory of Valuation*. International Encyclopedia of Unified Science, vol. II, no. 4. An introduction to a pragmatic theory of values or axiology. Chicago: University of Chicago Press.
- Dezalay, Y. and Garth, B. (2002). *The Internationalization of Palace Wars: Lawyers, Economists, and the Contest to Transform Latin American States*. Chicago: University of Chicago Press.
- Discovery Magazine. (2007). *Why Is the HPV Vaccine So Expensive? Good for the cervix, rough on the pocketbook*. <http://discovermagazine.com/2007/jun/hpv#.UkLkuNJ2aSo> (Accessed 4.8.2013).
- Djelic, M.-L. and Quack, S. (2010). Transnational Communities: Shaping Global Economic Governance. *Administrative Science Quarterly* 56(1): 144-146.
- Douglas, M. (1992). *Risk and blame: Essays in cultural theory*. London, New York: Routledge.
- Dumit, J. (2012). *Drugs for life: how pharmaceutical companies define our health*, Durham, N.C: Duke University Press.
- Durbach, N. (2005). *Bodily Matters. The anti-vaccination movement in England, 1853-1907*, Durham and London: Duke University Press.
- Epstein, S. (1996). *Impure science: AIDS, activism, and the politics of knowledge*. Berkeley: University of California Press.
- Epstein, S. (2007). *Inclusion: the politics of difference in medical research*. Chicago: University of Chicago Press.
- Epstein, S. (2010). The Great Undiscussable: Anal Cancer, HPV and Gay Men's Health. In: *Three Shots at Prevention. The HPV Vaccine and the Politics of Medicine's Simple Solutions*. K. Wailoo, J. Livingston, S. Epstein and R. Aronowitz.(eds) Baltimore: Johns Hopkins University
- Escobar, A. (2010). Latin America at a crossroads. *Cultural Studies* 24(1): 1-65
- Ewig, C. and Bello, A. (2009). Gender equity and health sector reform in Colombia: Mixed state-market model yields mixed results. *Social Science & Medicine*, 68(6), 1145-1152.
- Espeland, W. and Stevens, M. (2009). A Sociology of Quantification. *European Journal of Sociology (Archives Européennes de Sociologie)*, 49(3):401-436.
- Faulkner, A. (2010). How Law Makes Technoscience. The Shaping of Expectations, Actors and Accountabilities in Regenerative Medicine in Europe. *CSSP Electronic Working Paper Series*(1).
- Fernandez, C. (2012). I Want to Be One Less: The Rhetoric of Choice in Gardasil Ads. *The Communication Review* 15 (2): 144-158.

- Fierce Vaccines. (2013). *Rising vaccine prices mean fewer children immunized*. February 21, 2013. www.fiercevaccines.com/story/rising-vaccine-prices-means-fewer-children-immunized/2013-02-21 (Accessed 20.5.2013)
- Fisher, J. A. and Ronald, L. M. (2010). Sex, gender, and pharmaceutical politics: From drug development to marketing. *Gender Medicine* 7(4): 357-370.
- Florez Enciso, L. (2009). Colombia: economics, economic policy and economists. In: *Economists in the Americas*, V. Montesinos and John Markoff (eds). Cheltenham: Edward Elgar Publishing, Inc.
- Fourcade, M. (2013). The material and symbolic construction of the BRICs: Reflections inspired by the RIPE Special Issue. *Review of International Political Economy* 20(2): 256-267.
- Frenk, J., Bobadilla, J., Sepúlveda, J. and López, M. (1989). Health transition in middle-income countries: new challenges for health care. *Health policy and planning* 4 (1): 29-39.
- Frickel, S. and Moore, K. (2006). *The New Political Sociology of Science: Institutions, Networks, and Power*. Madison: University of Wisconsin Press.
- Frow, J. (1997). *Gift and commodity*. In: *Time and Commodity Culture: Essays in Cultural Theory and Postmodernity*. Oxford: Clarendon Press.
- GAVI Alliance. (2011). *Q&A: New Vaccine Window Decision*. Dhaka, Bangladesh – Nov 16-17, 2011. Geneva: GAVI Alliance.
- GAVI Alliance. (2013). Briefcase, Pricing. Geneva: GAVI Alliance.
- GAVI Alliance. (2014). HPV vaccination in Developing countries. Newsletter. <http://www.gavi.org/support/nvs/human-papillomavirus-vaccine-support/> (Accessed 18th July 2014)
- Gaviria, A. (2008). *Uribenomics y otras paradojas*. Bogotá: Norma Vitral.
- Glasby, J. and Beresford, P. (2006). Who knows best? Evidence-based practice and the service user contribution. *Critical Social Policy* 26(1):286-284.
- Goldie, S. J., Diaz, M., Constenla, D., Alvis, N., Andrus, J. K. and Kim, S. Y. (2008). Mathematical Models of Cervical Cancer Prevention in Latin America and the Caribbean. *Vaccine* 26: L59-L72.
- Gregg, J. (2011). An unanticipated source of hope: stigma and cervical cancer in Brazil. *Medical Anthropology Quarterly* 25(1):70-84
- Gregson, N., Sparrowhawk, K., Mauskopf, J. and Paul, J. (2005). Pricing medicines: theory and practice, challenges and opportunities. *Nature reviews, Drug discovery* 4 (Feb): 121-130.

- Griffin, S. and Claxton, K. (2011). Analysing uncertainty in cost-effectiveness for decision making. In: *Oxford Handbook of Health Economics*. S. Glied and P. Smith (eds). Oxford: Oxford University Press.
- Guerrero R, Gallego AI, Becerril-Montekio V, Vásquez J. (2011). Sistema de salud de Colombia. *Salud Publica Mex* 53 (2): S144-S155.
- Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, Atkins D, Kunz R, Brozek J, Montori V, Jaeschke R, Rind D, Dahm P, Meerpohl J, Vist G, Berliner E, Norris S, Falck-Ytter Y, Murad MH, Schunemann HJ. (2011). GRADE guidelines: 9. Rating up the quality of evidence. *Journal of Clinical Epidemiology* 64: 1311-1316.
- Haas, M., Ashton, T., Blum, K., Christiansen, T., Conis, E., Crivelli, L., Lim, M. K., Lisac, M., Macadam, M. and Schlette, S. (2009). Drugs, sex, money and power: an HPV vaccine case study. *Health policy* 92(2-3): 288.
- Hacking, I. (1975). *The emergence of probability: a philosophical study of early ideas about probability, induction and statistical inference*. London: Cambridge University Press.
- Hacking, I. (1990). *The taming of chance*. Cambridge: Cambridge University Press.
- Hacking, I. (2001). *An introduction to probability and inductive logic*. Cambridge: Cambridge University Press.
- Haraway, D. (1997). *Modest witness @ second millenium: femaleMan meets OncoMouse: feminism and technoscience*. London: Routledge.
- Harrison, S, Barnes, M & Mort, M. (1997). High Praise and Damnation: Mental Health User Groups and the Construction of Organisational Legitimacy. *Public Policy and Administration* 12(2): 4-16.
- Harrison, S. (1998). The Politics of Evidence-Based Medicine in the UK. *Policy and Politics* 26(1): 15-31.
- Harrison, S. and Mort, M. (1998). Which Champions, Which People? Public and User Involvement in Health Care as a Technology of Legitimation. *Social Policy & Administration* 32(1): 60-70.
- Harrison, S., Moran, M. and Wood, B. (2008). Policy emergence and policy convergence: the case of 'scientific-bureaucratic medicine' in the United States and United Kingdom. *The British Journal of Politics & International Relations* 4(1): 1-24.
- Hayles, K. (2002). *Writing Machines*. Cambridge, Massachusetts: MIT Press.
- Hedgecoe A. (2009). A form of Practical Machinery: The origins of Research Ethics Committees in the UK: 1967-1972, *Medical History* 53: 331-350.

- Hedgecoe A. (2012). Trust and regulatory organizations: the role of Local Knowledge and Facework in Research Ethics Review. *Social Studies of Science* 42(5): 662-683.
- Hénaff, M. (2010). *The Price of Truth: Gift, Money and Philosophy*. Stanford: Stanford University Press.
- Herper, M. (2012). *The Gardasil Problem: How The U.S. Lost Faith In A Promising Vaccine*, Forbes, 23rd April 2012.
- Hicken, A. (2011). Clientelism. *Annual Review of Political Science* 14: 289-310.
- Hilgartner, Stephen. (2000). *Science on Stage: Expert Advice as Public Drama*. Stanford: Stanford University Press.
- Hill, AB. (1965). The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine* 58:295–300.
- Hillemanns, P., Breugelmans JG, Giesecking F, Bénard S, Lamure E, Littlewood KJ, Petry KU. (2008). Estimation of the incidence of genital warts and the cost of illness in Germany: a cross-sectional study. *BMC Infectious Diseases* 2: 8-76.
- Hogarth, S., Hopkins, M. and Rodriguez, V. (2011). A molecular monopoly? HPV testing, the Pap smear and the molecularisation of cervical cancer screening in the USA. *Sociology of Health & Illness* 20(10): 1–17.
- IETS (Instituto para la Evaluación de Tecnologías en Salud), (2013). *Guía Metodológica para la elaboración de Guías de Práctica Clínica con Evaluación Económica en el Sistema General de Seguridad Social en Salud Colombiano*. Bogotá: COLCIENCIAS-IETS.
- Instituto Nacional de Cancerología (INC). (1994). *Guía Atención Integral Cáncer de cuello uterino*. Washington: PAHO.
- Instituto Nacional de Cancerología (INC). (2005). *Atlas de mortalidad por cáncer en Colombia*. Bogotá: Instituto Nacional de Cancerología.
- Intemann, K. and de Melo-Martin, I. (2010). Social values and scientific evidence: the case of the HPV vaccines. *Biology & Philosophy* 25(2): 203-213.
- International Agency for research on Cancer (IARC) (2007). *Monographs on the Evaluation of Carcinogenic Risks to Humans*. Volume 90. Lyon: IARC.
- Jaramillo C. (2011). *Situación y perspectivas del sistema de seguridad social en Colombia: Salud y pensiones*. Consultoría para el BID. Bogotá.
- Jasanoff, S. (2003). Technologies of humility. *Minerva*, 41(3): 223–244.

- Jasanoff, S. (2004). *Designs on Nature: Science and Democracy in Europe and the United States*. Princeton: Princeton University Press.
- Jasanoff, S. (2007). Technologies of humility. *Nature* 450 (7166)
- Jones, James. (1993). The Tuskegee Syphilis Experiment: A Moral Astigmatism. In: *The Racial Economy of Science*. 275-286.
- Kane, M. A., Sherris, J., Coursaget, P., Aguado, T. and Cutts, F. (2006). Chapter 15: HPV vaccine use in the developing world. *Vaccine* 24: S132-S139.
- King, N. (2002). Security, Disease, Commerce: Ideologies of Post-Colonial Global Health. *Social Studies of Science* 32(5/6): 763-789.
- Kjellberg, H., Mallard, A. (2013). (Diane-Laure Arjaliès, Patrik Aspers, Stefan Beljean, Alexandra Bidet, Alberto Corsin, Emmanuel Didier, Marion Fourcade, Susi Geiger, Klaus Hoeyer, Michèle Lamont, Donald MacKenzie, Bill Maurer, Jan Mouritsen, Ebba Sjögren, Kjell Tryggestad, François Vatin, and Steve Woolgar. Valuation Studies? Our Collective Two Cents. *Valuation Studies* 1(1): 11–30.
- Kwok, R. (2011). The real issues in vaccine safety. Hysteria about false vaccine risks often overshadows the challenges of detecting the real ones. *Nature* 473 (26): 437-442.
- Lakoff, A. (2005). *Pharmaceutical Reason: Knowledge and Value in Global Psychiatry*. Cambridge: Cambridge University Press
- Latour, B. (1987). *Science in action: how to follow scientists and engineers through society*. Cambridge, Mass: Harvard University Press.
- Latour, B. (1994). *We Have Never Been Modern*. Cambridge, Mass: Harvard University Press.
- Latour, B. (2004a). *Reassembling the Social. An Introduction to Actor-Network-Theory*. Oxford: Oxford University Press.
- Latour, B. (2004b). Why Has Critique Run Out of Steam? From Matter of Fact to Matters of Concern. *Critical Inquiry*, Winter, 30: 225-248
- Latour, B. and Woolgar, S. (1986). *Laboratory Life: the Social Construction of Scientific Facts*. Princeton: Princeton University Press.
- Law, J. (1994). *Organising Modernity*. Oxford: Blackwell.
- Law, J. (2001). Ordering and Obduracy. Centre for Science Studies. Lancaster University. <http://www.lancaster.ac.uk/sociology/research/publications/papers/law-ordering-and-obduracy.pdf> (Accessed 12th March 2014).

- Law, J. (2004). *After method* [electronic resource]: mess in social science research. London: Routledge.
- Leach, M. and Fairhead, J. (2007). *Vaccine Anxieties: Global Science, Child Health and Society*. London: Taylor & Francis.
- Leach, M. and Fairhead, J. (2008). Understandings of immunization: some West African perspectives. *Bulletin of the World Health Organization* 86(6): 418.
- Leach, Melissa. (2005). *MMR mobilisation: citizens and science in a British vaccine controversy*. Brighton: Institute of Development Studies.
- Lezaun, J. (2009). The pragmatic sanction of materials: notes for an ethnography of legal substances. (European Union) (Material Worlds: Intersections of Law, Science, Technology, and Society). *Journal of Law and Society* 39: 20-38.
- Linden, L. (2013). What do Eva and Anna have to do with cervical cancer? Constructing adolescent girl subjectivities in Swedish Gardasil advertisements. *Girlhood Studies*, 6(2): 83-100.
- Livingstone, J. (2012). *Improvising Medicine: An African Oncology Ward in an Emerging Cancer Epidemic*. Durham: Duke University Press.
- Livingstone, J. Wailoo, K., Cooper, B. (2010). Vaccination as governance: HPV Skepticism in the United States, Africa and the North-South Divide. In *Three Shots at Prevention: The HPV Vaccine and the Politics of Medicine's Simple Solutions*. K. Wailoo, J. Livingston, S. Epstein and R. Aronowitz (eds.). Baltimore: The Johns Hopkins University Press.
- Londoño, J. and Frenk, J. (1997). Structured pluralism: towards an innovative model for health system reform in Latin America. *Health Policy* 41:1-36.
- Löwy, I. (2011). *A woman's disease: The history of cervical cancer*. Oxford: Oxford University Press.
- Lynch, M. (1985). Discipline and the Material Form of Images: An Analysis of Scientific Visibility. *Social Studies of Science* 15(1): 37-66.
- Lynch, M. (1988). The externalized retina: Selection and mathematization in the visual documentation of objects in the life sciences. *Human Studies* 11 (2-3): 201-234.
- Mackenzie, A. (2013). *Distributive numbers: a neo-Baroque perspective on probability*. Lancaster: Lancaster University (Unpublished Paper).
- Mackenzie, A. (2014). Multiplying numbers differently: an epidemiology of contagious convolution. *Distinktion: Scandinavian Journal of Social Theory* 15(2): 189-207.
- Mackenzie, D. (1978). Statistical theory and social interests: a case-study. *Social studies of science* 8(1): 35.

- Mackenzie, D. (1981). *Statistics in Britain, 1865-1930: The Social Construction of Scientific Knowledge*. Edinburgh: Edinburgh University Press.
- Mackenzie, D. (2006). *An Engine, Not a Camera. How Financial Models Shape Markets*. Cambridge: MIT Press.
- Mahoney, R. T., Krattiger, A., Clemens, J. D. and Curtiss, R. (2007). The introduction of new vaccines into developing countries. IV: Global Access Strategies. *Vaccine* 25(20): 4003.
- Maldonado, O. J. (2011). Textualidad, interpretación y construcción del cuerpo. Políticas ontológicas de la interrupción voluntaria del embarazo en Colombia. Master in Sociology, Bogotá, Colombia: Universidad Nacional de Colombia.
- Malmqvist, E., Helgesson, G., Lehtinen, J., Natunen, K. and Lehtinen, M. (2011). The ethics of implementing human papillomavirus vaccination in developed countries. *Medicine Health Care and Philosophy* 14(1): 19-27.
- Mamo, L. and Epstein, S. (2014). The pharmaceuticalization of sexual risk: Vaccine development and the new politics of cancer prevention. *Social Science & Medicine* 101: 155-165.
- Mamo, L., A. Nelson & A. Clark. (2010). Producing and Protecting Risky Girlhoods: How the HPV Vaccine Became the Right Tool to Prevent Cervical Cancer. In: *Three Shots at Prevention: The HPV Vaccine and the Politics of Medicine's Simple Solutions*. K. Wailoo, J. Livingston, S. Epstein and R. Aronowitz (eds.). Baltimore: The Johns Hopkins University Press.
- Mankiw, G. (2011). *Principles of Economics* (6th ed.). Cengage Learning. ISBN 978-0-538-45305-9.
- Mansnerus, E. (2009). 'The lives of 'facts' in mathematical models: a story of population level disease transmission of haemophilus influenzae type B bacteria. *BioSocieties* 4:207-222.
- Mansnerus, E. (2013). Using model-based evidence in the governance of pandemics. Special issue Sociology of Pandemics: Crisis and Transparency in Social Order. *Sociology of Health and Illness* 35 (2): 280-291.
- Marcus, G. (1998). *Ethnography through thick and thin*, Princeton: Princeton University Press.
- Marx, W. (2013). Pakistan's Polio War. Financial Times, 7th June 2013
- Mattheij, I., Pollock, A. M. and Brhlikova, P. (2012). Do cervical cancer data justify HPV vaccination in India? Epidemiological data sources and comprehensiveness. *Journal of the Royal Society of Medicine* 105(6): 250.
- Mauss, M. (1954). *The gift: forms and functions of exchange in archaic societies*, London: Coehn & Kamp.

- Mayer, D. (2010). *Essential evidence-based medicine*. Cambridge: Cambridge University Press.
- Mayor Mora, A., Arias, A. and Menjura, F. H. (2010). *Cruzada interminable por la Niñez Colombiana. Historia del Programa Ampliado de Inmunizaciones -PAI- en Colombia 1979-2009*, Bogotá: Ministerio de la Protección-OPS/OMS Colombia.
- McGee, G. (2007). How much should Gardasil cost? *The Scientist*, 1st August 2007 <http://www.the-scientist.com/?articles.view/articleNo/25267/title/How-Much-Should-Gardasil-Cost/> (Accessed 10.10.2012).G
- Mckee, A. (2003). *Textual Analysis. A beginners guide*. London: SAGE.
- McNeil D. (2006). How a Vaccine Search Ended in Triumph. *The New York Times*. August 29. <http://www.nytimes.com/2006/08/29/health/29hvp.html>.
- McNeil, M. (2005). Introduction: Postcolonial Technoscience. *Science as Culture* 14(2): 105-112.
- Mirowski, P. (2002). *Machine Dreams: Economics Becomes a Cyborg Science*. Cambridge: Cambridge University Press.
- Mirowski, P. (2011). *SCIENCE-MART: Privatizing American Science*. Cambridge: Harvard University Press.
- Mishra, A. and Graham, J. (2012). Risk, choice and the 'girl' vaccine: Unpacking HPV Immunization. *Health, Risk & Society*. Vol 14(1): 57-69.
- Mol, A. (2008). *The Logic of Care: Health and the Problem of Patient Choice*. London: Routledge.
- Mol, A. (2002). *The body multiple: ontology in medical practice*, Durham and London: Duke University Press.
- Montgomery, C. (2010). The Co-production of Gender and Technology in HIV Programme. A Case Study of the Microbicides Development Programme. Department of Public Health & Policy, Doctor of Philosophy Thesis. London: London School of Hygiene and Tropical Medicine.
- Moreira, T. (2005). Diversity in clinical guidelines: the role of repertoires of evaluation. *Social Science & Medicine* 60(9): 1975.
- Moreira, T. (2007). Entangled evidence: knowledge making in systematic reviews in healthcare. *Sociology of Health & Illness* 29 (2):180-197.
- Moreira, T. (2012a). Health Care Standards and the Politics of Singularities: Shifting In and Out of Context. *Science, Technology and Human Values* 37: 307-331

- Moreira, T. (2012b). *The Transformation of Contemporary Health Care. The Market, the Laboratory, and the Forum*. New York-Oxon: Routledge.
- Moreira, T. and Will, C. (2010). *Medical proofs, social experiments: clinical trials in shifting contexts*, Edited by C. Will and T. Moreira. Farnham: Ashgate.
- Mosse, D. (2005). *Cultivating Development. An Ethnography of Aid Policy and Practice*, London: Pluto.
- Muniesa, F., Millo, Y., & Callon, M. (2007). An introduction to market devices. In: *Market devices*. M. Callon, Y. Millo & F. Muniesa (eds.). Malden, MA: Blackwell.
- Munira, S. L. and Fritzen, S. A. (2007). What influences government adoption of vaccines in developing countries? A policy process analysis. *Social Science and Medicine* 65:1751-1764.
- Muñoz, N., Bosch, F. X., de Sanjose, S., Herrero, R., Castellsague, X., Shah, K. V., Snijders, P. J. F., Meijer, C. and Int Agcy Res Canc Multicenter, C. (2003). Epidemiologic classification of human papillomavirus types associated with cervical cancer, *New England Journal of Medicine* 348(6): 518-527.
- Muñoz, N., Mendez, F., Posso, H., Molano, M., van den Brule, A. J. C., Ronderos, M., Meijer, C., Munoz, A. and Ist Nacl Cancerologia, H. P. V. S. G. (2004). Incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results. *Journal of Infectious Diseases* 190(12): 2077-2087.
- Murillo, R. (2008). Control del cáncer de cuello uterino en Colombia: triunfos y desafíos de la tamización basada en la citología cérvico-uterina. *Biomédica* 28(4): 467.
- Murillo, R., Almonte, M., Pereira, A., Ferrer, E., Gamboa, O. A., Jeronimo, J. and Lazcano-Ponce, E. (2008). 'Cervical Cancer Screening Programs in Latin America and the Caribbean', *Vaccine* 26: L37-L48.
- Murray CJ and Frenk, J. (2000). World Health Report 2000: a step towards evidence-based health policy. *Lancet* 357: 1698–1700
- Murray, CJ and Lopez AD. (1996). *Global Burden of Disease: A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020*. Cambridge, MA: Harvard University Press.
- Murray, CJ. (1994). Quantifying the burden of disease: the technical basis for disability-adjusted life years. *Bulletin of the World Health Organisation* 72(3): 429–445.
- Murray, CJ; Ezzati M; Flaxman AD, Lim S, Lozano R, Michaud C, Naghavi M, Salomon JA, Shibuya K, Vos T, Lopez AD. (2012). GBD 2010: a multi-investigator collaboration for global comparative descriptive epidemiology. *Lancet* 15: 380.

- Myers, G. (1996). Strategic Vagueness in Academic Writing. In: *Academic Writing: Intercultural and textual issues*. Anna Mauranen (ed.). Amsterdam: John Benjamins Publishing Company.
- Next Generation Pharmaceuticals (NGP). 2007. A Vaccine gives marketing lessons. <http://www.ngpharma.com/article/A-Vaccine-Gives-Marketing-Lessons/> (Accessed, 29.06.2013)
- Nguyen A, Datta SD, Schwalbe N, Summers D, Adlidge G, and the GAVI Alliance. (2011). Working towards affordable pricing for HPV vaccines for developing countries: The role of GAVI. GTF. *CCC Working Paper and Background Series*, No. 3, Harvard Global Equity Initiative.
- Noorbakhsh, F. (1998). The Human Development index: Some technical issues and Alternative indices. *Journal of International Development* 10: 589-605
- Núñez, J; Zapata, J; Castañeda, C; Fonseca, S. and Ramírez, J. (2012). *La Sostenibilidad Financiera del Sistema de Salud Colombiano -Dinámica del gasto y principales retos de cara al futuro*. Bogotá: Fedesarrollo.
- Oshinowo, B., Ng-Haing, J. and Grosvenor, A. (2011). Critical Success Factors for uptake of Novel Vaccines into National Immunization Programs. *ISPOR 16th Annual International Meeting. 21-25 May 2011*, Baltimore.
- Oudshoorn, N. (2003). *The Male Pill. A biography of a Technology in the Making*. Durham and London: Duke University Press.
- Padmanabhan, S., Amin, T., Sampat, B., Cook-Deegan, R. and Chandrasekharan, S. (2012). Intellectual property, technology transfer and manufacture of low-cost HPV vaccines in India. *Nature biotechnology* 28(7): 671.
- Pagliusi, S. R. and Teresa Aguado, M. (2004). Efficacy and other milestones for human papillomavirus vaccine introduction. *Vaccine* 23(5): 569.
- PAHO and Institute Sabin. (2008). Carga de enfermedad por el Virus del VPH en Latino-américa y el Caribe y costo efectividad de la vacunación, en I Reunión Latinoamericana sobre control de cáncer de cuello cérvico-uterino. 2008: México DF. http://www.sabin.org/files/dagna_o._constenla.pdf (Accessed 4th September 2012).
- PAHO. (2013). PAHO Revolving Fund. Description and Guidelines. www.paho.org/hq/index.php?option=com_docman&task (Accessed 01.09.2013).
- PAHO. Organización Panamericana de la Salud. (2011). Grupo técnico asesor sobre enfermedades prevenibles por vacunación. Buenos Aires, Argentina, 6 a 8 de julio de 2011.
- Parry J, and Bloch M. (1989). *Money and the Morality of Exchange*. Cambridge: Cambridge University Press

- PATH-IAVI. (International AIDS Vaccine Initiative/Program for Appropriate Technology in Health). (2007). *HPV Vaccine Adoption in Developing Countries: Cost and Financing Issues*. IAVI-PATH, New York.
- Peirce, C. (1982). *Writings of Charles S. Peirce: A chronological edition*. Bloomington: Indiana University Press.
- Peirce, C. (1998). *The Essential Peirce. Volume 2. Eds. Peirce edition Project*. Bloomington: Indiana University Press.
- Petryna, A. (2011). *The competitive logic of global clinical trials*.(Part II: Buying and Selling the Body)(Essay). *Social Research* 78(3): 949.
- Petryna, A., Lakoff, A. and Kleinman, A. (2006) *Global pharmaceuticals: ethics, markets, practices*, Durham: Duke University Press.
- Pharma Innovation Hub. (2009). The story of Gardasil. Innovation Awards. www.innovation.org/index.cfm/StoriesofInnovation/InnovatorStories/The_Story_of_Gardasil (Accessed 20.8.2012)
- Pinch, T., Ashmore, M. and Mulkay, M. (2000). Cost Benefit analysis in practice: option appraisal in the UK National Health Service and the politics of rational decision-making. In: *Facts and Figures: Economic Representations and Practices*. R. Rottenburg, H. Kalthoff and H-J. Wagener, (eds). (Ökonomie und Gesellschaft, Jahrbuch 16), Marburg: Metropolis-Verlag. 87-116,
- Piñeros, M., Cendales, R., Murillo, R., Wiesner, C. and Tovar, S. (2007). Pap test coverage and related factors in Colombia, 2005, *Revista de Salud Publica* 9(3): 327-41.
- Plaza, B. (1997). *Cost effectiveness & priority setting*. Case study. Washington: World Bank.
- Porter, T. (1992). Objectivity as Standardization: The Rhetoric of Impersonality in Measurement, Statistics, and Cost-Benefit Analysis. *Annals of Scholarship*, 9 (1992): 19-59; reprinted in Allan Megill, ed., *Rethinking Objectivity* (Durham: Duke University Press, 1994), 197-237.
- Porter, T. (1995). *Trust in Numbers: The Pursuit of Objectivity in Science and Public Life*. Princeton: Princeton University Press.
- Porter, T. (2008). Locating the Domain of Calculation. *Journal of Cultural Economy* 1 (1): 39-50.
- Profamilia. (2011). *Encuesta Nacional de Demografía y Salud 2010, Bogotá, Colombia: Profamilia, USAID*, Bogotá: Ministerio de Protección social and Instituto Colombiano de Bienestar Familiar.
- Rabeharisoa, V., Moreira, T. and Akrich, M. (2014). Evidence-based activism: Patients', users' and activists' groups in knowledge society. *Biosocieties* 9(2): 111-128.

- Ramogola-Masire, D. 2010. Cervical Cancer, HIV, and the HPV Vaccine in Botswana. In: *Three Shots at Prevention: The HPV Vaccine and the Politics of Medicine's Simple Solutions*. K. Wailoo, J. Livingston, S. Epstein and R. Aronowitz (eds.). Baltimore: The Johns Hopkins University Press.
- Reid, BL; French PW, Singer A, Hagan BE. (1978). Coppleson M. Sperm basic proteins in cervical carcinogenesis: Correlation with socioeconomic class. *Lancet* 8(2):60–62.
- Restrepo Forero, Olga. (2003). *On writing review article and constructing fields of study*. Ph.D. Thesis. Department of Sociology, University of York, York, United Kingdom.
- Reynolds, L. and Tansey, E. (2009). History of Cervical Cancer and the Role of the Human Papillomavirus, 1960-2000. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 38. London: Wellcome Trust.
- Roalkvam, S. and Sandberg , K. (2010). Vaccines and the global system/or why study vaccines. *Forum for Development Studies* 37(3): 293-299.
- Roberts, C. (2010). Early puberty and public health: a social scientific pinboard. *Critical Public Health* 20(4): 429-438.
- Rose, N. (2001). The politics of life itself. *Theory, culture and society* 18: 1-30.
- Safford, F and Palacios, M. (2002). *Colombia: Fragmented Land, Divided Society*. Oxford: Oxford University Press.
- Sandberg, K. I., Andresen, S. and Bjune, G. (2010). A new approach to global health institutions? A case study of new vaccine introduction and the formation of the GAVI Alliance. *Social Science & Medicine* 71(7): 1349-1356.
- Sassi, F. (2006). Calculating QALYs, comparing QALY and DALY calculations. *Health Policy and Planning* 21(5): 402-408.
- Scotto, J and Bailard, J. (1969). Rigoni Stern and medical statistics: A nineteenth-century approach to cancer research. *Journal of the History of Medicine and Allied Sciences* 24(1): 65–75.
- Sen, A. (1998). The Possibility of Social Choice, Nobel lecture. http://nobelprize.org/nobel_prizes/economics/laureates/1998/sen-lecture.pdf. (Accessed 20th August 2013)
- Shapin, S. (1984). Pump and Circumstance: Robert Boyle's Literary Technology. Steven Shapin. *Social Studies of Science* 14(4): 481-520.
- Shapin, S. and Schaffer, S. (1985). *Leviathan and the air-pump: Hobbes, Boyle, and the experimental life*. Princeton: Princeton University Press.

- Singleton, V. & Law, J. (2013). Devices as rituals: notes on enacting resistance. *Journal of Cultural Economy* 6(3): 259-277.
- Singleton, V. (1998). Stabilizing instabilities: The role of the laboratory in the United Kingdom Cervical Screening programme. In: *Difference in Medicine: Unraveling Practices, Techniques and Bodies*. A. Mol & M. Berg (eds.) Durham and London: Duke University Press.
- Singleton, V. and Michael, M. (1993). Actor-Networks and Ambivalence: General Practitioners in the UK Cervical Screening Programme. *Social Studies of Science* 23(2): 227-264.
- Sjögren, E. and Helgesson, C.F. (2007). The Q(u)ALYfying hand: health economics and medicine in the shaping of Swedish markets for subsidized. In: *Market devices*. M. Callon, Y. Millo & F. Muniesa (eds). Malden, MA: Blackwell.
- Sloan, F. A. (ed.). (1995). *Valuing Health Care*. Cambridge: Cambridge University Press.
- Smith R., Beaglehole R., Woodward D., Drager N. (ed.). (2003). *Global Public Goods for Health: health economics and public health perspectives*. Oxford: Oxford University Press.
- Smith, D. (1978). 'K is Mentally Ill' the Anatomy of a Factual Account. *Sociology* 12 (1): 25-53.
- Smith, D. (2001). Texts and the ontology of organizations and institutions. *Studies in Cultures, Organizations and Societies* 7(2): 159-198.
- Smith, D. (2005). *Institutional ethnography: A sociology for people*. Walnut Creek, CA: AltaMira Press.
- Smithin, J. (2000). *What is money*. London and New York: Routledge.
- Sonnenberg, F. and Beck, J. (1993). Markov models in medical decision making: a practical guide. *Medical Decision Making* 13(4):322-38.
- Stanley, M. 2010. HPV-immune response to infection and vaccination. *Infect Agent Cancer* 5: 19.
- Stark, D. (2009). The sense of dissonance. *Accounts of worth in economic life*, Princeton and Oxford: Princeton University Press.
- Stevens, A. J. (2001). *The Advanced Handbook of Methods in Evidence Based Healthcare*. London: SAGE Publications.
- Stöckl, A. (2010). Public Discourses and Policymaking: The HPV Vaccination from the European Perspective. In: *Three Shots at Prevention. The HPV Vaccine and the Politics of Medicine's Simple Solutions*. K. Wailoo, S. Epstein and R. Aronowitz. (ed) Baltimore: The Johns Hopkins University University Press.
- Suchman, L. (2000). Organising alignment: a case of bridge-building. *Organization* 7 (2): 311-327.

- Suchman, L. (2012). Configuration. In: *Inventive Methods*. C. Lury and N. Wakeford (eds.) London: Routledge. 48-60.
- Sunder Rajan, K. (2006). *Biocapital: The Constitution of Post-Genomic Life*. Durham: Duke University Press.
- Sunder Rajan, K. (2007). Experimental Values: Indian Clinical Trials and Surplus Health. *New Left Review* 45:67-88
- Teixeira, L. and Löwy, I. (2011). Imperfect tools for a difficult job: Colposcopy, colpocytology and screening for cervical cancer in Brazil. *Social Studies of Science* 41(4): 585-608.
- Timmermans, S. and Berg, M. (2003). *The gold standard: the challenge of evidence-based medicine and standardization in health care*. Philadelphia: Temple University Press.
- Titmuss, R. M. (1997). *The gift relationship: from human blood to social policy*. London: London School of Economics.
- Tomljenovic, L. (2011). Human papillomavirus (HPV) vaccine policy and evidence-based medicine: are they at odds? *Annals of Medicine* 45(2):182-93
- UNFPA-WHO. (2006). *Preparing for the introduction of HPV vaccines: policy and programme guidance for countries*. Geneva: WHO Press.
- Universidad Nacional de Colombia (UNAL). (2009). Estudio de costo-effectividad para la introducción de la vacuna contra Papiloma humano en Colombia. Bogotá, Colombia.
- Universidad Nacional de Colombia (UNAL). (2011). *Estudio de costo-effectividad para la introducción de la vacuna contra Papiloma humano en Colombia*. Bogotá.
- Vardeman-Winter, J. (2012). Medicalization and Teen Girls' Bodies in the Gardasil Cervical Cancer Vaccine Campaign, *Feminist Media Studies*, 12 (2): 281-304.
- Verran, H. (2012a). Number. In: *Inventive Methods: The Happening of the Social*. C. Lury and N. Wakeford (eds). London: Routledge Books.
- Verran, H. (2012b). The changing lives of measures and values: from centre stage in the fading 'disciplinary' society to pervasive background instrument in the emergent 'control' society. *The Sociological Review*. Special Issue: Sociological Review Monograph Series: Measure and Value, L. Adkins and C. Lury (eds) 59 (s2): 60-72.
- Victoria State Government. (2001). Victorian Burden of Disease Study. [http://docs.health.vic.gov.au/docs/doc/6AEAFAB1BAE696B9CA257886000158A0/\\$FILE/bod_2001.pdf](http://docs.health.vic.gov.au/docs/doc/6AEAFAB1BAE696B9CA257886000158A0/$FILE/bod_2001.pdf) (Accessed 5th May 2014).

- Waldby, C. (2002). Stem cells, tissue cultures and the production of biovalue. *Health* 6(3): 305-323.
- Waldby, C. and Mitchell, R. (2006). *Tissue economies: blood, organs, and cell lines in late capitalism*. Durham: Duke University Press.
- Walden, M. (2008). Price versus cost. http://www.ncsu.edu/project/calscommblogs/economic/archives/2008/06/price_versus_co.html (Accessed 15.09.2013).
- WHO. (World Health Organisation). (2002). *Global Burden of disease 2002*. <http://www.who.int/healthinfo/paper54.pdf> (Accessed 25th January 2014).
- WHO. (2007). Strengthening cervical cancer prevention in Europe: meeting of policy-makers and programme managers, Copenhagen, Denmark, 29-31 May 2007. Copenhagen: WHO Regional Office for Europe.
- WHO. (2008). *Cervical cancer, human papillomavirus (HPV) and HPV vaccines: key points for policy-makers and health professionals*. Geneva: World Health Organization.
- WHO. (2009). Human papillomavirus vaccines. *WHO position Paper. Weekly Epidemiological Record* 84:118-31.
- WHO. (2011a). Strategic Advisory Group of Experts (SAGE) on Immunization. <http://www.who.int/immunization/sage/en/>. (Consulted 12th December 2012).
- WHO. (2011b). Guidance for the Development of Evidence-Based Vaccine related Recommendations. Version 12 August 2011. (Consulted 12th December 2012).
- WHO. (2012). Global burden of disease. Guidelines and definitions. http://www.who.int/topics/global_burden_of_disease/en/ (Accessed 2nd December 2012).
- WHO. (2013). HPV vaccines and Human Papillomavirus. http://www.who.int/reproductivehealth/publications/cancers/IVB_07.05/en. (Accessed 12th May 2013).
- WHO, (2014). Cost effectiveness and strategic planning (WHO-CHOICE). <http://www.who.int/choice/description/en/> (Accessed, 19th February 2014).
- WHO/ICO. (2010). Information Centre on HPV and Cervical Cancer (HPV Information Centre). *Human Papillomavirus and Related Cancers in Colombia. Summary Report 2010*. [12/08/2012]. Available at www.who.int/hpvcentre/.
- Wiesner, C. Murillo, R., Piñeros, M. Lourdes, S., Cendales, R. and Cielo, M. (2009). Control del cáncer cervicouterino en Colombia: la perspectiva de los actores del sistema de salud Control of cervical cancer in Colombia: the perspective of the health system. *Revista Panamericana de Salud Pública* 25(1): 1.

- Wiesner, C., Acosta, J., Díaz del Castillo, A. and Tovar, S. (2012). Social Representations of Human Papillomavirus in Bogotá, Colombia. *Medical Anthropology* 31(1): 77-92.
- Wiesner, C., Cendales, R., Murillo, R., Piñeros, M. and Tovar, S. (2010a). Following-up females having an abnormal Pap smear in Colombia. *Revista de Salud Publica* 12(1): 1-13.
- Wiesner, C., M. Piñeros, L. M. Trujillo, C. Cortés, and J. Ardila. (2010). Human papillomavirus (HPV) vaccine acceptability amongst parents of adolescents in four Colombian areas. *Revista de Salud Publica* 12(1):961-73.
- Woodman, CB; Collins, SI; Young LS. (2007). The natural history of cervical HPV infection: unresolved issues. *Nature Reviews Cancer* 7(1):11-22.
- World Bank. (1993). *World Development Report: Investing in Health*. Washington: World Bank.
- World Bank. (2014). Middle income countries. <http://www.worldbank.org/en/country/mic> (Accessed, 20th July 2014).
- Wynne, B. (2010). *Rationality and Ritual: Participation and Exclusion in Nuclear Decision-making*. London: Earthscan.
- Yuen, W.-m. (2012). Systematic review on the cost effectiveness of human papillomavirus vaccination in Asia and its implication in Hong Kong. Master in Public Health Dissertation. Hong Kong: University of Hong Kong .
- Zeifel, P. Breyer, F. and Kifmann, M. (2009). *Health Economics*. Oxford: Oxford University Press.
- Zelizer, V. (1998). The Proliferation of Social Currencies. In: *The Laws of the Markets*. M. Callon (ed.) Oxford: Blackwell. 58-68.
- Zur Hausen, H. (1996). Papillomavirus infections: A major cause of human cancers. *Biochimica Et Biophysica Acta-Reviews on Cancer* 1288(2): F55-F78.
- Zweifel, P. (2009). *Health economics*. New York: Springer.

Official documents and Policies

Ministry of Health, National Committee of immunisations, expanded programme of immunisations.
República de Colombia.

1. Agenda National Committee of immunisation practices, 3rd May 2012. Bogotá: Ministry of Health.
2. Meeting minute SGC-F03. "Definition of introduction of vaccine against HPV and Hepatitis A into Extended Programme of Immunisations". National Committee of immunisation practices, 3rd May 2012. Bogotá: Ministry of Health.
3. Statistics Vaccination Journey against Human Papillomavirus. Subdirection of transmittable diseases. Ministry of Health.
4. Agreement No 01 of 2011, 4th August of 2011. "Definition of operative rules of the National Committee of immunisation practices" Bogotá: Ministry of Health.
5. Final Inform Project Ministry of Health. **2009. Cost-effectiveness of vaccines against HPV in Colombia I.** Team: Fernando De la Hoz Restrepo, Nelson Alvis Guzmán and Carlos Andrés Castañeda. Universidad Nacional de Colombia.
6. Final Inform Project Ministry of Health. **2011. Cost-effectiveness of vaccines against HPV in Colombia II.** Team: Fernando De la Hoz Restrepo, Nelson Alvis Guzmán and Carlos Andrés Castañeda. Universidad Nacional de Colombia.
7. Commercial National Vaccination Journey against Cervical Cancer. Colombia. 2012.
8. MPS. (Ministerio de Protección Social). 2008. "Lineamientos Para La Introducción De Nuevas Vacunas En El Programa Ampliado De Inmunizaciones." edited by República de Colombia. Ministerio de la Protección Social and Programa ampliado de inmunizaciones Dirección General de Salud Pública. Bogotá, Colombia.
9. MPS. (Ministerio de Protección Social). 2012. "Lineamientos Técnicos Y Operativos Para La Vacunación Contra El Virus Del Papiloma Humano (Vph). Primera Fase". Programa Ampliado de Inmunizaciones. Subdirección de enfermedades transmisibles. Dirección de Promoción y Prevención. Ministerio de Protección social. República de Colombia. Bogotá, Colombia: Ministerio de Protección Social.
10. Technical statement about Law project L 260-2012 and arguments of cost-effectiveness vaccine against HPV. 6th November of 2012. Radication No.: 201221102384491. Bogotá: Ministry of Health.
11. "Cruzada interminable por la niñez colombiana" History of the extended programme of immunisations in Colombia 1979-2009. Bogotá: Ministry of Health.

12. Guzmán, Lely Stella. La vacuna contra el virus del papilloma humano. ¿es una alternativa de protección de la vida sin mayor riesgo? Master in Bioethics dissertation. Bogotá: Universidad El Bosque. 2010.

Colombian National Cancer Institute

Technical Guidelines:

1. Normas técnicas y administrativas. Guía de implementación. Detección y control del cáncer de cuello uterino. Bogotá: Instituto Nacional de Cancerología. 1994.
2. Manual de normas y procedimientos para el control del cáncer de cuello terino. Washington: OMS-OPS. 1990.
3. Manual de normas técnico-administrativas. Ministerio de Salud. República de Colombia. Bogotá: PATHfinder. 1987.
4. Memorias II Convención Colombiana de Obstetricia y Ginecología. Nov. 29. Cali, Colombia. 1955.
5. Villegas P, Octavio. Resultados inmediatos de la Radioterapia en algunos casos de cancer de cuello uterino. Bogotá: Universidad Nacional de Colombia. 1936.

Colombian National Institute for Food and Drug Surveillance (INVIMA)

1. Resolution No 2012001420 26th January of 2012.
2. INVIMA. "Acta 17." edited by Ministerio de la Protección Social. República de Colombia Sala especializada de medicamentos y productos biológicos de la comisión revisora. Instituto Nacional de Vigilancia de Medicamentos y Alimentos INVIMA. Bogotá, Colombia, 2006.
3. ———. "Acta 34." edited by Ministerio de la Protección Social. República de Colombia Sala especializada de medicamentos y productos biológicos de la comisión revisora. Instituto Nacional de Vigilancia de Medicamentos y Alimentos INVIMA. Bogotá, Colombia, 2006.
4. ———. "Acta 52." edited by Sala especializada de medicamentos y productos biológicos. Instituto Nacional de Vigilancia de Medicamentos y Alimentos. Ministerio de Protección Social. Bogotá, Colombia, 2011.
5. ———. "Acta 58." edited by Sala especializada de medicamentos y productos biológicos de la comisión revisora. Instituto Nacional de Vigilancia de Medicamentos y Alimentos. Ministerio de Protección Social. Bogotá, Colombia. 2009.
6. ———. "Edicto 2011002578." edited by Instituto Nacional de Vigilancia de Medicamentos y Alimentos. Ministerio de Protección social. República de Colombia. Bogotá, Colombia, 2011.
7. ———. "Invima Solicita Vigilancia Activa a Mujeres Vacunadas Contra El Virus Del Papiloma Humano." edited by Instituto Nacional de Vigilancia de Medicamentos y Alimentos. Bogotá, Colombia: INVIMA, 2009.
8. ———. "Registro Sanitario 2006m-006714 Gardasil Reg. Vacuna Recombinante Tetravalente Contra El Vph Tipos 6. 11. 16. 18." edited by Instituto Nacional de Vigilancia de Medicamentos y Alimentos. Ministerio de Protección social.

República de Colombia., 2006.

Bogotá City Council

1. Project of Agreement No. 188 of 2009. “Through it is established the Annual programme for promoting the boost of complete vaccination schema for adolescents and women in reproductive age”.
2. Project of Agreement No. 259 of 2010. “Through there are established prevention actions in the programme of detection and control of cervical cancer in Bogota and other rules”
3. Agreement No 461 of 2011. “Through there are established prevention actions in the programme of detection and control of cervical cancer in Bogota and other rules”

Council of State, República de Colombia

- Class Action. Radication No 25000 2315 000 2010 02728 01. Actor: María Teresa Tovar Rojas. Author: Doctor Marco Antonio Velilla Moreno. 16th February of 2012. Council of State. Republic of Colombia. Bogotá, Colombia, 2012.
- Documental support of the process Class Action. Radication No 25000 2315 000 2010 02728 01. Actor: María Teresa Tovar Rojas. Council of State. Republic of Colombia. Bogotá, Colombia, 2012. Notebook: 1. 430 pages.
 1. Answer Class Action. Radication No 25000 2315 000 2010 02728 01. Actor: María Teresa Tovar Rojas. Council of State. Ministerio de la Protección Social. República de Colombia. Oficina Asesora Jurídica y de Apoyo Legislativo. 30th September of 2010.
 2. Audiencia Especial. Tribunal Administrativo de Cundinamarca. Sección Primera. Sub sección b. 24th September of 2010.
 3. Answer Class Action. Radication No 25000 2315 000 2010 02728 01. Actor: María Teresa Tovar Rojas. CRES, National Health Regulation Commission. 14th March of 2011.
 4. Memorando radicado: 284195, solicitud de concepto técnico radicación 2010-02728. Dirección Nacional de Salud Pública. Ministerio de la Protección Social. República de Colombia. 28th September of 2010.
 5. Memorando Superintendencia de Salud. Answer Class Action Radication No 25000 2315 000 2010 02728 01. Actor: María Teresa Tovar Rojas. Council of State. 22nd June of 2012.
 6. Respuesta radicado 195223 - vacuna contra el Virus del Papiloma Humano — VPH, Acción popular 2010.2728, Accionante María Teresa Tovar Rojas. Ministerio de la Protección Social. República de Colombia. 12th July of 2011.
 7. Impacto epidemiológico y económico de la introducción de la vacuna para virus del papiloma humano. Power point presentation. 2nd July of 2012.
 8. Answer to Cundinamarca Supreme Court. Class Action. Radication No 2010 02728 01. Actor: María Teresa Tovar Rojas. Council of State.

Ministerio de la Protección Social. República de Colombia. 26th July of 2012.

9. Answer to Cundinamarca Supreme Court Class Action. Radication No 25000 2315 000 2010 02728 01. Actor: María Teresa Tovar Rojas. Council of State. CRES, National Health Regulation Commission. 27th July of 2011.
10. Apelación Sentencia primera instancia. Class Action. Radication No 2010 02728 01. Actor: María Teresa Tovar Rojas. Council of State. Ministerio de la Protección Social. República de Colombia. 15th September of 2011.
11. Contrato Interadministrativo N° 375 suscrito entre el Ministerio de la Protección Social y la Universidad Nacional de Colombia. 17th August of 2011.
12. Answer to Council of State Class Action. Radication No 25000 2315 000 2010 02728 01. Actor: María Teresa Tovar Rojas. Council of State. CRES, National Health Regulation Commission. 11th January of 2012.
13. Informe de cumplimiento a fallo. . Class Action. Radication No 2010 02728 01. Actor: María Teresa Tovar Rojas. Council of State. Ministerio de la Protección Social. República de Colombia. 28th May of 2012.

CRES, National Health Regulation Commission

1. Inform of Health technology assessment HTA. Vaccine against Human Papillomavirus. National Health Regulation Commission. October, 2011.
2. Inform of vaccine against Human Papillomavirus. Analysis of financial impact of “UPC” for contributive and subsided regimes”. National Health Regulation Commission. November, 2011.
3. Agreement No 029 of 2011. “Through it is substituted Agreement 028 of 2011 that defines and updates the mandatory health planning”. CRES, National Health Regulation Commission. Republic of Colombia. Bogotá, Colombia, 2011.

Department of Health, Bogotá Mayor Office

- Report vaccination against HPV... for a possible world with women without cervical cancer. (Unpublished). Department of Health, Bogotá Mayor Office. March, 2012.

Congreso Nacional República de Colombia

1. Díaz Ortiz, Gloria, Rafael Romero Piñeros, José Florez Asprilla, and Armando Zabaraín. "Ponencia para primer Debate al proyecto de Ley 028 De 2011 Cámara. “Por medio del cual se garantiza la vacunación gratuita y obligatoria a la población colombiana objeto de la misma, se adoptan medidas integrales para la prevención del cáncer cérvico uterino y se dictan otras disposiciones. [prevención del cáncer cérvico uterino]”." In Gaceta del Congreso, Senado y Cámara, edited by Cámara de Representantes. Bogotá, Colombia: Congreso de la República de Colombia, 2011.
2. Representantes, Cámara de. "Acta numero 23 de 2012. Actas de comisión de la cámara de representantes. comisión séptima constitucional permanente." In

Gaceta del Congreso Senado y Cámara, edited by Cámara de Representantes. Bogotá, Colombia: Congreso de la República de Colombia, 2012.

3. ———. "Ponencia para el segundo debate al proyecto de Ley 028 de 2011 Cámara. "Por medio del cual se garantiza la vacunación gratuita y obligatoria a la población colombiana objeto de la misma, se adoptan medidas integrales para la prevención del cáncer cérvico uterino y se dictan otras disposiciones. [prevención del cáncer cérvico uterino]"." In Gaceta del Congreso, Senado y Cámara, edited by Cámara de Representantes. Bogotá, Colombia: Congreso de la República de Colombia, 2012.
4. Salas, Luis Enrique. "Proyecto De Ley 028 De 2011 Cámara. "Por medio del cual se garantiza la vacunación gratuita y obligatoria a la población colombiana objeto de la misma, se adoptan medidas integrales para la prevención del cáncer cérvico uterino y se dictan otras disposiciones. [prevención del cáncer cérvico uterino]"." In Gaceta del Congreso, Senado y Cámara, edited by Cámara de Representantes. Bogotá, Colombia: Congreso de la República de Colombia., 2011.

Appendix I

These are the parameters used in the Markov chain modelling of the Natural History of Cervical Cancer in Colombia (UNAL, 2011).

Edad	Base	Rango análisis de sensibilidad		Fuente
Incidencia de Verrugas Genitales (Probabilidad de progresión Normal a VG)				
10	0.00000	0.00000	0.00000	(31)
14	0.00171	0.00163	0.00179	
26	0.00157	0.00150	0.00163	
46	0.00036	0.00035	0.00038	
66	0.00000	0.00000	0.00000	
85	0.00000	0.00000	0.00000	
14-65	0.00114	0.00109	0.00119	
Todas las edades	0.00076	0.00073	0.00079	
Probabilidad de infección VPH alto riesgo por edad (años)				
10	0	0	0	(32, 33)
14	0	0	0	
15	0	0	0	
16	0.1	0.05	0.2	
17	0.12	0.06	0.24	
18	0.15	0.08	0.3	
19	0.17	0.09	0.34	
20	0.15	0.08	0.3	
21	0.12	0.06	0.24	
31	0.07	0.04	0.14	
50	0.07	0.04	0.14	
85	0	0	0	
Probabilidad de infección VPH bajo riesgo por edad (años)				
10	0	0	0	(32, 33)
14	0	0	0	
15	0	0	0	
16	0.01	0.01	0.02	
17	0.02	0.01	0.05	
18	0.04	0.02	0.07	
19	0.05	0.02	0.1	
20	0.06	0.03	0.12	
21	0.06	0.03	0.12	
51	0.02	0.01	0.04	
82	0.05	0.03	0.1	
83	0.05	0.03	0.11	
84	0.05	0.03	0.11	

Edad	Base	Rango análisis de sensibilidad		Fuente
85	0.06	0.03	0.11	
Probabilidad de regresión desde VPH bajo riesgo a normal				
10	0	0	0	
14	0	0	0	
15	0.82	0.7	0.9	(34)
85	0.82	0.7	0.9	
Probabilidad de regresión desde VPH alto riesgo a normal				
10	0	0	0	
14	0	0	0	
15	0.55	0.39	0.72	(34)
32	0.14	0.09	0.18	
85	0.14	0.09	0.18	
Probabilidad de progresión desde VPH alto riesgo a LSIL				
10	0	0	0	
14	0	0	0	
15	0.07	0.05	0.11	(35)
85	0.07	0.05	0.11	
Probabilidad de progresión desde VPH bajo riesgo a LSIL				
10	0	0	0	
14	0	0	0	
15	0.04	0.03	0.05	(36)
85	0.04	0.03	0.05	
Probabilidad de progresión VPH alto riesgo a HSIL				
10	0	0	0	
14	0	0	0	
15	0	0	0.01	(35)
85	0.02	0.01	0.04	
Probabilidad de regresión desde LSIL a normal				
10	0	0	0	
14	0	0	0	
15	0.16	0.14	0.24	(35)
85	0.08	0.07	0.16	
Probabilidad de regresión desde LSIL a infección por VPH				
10	0	0	0	
14	0	0	0	
15	0.16	0.14	0.24	(35)
85	0.08	0.07	0.16	
Probabilidad de progresión desde LSIL a HSIL				
10	0	0	0	
14	0	0	0	
15	0.02	0.02	0.06	(35)
85	0.07	0.07	0.11	
Probabilidad de regresión desde HSIL a normal				
10	0	0	0	
14	0	0	0	
15	0.07	0.06	0.11	(35)
85	0.07	0.06	0.11	
Probabilidad de regresión desde HSIL a infección por VPH				
10	0	0	0	
14	0	0	0	
15	0.05	0	0.1	(36)
85	0.05	0	0.1	
Probabilidad de regresión desde HSIL a LSIL				
10	0	0	0	
14	0	0	0	
15	0.1	0.1	0.11	(35)
85	0.1	0.1	0.11	
Probabilidad de progresión desde HSIL a cáncer estado I				
10	0	0	0	
14	0	0	0	
15	0.01	0.005	0.02	(35)
40	0.02	0.01	0.03	
85	0.05	0.04	0.07	
Probabilidades de progresión cáncer cervical				
Cáncer estado I a cáncer estado II				
10	0	0	0	
14	0	0	0	
15	0.4	0	0.5	(36)
85	0.4	0	0.5	
Cáncer estado II a cáncer estado III				
10	0	0	0	
14	0	0	0	
15	0.5	1	0.6	(36)
85	0.5	1	0.6	

Edad	Base	Rango análisis de sensibilidad		Fuente
Cáncer estado III a cáncer estado IV				
10	0	0	0	(36)
14	0	0	0	
15	0.7	0.7	0.7	
85	0.7	0.7	0.7	
Probabilidad de supervivencia y muerte				
Supervivencia CeCa1	0.97	0.85	0.99	(36)
Supervivencia CeCa2	0.91	0.78	0.92	
Supervivencia CeCa3	0.71	0.58	0.72	
Supervivencia CeCa4	0.40	0.27	0.41	
Muerte Cáncer I	0.03	0.15	0.01	
Muerte Cáncer II	0.09	0.22	0.08	
Muerte Cáncer III	0.29	0.42	0.28	
Muerte Cáncer IV	0.60	0.73	0.59	
Probabilidad de síntomas				
Verrugas Genitales	0.15	0.12	0.18	(36)
Cáncer I	0.15	0.12	0.18	
Cáncer II	0.23	0.20	0.25	
Cáncer III	0.70	0.67	0.73	
Cáncer IV	0.90	0.87	0.93	
Tasa de descuento costos	3%	3%	5%	Supuesto
Tasa de descuento resultados	3%	3%	5%	
Cobertura de Vacunación	60%	40%	80%	Supuesto
Desperdicio	3%	3%	5%	Supuesto
Edad de Colocación de la vacuna	12			Supuesto
Proporción de VPH 6 y 11 en Verrugas Genitales y CIN1	90%	90%	100%	(31)
Proporción de VPH 16 y 18 en infección por VPH alto riesgo o NIC 1+	63%	50%	70%	(37)
Proporción de otros VPH de alto riesgo (31, 33, 52, 56, 58, 59) en infección por VPH alto riesgo o NIC 1+	24%	12%	39%	
Proporción de otros VPH de alto riesgo (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) en infección por VPH alto riesgo o NIC 1+	37%	30%	50%	
Cobertura de Vacunación	60%	40%	80%	Supuesto
Eficacia de la Vacuna Bivalente				
Eficacia de la Bivalente en la reducción de infección por VPH 16-18	97%	92%	99%	(38-40)
Eficacia de la Bivalente en la reducción de infección por otros VPH de alto riesgo	8%	-3%	19%	
Reducción (calculada) de la probabilidad de infección por VPH de alto riesgo	63.90%	44.83%	78.53%	
Eficacia de la Vacuna Tetravalente				
Eficacia de la Tetravalente en la reducción de infección por VPH 16-18	98%	92%	100%	(38, 41, 42)
Eficacia de la Tetravalente en la reducción de infección por otros VPH de alto riesgo	25%	8%	41%	
Eficacia de la Tetravalente en la reducción de infección por VPH 6 y 11	99%	96%	100%	
Reducción (calculada) de la probabilidad de infección por VPH 6-11	89.10%	86.58%	99.80%	
Reducción (calculada) de la probabilidad de infección por VPH de alto riesgo	67.86%	46.95%	86.07%	
Citología				
Sensibilidad (umbral ASCUS)	73%	50%	82%	(43)
Especificidad	92%	90%	94%	
Prueba VPH				
Sensibilidad	90%	87%	93%	(43)
Especificidad	86%	83%	90%	
Colposcopia				
Sensibilidad	87%	24%	90%	(44)
Especificidad	87%	68%	97%	
Cobertura de la Citología	90%	48%	94%	(45)
Efectividad tratamiento Verrugas Genitales	53%	37%	70%	(46)
Efectividad tratamiento NIC 1	91%	87%	99%	(47, 48)
Efectividad tratamiento NIC 2,3	95%	91%	98%	(49)
Efectividad tratamiento Cáncer I	58%	37%	91%	(47, 48)
Efectividad tratamiento Cáncer II	47%	30%	74%	(47, 48)
Efectividad tratamiento Cáncer III	47%	30%	74%	(47, 48)
Efectividad tratamiento Cáncer IV	47%	30%	74%	(47, 48)
% de Verrugas genitales Tratadas	100%	60%	100%	Supuesto
% de NIC1 Tratadas	0%	0%	0%	Supuesto
% de NIC2,3 Tratadas	70%	60%	100%	Supuesto
% de NIC2,3 persistentes Tratadas	70%	60%	100%	Supuesto
% de Cáncer Cervical I Tratados	70%	60%	100%	Supuesto
% de Cáncer Cervical II Tratados	70%	60%	100%	Supuesto
% de Cáncer Cervical III Tratados	70%	60%	100%	Supuesto
% de Cáncer Cervical IV Tratados	70%	60%	100%	Supuesto
% de seguimiento de los pacientes	46%	46%	80%	(45)

Edad	Base	Rango análisis de sensibilidad		Fuente
PESO DE LA DISCAPACIDAD (Usado en el modelo)				
Verrugas Genitales			0.00833	
Cáncer Cervical I			0.08	
Cáncer Cervical I Tratados			0.43	
Cáncer Cervical II			0.75	
Cáncer Cervical II Tratados			0.43	(50)
Cáncer Cervical III			0.75	
Cáncer Cervical III Tratados			0.43	
Cáncer Cervical IV			0.75	
Cáncer Cervical IV Tratados			0.93	
Costo Intervención	Base	LI	LS	Referencia
Costo por Vacuna Bivalente	13.48	13.48	30.22	MPS
Costo por Vacuna Tetravalente	15.15	15.15	33.96	MPS
Costo esquema bivalente	44.47	44.47	94.68	MPS
Costo esquema tetravalente	49.48	49.48	105.91	MPS
Costo Administración por dosis de vacuna	1.00	1.00	5.00	Supuesto
Costo tratamiento verruga genital	381.46			
Costo Citología	7.42	6.90	21.45	
Costo Colposcopia	53.35	49.67	106.70	
Costo Colposcopia + Biopsia	159.02	98.26	229.28	
Costo Prueba ADN-VPH	14.15	9.71	73.14	
Tratamiento de NIC I	79.35	79.35	644.03	
Tratamiento para NIC II, III (LEEP)	261.64	243.54	1,504.02	(33)
Tratamiento para Cáncer I	3,451.21	3,212.51	6,902.42	
Tratamiento para Cáncer II	4,381.13	4,078.10	8,427.95	
Tratamiento para Cáncer III	4,381.13	4,078.10	8,427.95	
Tratamiento para Cáncer IV	4,381.13	4,078.10	8,427.95	
Seguimiento de NIC II, III	1,117.48	202.46	1,536.53	
Seguimiento de Cáncer invasivo	1,898.92	1,767.59	2,848.38	
Verificación de Diagnóstico para NIC I, II, III	270.81	252.08	455.75	

Literature that supports the assumption of the model

The items have been ordered keeping the numeration of the original report in order to show the relation between journal articles, assumptions and probability in the model.

31. Hillemanns P, Breugelmans JG, Giesecking F, Benard S, Lamure E, Littlewood KJ, et al. Estimation of the incidence of genital warts and the cost of illness in Germany: a cross-sectional study. *BMC Infect Dis.* 2008;8:76.
32. Munoz N, Mendez F, Posso H, Molano M, van den Brule AJ, Ronderos M, et al. Incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results. *J Infect Dis.* 2004 Dec 15;190(12):2077-87.
33. Andres-Gamboa O, Chicaiza L, Garcia-Molina M, Diaz J, Gonzalez M, Murillo R, et al. Cost-effectiveness of conventional cytology and HPV DNA testing for cervical cancer screening in Colombia. *Salud publica de Mexico.* 2008 Jul-Aug;50(4):276-85.
34. Molano M, Van den Brule A, Plummer M, Weiderpass E, Posso H, Arslan A, et al. Determinants of clearance of human papillomavirus infections in Colombian women with normal cytology: a population-based, 5-year follow-up study. *Am J Epidemiol.* 2003 Sep 1;158(5):486-94.

35. Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. *Am J Epidemiol.* 2000 Jun 15;151(12):1158--71
36. Sanders GD, Taira AV. Cost---effectiveness of a potential vaccine for human papillomavirus. *Emerg Infect Dis.* 2003 Jan;9(1):37---48.
37. María Teresa Valenzuela, Fernando Pío de la Hoz, Emilia H. Koumans, María Nazzarena Labbo, Catherine Koss, Hector Posso, et al. HUMAN PAPILOMAVIRUS (HPV) and RELATED BURDEN OF DISEASE IN LATIN AMERICA AND THE CARIBBEAN. Washington D.C.: Sabin Institute 2009.
38. Lu B, Kumar A, Castellsague X, Giuliano AR. Efficacy and safety of prophylactic vaccines against cervical HPV infection and diseases among women: a systematic review & meta---analysis. *BMC Infect Dis.* 2011;11:13.
39. Lehtinen M, Paavonen J, Wheeler CM, Jaisamrarn U, Garland SM, Castellsague X, et al. Overall efficacy of HPV---16/18 AS04---adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4---year end---of---study analysis of the randomised, double---blind PATRICIA trial. *Lancet Oncol.* 2011 Nov 8.
40. Wheeler CM, Castellsague X, Garland SM, Szarewski A, Paavonen J, Naud P, et al. Cross---protective efficacy of HPV---16/18 AS04---adjuvanted vaccine against cervical infection and precancer caused by non---vaccine oncogenic HPV types: 4--- year end---of---study analysis of the randomised, double---blind PATRICIA trial. *Lancet Oncol.* 2011 Nov 8.
41. Quadrivalent vaccine against human papillomavirus to prevent high---grade cervical lesions. *N Engl J Med.* 2007 May 10;356(19):1915---27.
42. Garland SM, Hernandez---Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med.* 2007 May 10;356(19):1928---43.
43. Koliopoulos G, Arbyn M, Martin---Hirsch P, Kyrgiou M, Prendiville W, Paraskevidis E. Diagnostic accuracy of human papillomavirus testing in primary cervical screening: a systematic review and meta---analysis of non---randomized studies. *Gynecol Oncol.* 2007 Jan;104(1):232---46.
44. Olaniyan OB. Validity of colposcopy in the diagnosis of early cervical neoplasia-----a review. *Afr J Reprod Health.* 2002 Dec;6(3):59---69.
45. Profamilia. Capítulo 15. Detección temprana del cáncer de cuello uterino y de mama. Encuesta Nacional de Demografía y Salud: Salud sexual y reproductiva. Bogota 2010.
46. Kodner CM, Nasraty S. Management of genital warts. *Am Fam Physician.* 2004 Dec 15;70(12):2335--42.
47. Martin---Hirsch PP, Paraskevidis E, Bryant A, Dickinson HO, Keep SL. Surgery for cervical intraepithelial neoplasia. *Cochrane Database Syst Rev.* 2010(6):CD001318.
48. Rosa MI, Medeiros LR, Rosa DD, Bozzeti MC, Silva FR, Silva BR. [Human papillomavirus and cervical neoplasia]. *Cad Saude Publica.* 2009 May;25(5):953--- 64.
49. Martin---Hirsch PL, Paraskevidis E, Kitchener H. Surgery for cervical intraepithelial neoplasia. *Cochrane Database Syst Rev.* 2000(2):CD001318.

50. Vos T, Begg S. The victorian burden of disease study: Morbidity, D.o.P.S. Public Health Division, State of Victoria (Australia). Melbourne1999.

51. Denny L, Quinn M, Sankaranarayanan R. Chapter 8: Screening for cervical cancer in developing countries. Vaccine. 2006 Aug 31;24 Suppl 3:S3/71---7. 52. Duarte HG, Romero JA, Schmalbach JE. [Association between the cervico--- vaginal inflammatory cytology and the intraepithelial cervical lesion in patients from a sexual and reproductive health clinic in Bogota, Colombia, 1999---2003]. Rev Salud Publica (Bogota). 2004 Sep---Dec;6(3):253---69.

Appendix II

Interviews

Date: October 2012 – November 2013 (Some of these interviews were held online from Lancaster)
Place: Bogotá, Colombia and London, United Kingdom.

Institution	Position	No interviews
Ministry of Health, Extended Immunisation Programme	Extended Immunisation Programme Head Technical advisor, Epidemiologist Technical advisor, Epidemiologist and Bioethics consultant Committee member 1 Committee member 2 Committee member 3 Committee member 4 Committee member 5 Committee member 6 Committee member 7 Committee member 8	11
Colombian National Cancer Institute	Senior Researcher HPV programme. Senior Researcher HPV programme. Senior Researcher HPV programme. Head Clinical trial FUTURE in Colombia, Researcher HPV programme. Speaker of MSD and GSK. General Director Colombian National Cancer Institute Emeritus Researcher Colombian National Cancer Institute, Researcher IARC-WHO, Lyon France. Scientific advisor Bayer Colombia. Former researcher National Cancer Institute. Speaker of Bayer, MSD.	8
Colombian National Institute for Food and Drug Surveillance	Senior member, Biological and medicaments committee Chair Sanitary Register Biological and medicaments Technical officer Register Biologics and medicaments	3
CRES, National Health Regulation Commission	Technical Advisor	1
Department of Health, Bogotá Mayor Office	Head Epidemiological Surveillance Forensic Physician, Technical advisor Epidemiological Surveillance Scientific Advisor, Laboratory of Public Health, Department of Health, Bogotá Mayor Office	3

Universidad Nacional de Colombia, Public Health School	Professor of Epidemiology at Universidad Nacional and consultant in health economics of Ministry of Health.	1
National Health Institute Colombia	General Director	1
Merck MSD Colombia Headquarters	Communication office	1
GSK Colombia Headquarters	Communication office	1
NICE International	Sr. International consultant	2

Quantitative training

Course	University
Demography	University of Manchester
STATA	Lancaster University
R	University of Leeds
Health economics Workshop	Lancaster University
Programming for social science, agent based simulation	University of Leeds

Appendix III

Medical and epidemiological literature about HPV vaccines and cervical cancer

- Almonte, M., Albero, G., Molano, M., Carcamo, C., Garcia, P. J. and Perez, G. 2008 'Risk factors for Human Papillomavirus Exposure and Co-factors for Cervical Cancer in Latin America and the Caribbean', *Vaccine* 26: L16-L36.
- Alvarez-Rosero, R. E., Rodriguez-Argote, J., Arboledo-Moreno, Y. Y., Munoz-Benitez, S. L. and Sierra-Torres, C. H. 2008 'Chromosome Aberrations in Peripheral Blood Lymphocytes of High-Risk HPV-Infected Women with HGSIL', *Environmental and Molecular Mutagenesis* 49(9): 688-694.
- Arias-Pulido, H., Peyton, C. L., Joste, N. E., Vargas, H. and Wheeler, C. M. 2006 'Human papillomavirus type 16 integration in cervical carcinoma in situ and in invasive cervical cancer', *Journal of Clinical Microbiology* 44(5): 1755-1762.
- Au, W. W., Abdou-Salama, S., Sierra-Torres, C. H. and Al-Hendy, A. 2007 'Environmental risk factors for prevention and molecular intervention of cervical cancer', *International Journal of Hygiene and Environmental Health* 210(6): 671-678.
- Au, W. W., Sierra-Torres, C. H. and Tyring, S. K. 2003 'Acquired and genetic susceptibility to cervical cancer', *Mutation Research-Reviews in Mutation Research* 544(2-3): 361-364.
- Ault, K. A., Jaura, E. A., Kjaer, S. K., Iversen, O. E., Wheeler, C. M., Perez, G., Brown, D. R., Koutsky, L. A., Garland, S. M., Olsson, S. E., Tang, G. W. K., Ferris, D. G., Paavonen, J., Steben, M., Bosch, F. X., Majewski, S., Munoz, N., Sings, H. L., Harkins, K., Rutkowski, M. A., Haupt, R. M., Garner, E. I. O. and Grp, F. I. I. S. 2011 'Adenocarcinoma in situ and associated human papillomavirus type distribution observed in two clinical trials of a quadrivalent human papillomavirus vaccine', *International Journal of Cancer* 128(6): 1344-1353.
- Bedoya, A. M., Gaviria, A. M., Baena, A., Borrero, M., Duarte, D. F., Combata, A. L., Castano, J., Grisales, H. and Sanchez, G. I. 2012 'Age-Specific Seroprevalence of Human Papillomavirus 16, 18, 31, and 58 in Women of a Rural Town of Colombia', *International Journal of Gynecological Cancer* 22(2): 303-310.
- Bosch, F. X., Munoz, N., Desanjose, S., Izarzugaza, I., Gili, M., Viladiu, P., Tormo, M. J., Moreo, P., Ascunce, N., Gonzalez, L. C., Tafur, L., Kaldor, J. M., Guerrero, E., Aristizabal, N., Santamaria, M., Deruiz, P. A. and Shah, K. 1992 'RISK-FACTORS FOR CERVICAL-CANCER IN COLOMBIA AND SPAIN', *International Journal of Cancer* 52(5): 750-758.
- Bosch, F. X., Munoz, N., Desanjose, S., Navarro, C., Moreo, P., Ascunce, N., Gonzalez, L. C., Tafur, L., Gili, M., Larranaga, I., Viladiu, P., Daniel, R. W., Deruiz, P. A., Aristizabal, N., Santamaria, M., Guerrero, E. and Shah, K. V. 1993 'HUMAN PAPILLOMAVIRUS AND CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE-3 CARCINOMA IN-SITU - A CASE-CONTROL

- STUDY IN SPAIN AND COLOMBIA', *Cancer Epidemiology Biomarkers & Prevention* 2(5): 415-422.
- Bosch, F. X., Burchell, A. N., Schiffman, M., Giuliano, A. R., de Sanjose, S., Bruni, L., Tortolero-Luna, G., Kjaer, S. K. and Munoz, N. 2008 'Epidemiology and Natural History of Human Papillomavirus Infections and Type-Specific Implications in Cervical Neoplasia', *Vaccine* 26: K1-K16.
- Boyce T, Holmes A. 2012. Addressing health inequalities in the delivery of the human papillomavirus vaccination programme. *PLoS One* 2012;7:e43416.
- Boyce, T. 2007 *Health, risk and news*, New York: P. Lang.
- Bravo, M. M., Gonzalez, H., Molano, M., Arias, H., Combata, A., Moreno, P., Molina, C., Arbelaez, J. and Orozco, O. 1998 Decrease in Human Papilloma virus detection (HPV) in cervical cancer after radiotherapy, 40128 Bologna: Medimond S R L.
- Calleja-Macias, I. E., Villa, L. L., Prado, J. C., Kalantari, M., Allan, B., Williamson, A. L., Chung, L. P., Collins, R. J., Zuna, R. E., Dunn, S. T., Chu, T. Y., Cubie, H. A., Cuschieri, K., von Knebel-Doerberitz, M., Martins, C. R., Sanchez, G. I., Bosch, F. X., Munoz, N. and Bernard, H. U. 2005 'Worldwide genomic diversity of the high-risk human papillomavirus types 31, 35, 52, and 58, four close relatives of human papillomavirus type 16', *Journal of Virology* 79(21): 13630-13640.
- Calvo, J. C., Choconta, K. C., Diaz, D., Orozco, O., Bravo, M. M., Espejo, F., Salazar, L. M., Guzman, F. and Patarroyo, M. E. 2003 'An alpha helix conformationally restricted peptide is recognized by cervical carcinoma patients' sera', *Journal of Medicinal Chemistry* 46(25): 5389-5394.
- Camargo, M., Soto-De Leon, S. C., Sanchez, R., Perez-Prados, A., Patarroyo, M. E. and Patarroyo, M. A. 2011b 'Frequency of Human Papillomavirus Infection, Coinfection, and Association with Different Risk Factors in Colombia', *Annals of Epidemiology* 21(3): 204-213.
- Camargo, M., Soto-De Leon, S., Sanchez, R., Munoz, M., Vega, E., Beltran, M., Perez-Prados, A., Patarroyo, M. E. and Patarroyo, M. A. 2011a 'Detection by PCR of human papillomavirus in Colombia: Comparison of GP5+/6+ and MY09/11 primer sets', *Journal of Virological Methods* 178(1-2): 68-74.
- Castellsague, X., Munoz, N., Pitisuttithum, P., Ferris, D., Monsonogo, J., Ault, K., Luna, J., Myers, E., Mallery, S., Bautista, O. M., Bryan, J., Vuocolo, S., Haupt, R. M. and Saah, A. 2011 'End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age', *British Journal of Cancer* 105(1): 28-37.
- Castillo, A. 2011 'HPV infection and carcinogenesis in the upper aero-digestive tract', *Colombia Medica* 42(2): 233-242.
- Castillo, A., Aguayo, F., Koriyama, C., Shuyama, K., Akiba, S., Herrera-Goepfert, R., Carrascal, E., Klinge, G., Sanchez, J. and Eizuru, Y. 2006 'Human papillomavirus in lung carcinomas among three Latin American countries', *Oncology Reports* 15(4): 883-888.

- Castillo, A., Koriyama, C., Higashi, M., Anwar, M., Bukhari, M. H., Carrascal, E., Mancilla, L., Okumura, H., Matsumoto, M., Sugihara, K., Natsugoe, S., Eizuru, Y. and Akiba, S. 2011 'Human papillomavirus in upper digestive tract tumors from three countries', *World Journal of Gastroenterology* 17(48): 5295-5304.
- Cendales, R., Wiesner, C., Murillo, R. H., Piñeros, M., Tovar, S. and Mejía, J. C. 2010 '[Quality of vaginal smear for cervical cancer screening: a concordance study].', *Biomedica* 30(1): 107-15.
- Clifford, G., Franceschi, S., Diaz, M., Munoz, N. and Villa, L. L. 2006 'HPV type-distribution in women with and without cervical neoplastic diseases', *Vaccine* 24: 26-34.
- Combata, A. L., Bravo, M. M., Touze, A., Orozco, O. and Coursaget, P. 2002 'Serologic response to human oncogenic papillomavirus types 16, 18, 31, 33, 39, 58 and 59 virus-like particles in colombian women with invasive cervical cancer', *International Journal of Cancer* 97(6): 796-803.
- Cortazar Garcia, J. 1984 'Trabajos científicos elaborados en el Instituto', *Revista del Instituto Nacional de Cancerología* Vol, 5, Supl(Julio).
- Crager, S. E., Guillen, E. and Price, M. 2009 'University Contributions to the HPV Vaccine and Implications for Access to Vaccines in Developing Countries: Addressing Materials and Know-How in University Technology Transfer Policy', *American Journal of Law and Medicine* 35: 253-700.
- Dao, D. D., Sierra-Torres, C. H., Robazetti, S. C., de Gomez, M. N., Konig, R., Lema, C., Lester, L. J., Au, W. W. and Tying, S. K. 2005 'HLA-DQB1 and cervical cancer in Venezuelan women', *Gynecologic Oncology* 96(2): 349-354.
- De Sanjose, S., Bosch, F. X., Tafur, L. A., Nascimento, C. M., Izarzugaza, I., Izquierdo, A., Barricarte, A., Shah, K. V., Meijer, C. and Munoz, N. 2003 'Clearance of HPV infection in middle aged men and women after 9 years' follow up', *Sexually Transmitted Infections* 79(4): 348-348.
- De Villiers, E. M., Fauquet, C., Broker, T. R., Bernard, H. U. and zur Hausen, H. 2004 'Classification of papillomaviruses', *Virology* 324(1): 17-27.
- De Sanjose, S., Bosch, F. X., Munoz, N., Tafur, L., Gili, M., Izarzugaza, I., Izquierdo, A., Navarro, C., Vergara, A., Munoz, M. T., Ascunce, N. and Shah, K. V. 1996 'Socioeconomic differences in cervical cancer: Two case-control studies in Colombia and Spain', *American Journal of Public Health* 86(11): 1532-1538.
- De Sanjose, S., Hamsikova, E., Munoz, N., Bosch, F. X., Hofmannova, V., Gili, M., Izarzugaza, I., Viladiu, P., Tormo, M. J., Moreo, P., Munoz, M. T., Ascunce, N., Tafur, L., Shah, K. V. and Vonka, V. 1996 'Serological response to HPV16 in CIN-III and cervical-cancer patients. Case-control studies in Spain and Colombia', *International Journal of Cancer* 66(1): 70-74.
- De Sanjose, S., Munoz, N., Bosch, F. X., Reimann, K., Pedersen, N. S., Orfila, J., Ascunce, N., Gonzalez, L. C., Tafur, L., Gili, M., Lette, I., Viladiu, P., Tormo, M. J., Moreo, P., Shah, K. and Wahren, B. 1994 'SEXUALLY-TRANSMITTED AGENTS AND CERVICAL NEOPLASIA IN COLOMBIA AND SPAIN', *International Journal of Cancer* 56(3): 358-363.

- Eltoum, I. A. and Roberson, J. 2007 'Impact of HPV testing, HPV vaccine development, and changing screening frequency on national Pap test volume - Projections from the National Health Interview Survey (MMIS)', *Cancer Cytopathol.* 111(1): 34-40.
- Esguerra Gómez, A. 1920 'Cáncer del cuello uterino', Bogotá: Facultad de medicina. Universidad Nacional de Colombia.
- Fernández, M. E., Allen, J. D., Mistry, R. and Kahn, J. A. 2010 'Integrating clinical, community, and policy perspectives on human papillomavirus vaccination.', *Annu Rev Public Health* 31: 235-52.
- Field, R. I. and Caplan, A. L. 2008 'A proposed ethical framework for vaccine mandates: Competing values and the case of HPV', *Kennedy Institute of Ethics Journal* 18(2): 111-124.
- Franceschi, S., Smith, J. S., Van Den Brule, A., Herrero, R., Arslan, A., Anh, P. T. H., Bosch, F. X., Hieu, N. T., Matos, E., Posso, H., Qiao, Y. L., Shin, H. R., Sukvirach, S., Thomas, J. O., Snijders, P. J. F., Munoz, N. and Meijer, C. 2007 'Cervical infection with Chlamydia trachomatis and Neisseria gonorrhoeae in women from ten areas in four continents', *Sexually Transmitted Diseases* 34(8): 563-569.
- Franco, E. L., Tsu, V., Herrero, R., Lazcano-Ponce, E., Hildesheim, A., Munoz, N., Murillo, R., Sanchez, G. I. and Andrus, J. K. 2008 'Integration of Human Papillomavirus Vaccination and Cervical Cancer Screening in Latin America and the Caribbean', *Vaccine* 26: L88-L95.
- Gamboa, A. O., Chicaiza, L., Garcia-Molina, M., Diaz, J., Gonzalez, M., Murillo, R., Ballesteros, M. and Sanchez, R. 2008 'Cost-effectiveness of conventional cytology and HPV DNA testing for cervical cancer screening in Colombia', *Salud Publica De Mexico* 50(4): 276-285.
- Garces-Palacio, I. C. and Scarinci, I. C. 2012 'Factors Associated with Perceived Susceptibility to Cervical Cancer Among Latina Immigrants in Alabama', *Maternal and Child Health Journal* 16(1): 242-248.
- Garcia, D. A., Briceno, I., Castillo, M. and Aristizabal, F. A. 2011 'Detection of gene amplification in MYCN, C-MYC, MYCL1, ERBB2, EGFR, AKT2, and human papilloma virus in samples from cervical smear normal cytology, intraepithelial cervical neoplasia (CIN I, II, III), and cervical cancer', *Colombia Medica* 42(2): 144-153.
- Garland, S. M., Hernandez-Avila, M., Wheeler, C. M., Perez, G., Harper, D. M., Leodolter, S., Tang, G. W. K., Ferris, D. G., Steben, M., Bryan, J., Taddeo, F. J., Railkar, R., Esser, M. T., Sings, H. L., Nelson, M., Boslego, J., Sattler, C., Barr, E., Koutsky, L. A. and Investigators, F. I. 2007a 'Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases', *New England Journal of Medicine* 356(19): 1928-1943.
- Garland, S. M., Steben, M., Hernandez-Avila, M., Koutsky, L. A., Wheeler, C. M., Perez, G., Harper, D. M., Leodolter, S., Tang, G. W. K., Ferris, D. G., Esser, M. T., Vuocolo, S. C., Nelson, M., Railkar, R., Sattler, C., Barr, E. and Study, I. 2007b 'Noninferiority of antibody response to human papillomavirus type 16 in subjects vaccinated with monovalent and quadrivalent L1 virus-like particle vaccines', *Clinical and Vaccine Immunology* 14(6): 792-795.

- Giuliano, A. R., Tortolero-Luna, G., Ferrer, E., Burchell, A. N., de Sanjose, S., Kjaer, S. K., Munoz, N., Schiffman, M. and Bosch, F. X. 2008 'Epidemiology of Human Papillomavirus Infection in Men, Cancers other than Cervical and Benign Conditions', *Vaccine* 26: K17-K28.
- Grisales, H., Vanegas, A. P., Gaviria, A. M., Castano, J., Mora, M. A., Borrero, M., Rojas, C., Arbelaez, M. P. and Sanchez, G. I. 2008 'Prevalence of epithelial squamous cell abnormalities and associated factors in women of a rural town of Colombia', *Biomedica* 28(2): 271-283.
- Guerrero, E., Daniel, R. W., Bosch, F. X., Castellsague, X., Munoz, N., Gili, M., Viladiu, P., Navarro, C., Zubiri, M. L., Ascunce, N., Gonzalez, L. C., Tafur, L., Izarzugaza, I. and Shah, K. V. 1992 'COMPARISON OF VIRAPAP, SOUTHERN HYBRIDIZATION, AND POLYMERASE CHAIN-REACTION METHODS FOR HUMAN PAPILOMAVIRUS IDENTIFICATION IN AN EPIDEMIOLOGIC INVESTIGATION OF CERVICAL-CANCER', *Journal of Clinical Microbiology* 30(11): 2951-2959.
- Hanisch, R., Gustat, J., Hagensee, M. E., Baena, A., Salazar, J. E., Castro, M. V., Gaviria, M. and Sanchez, G. I. 2008 'Knowledge of Pap screening and human papillomavirus among women attending clinics in Medellin, Colombia', *International Journal of Gynecological Cancer* 18(5): 1020-1026.
- Herrero, R., Ferreccio, C., Salmeron, J., Almonte, M., Sanchez, G. I., Lazcano-Ponce, E. and Jeronimo, J. 2008 'New Approaches to Cervical Cancer Screening in Latin America and the Caribbean', *Vaccine* 26: L49-L58.
- Ho, G. Y. F., Bierman, R., Beardsley, L., Chang, C. J. and Burk, R. D. 1998 'Natural history of cervicovaginal papillomavirus infection in young women', *New England Journal of Medicine* 338(7): 423-428.
- Insinga, R. P., Perez, G., Wheeler, C. M., Koutsky, L. A., Garland, S. M., Leodolter, S., Joura, E. A., Ferris, D. G., Steben, M., Hernandez-Avila, M., Brown, D. R., Elbasha, E., Munoz, N., Paavonen, J., Haupt, R. M. and Investigators, F. I. 2011 'Incident Cervical HPV Infections in Young Women: Transition Probabilities for CIN and Infection Clearance', *Cancer Epidemiology Biomarkers & Prevention* 20(2): 287-296.
- Joura, E. A., Leodolter, S., Hernandez-Avila, M., Wheeler, C. M., Perez, G., Koutsky, L. A., Garland, S. M., Harper, D. M., Tang, G. W. K., Ferris, D. G., Steben, M., Jones, R. W., Bryan, J., Taddeo, F. J., Bautista, O. M., Esser, M. T., Sings, H. L., Nelson, M., Boslego, J. W., Sattler, C., Barr, E. and Paavonen, J. 2007 'Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials', *Lancet* 369(9574): 1693-1702.
- Koulova, A., Tsui, J., Irwin, K., Van Damme, P., Biellik, R. and Aguado, M. T. 2008 'Country recommendations on the inclusion of HPV vaccines in national immunization programmes among high-income countries, June 2006-January 2008', *Vaccine* 26(51): 6529.
- Koutsky, L. A., Ault, K. A., Wheeler, C. M., Brown, D. R., Barr, E., Alvarez, F. B., Chiacchierini, L. M., Jansen, K. U. and Proof Principle Study, I. 2002 'A controlled trial of a human papillomavirus type 16 vaccine', *New England Journal of Medicine* 347(21): 1645-1651.

- Larson, H. J., Cooper, L. Z., Eskola, J., Katz, S. L. and Ratzan, S. 'Addressing the vaccine confidence gap', *The Lancet* 378(9790): 526-535.
- Louie, K. S., Castellsague, X., de Sanjose, S., Herrero, R., Meijer, C. J., Shah, K., Munoz, N., Bosch, F. X. and Int Agcy Res Canc, M. 2011 'Smoking and Passive Smoking in Cervical Cancer Risk: Pooled Analysis of Couples from the IARC Multicentric Case-Control Studies', *Cancer Epidemiology Biomarkers & Prevention* 20(7): 1379-1390.
- Madkan, V. K., Cook-Norris, R. H., Steadman, M. C., Arora, A., Mendoza, N. and Tyring, S. K. 2007. 'The oncogenic potential of human papillomaviruses: a review on the role of host genetics and environmental cofactors', *British Journal of Dermatology* 157(2): 228-241.
- Mendez, F., Munoz, N., Posso, H., Molano, M., Moreno, V., van den Brule, A. J. C., Ronderos, M., Meijer, C., Munoz, A. and Inst Natl Canc Human, P. 2005 'Cervical coinfection with human papillomavirus (HPV) types and possible implications for the prevention of cervical cancer by HPV vaccines', *Journal of Infectious Diseases* 192(7): 1158-1165.
- Milstien, J., Munira, S. L. and McKinney, S. L. 2003. Issues in selection of DTwP-based combination vaccines. *Vaccine* 21(15): 1658-64.
- Molano, M., Posso, H., Weiderpass, E., van den Brule, A. J. C., Ronderos, M., Franceschi, S., Meijer, C., Arslan, A., Munoz, N. and Grp, H. P. V. S. 2002a 'Prevalence and determinants of HPV infection among Colombian women with normal cytology', *British Journal of Cancer* 87(3): 324-333.
- Molano, M., van den Brule, A. J. C., Posso, H., Weiderpass, E., Ronderos, M., Franceschi, S., Meijer, C., Arslan, A., Munoz, N. and Grp, H. P. V. S. 2002b 'Low grade squamous intra-epithelial lesions and human papillomavirus infection in Colombian women', *British Journal of Cancer* 87(12): 1417-1421.
- Molano, M., van den Brule, A., Plummer, M., Weiderpass, E., Posso, H., Arslan, A., Meijer, C., Munoz, N., Franceschi, S. and Grp, H. P. V. S. 2003a 'Determinants of clearance of human papillomavirus infections in Colombian women with normal cytology: A population-based, 5-year follow-up study', *American Journal of Epidemiology* 158(5): 486-494.
- Molano, M., Weiderpass, E., Posso, H., Morre, S. A., Ronderos, M., Franceschi, S., Arslan, A., Meijer, C., Munoz, N., van den Brule, A. J. C. and Grp, H. P. V. S. 2003b 'Prevalence and determinants of Chlamydia trachomatis infections in women from Bogota, Colombia', *Sexually Transmitted Infections* 79(6): 474-478.
- Moreno-Acosta, P., Molano, M., Huertas, A., de Gomez, M. S., Romero, A., Gonzalez, M., Bravo, M. M. and Garcia-Carranca, A. 2008 'A non-radioactive PCR-SSCP analysis allows to distinguish between HPV 16 European and Asian-American variants in squamous cell carcinomas of the uterine cervix in Colombia', *Virus Genes* 37(1): 22-30.
- Muñoz N, Bosch FX, de San José S, Herrero R, Castellsagué X, Shah KV. 2003. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med*. Feb 6;348(6):518-27.

- Muñoz, N. and Jacquard, A. C. 2008 'What should be known for the introduction of an HPV vaccine?', *Presse Medicale* 37(10): 1377-1390.
- Muñoz, N., Bosch, F. X., Desanjose, S., Tafur, L., Izarzugaza, I., Gili, M., Viladiu, P., Navarro, C., Martos, C., Asuncion, N., Gonzalez, L. C., Kaldor, J. M., Guerrero, E., Lorincz, A., Santamaria, M., Deruiz, P. A., Aristizabal, N. and Shah, K. 1992 'THE CAUSAL LINK BETWEEN HUMAN PAPILLOMAVIRUS AND INVASIVE CERVICAL-CANCER - A POPULATION-BASED CASE-CONTROL STUDY IN COLOMBIA AND SPAIN', *International Journal of Cancer* 52(5): 743-749.
- Muñoz, N., Bosch, F. X., Desanjose, S., Vergara, A., Delmoral, A., Munoz, M. T., Tafur, L., Gili, M., Izarzugaza, I., Viladiu, P., Navarro, C., Deruiz, P. A., Aristizabal, N., Santamaria, M., Orfila, J., Daniel, R. W., Guerrero, E. and Shah, K. V. 1993 'RISK-FACTORS FOR CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE-3 CARCINOMA IN-SITU IN SPAIN AND COLOMBIA', *Cancer Epidemiology Biomarkers & Prevention* 2(5): 423-431.
- Muñoz, N., Castellsague, X., Bosch, F. X., Tafur, L., deSanjose, S., Aristizabal, N., Ghaffari, A. M. and Shah, K. V. 1996a 'Difficulty in elucidating the male role in cervical cancer in Colombia, a high-risk area for the disease', *Journal of the National Cancer Institute* 88(15): 1068-1075.
- Muñoz, N., Franco, E. L., Herrero, R., Andrus, J. K., de Quadros, C., Goldie, S. J. and Bosch, F. X. 2008a 'Recommendations for Cervical Cancer Prevention in Latin America and the Caribbean', *Vaccine* 26: L96-L107.
- Muñoz, N., Kato, I., Bosch, F. X., Desanjose, S., Sundquist, V. A., Izarzugaza, I., Gonzalez, L. C., Tafur, L., Gili, M., Viladiu, P., Navarro, C., Moreo, P., Guerrero, E., Shah, K. V. and Wahren, B. 1995 'CERVICAL-CANCER AND HERPES-SIMPLEX VIRUS TYPE-2 - CASE-CONTROL STUDIES IN SPAIN AND COLOMBIA, WITH SPECIAL REFERENCE TO IMMUNOGLOBULIN-G SUBCLASSES', *International Journal of Cancer* 60(4): 438-442.
- Muñoz, N., Kato, I., Bosch, F. X., ElufNeto, J., deSanjose, S., Asuncion, N., Gili, M., Izarzugaza, I., Viladiu, P., Tormo, M. J., Moreo, P., Gonzalez, L. C., Tafur, L., Walboomers, J. M. M. and Shah, K. V. 1996b 'Risk factors for HPV DNA detection in middle-aged women', *Sexually Transmitted Diseases* 23(6): 504-510.
- Muñoz, N., Reina, J. C. and Sanchez, G. I. 2008 'The human papillomavirus vaccine: A powerful tool for the primary prevention of cervical cancer', *Colombia Medica* 39(2): 196-204.
- Murillo, R., Cendales, R., Wiesner, C., Piñeros, M. and Tovar, S. 2009 '[Effectiveness of cytology-based cervical cancer screening in the Colombian health system].', *Biomedica* 29(3): 354-61.
- Natunen, K., Lehtinen, J., Namujju, P., Sellors, J. and Lehtinen, M. 2011 'Aspects of Prophylactic Vaccination against Cervical Cancer and Other Human Papillomavirus-Related Cancers in Developing Countries', *Infectious Diseases in Obstetrics and Gynecology* 96(4).
- Orjuela, K., Amador, C. and Patarroyo, M. A. 2007. Synthetic genes: a tool for identifying human papillomavirus genotypes by hybridization and polymerase chain reaction-based assays, *Diagnostic Microbiology and Infectious Disease* 59(1): 101-104.

- Parkin, D. M., Almonte, M., Bruni, L., Clifford, G., Curado, M. P. and Pineros, M. 2008a 'Burden and Trends of Type-Specific Human Papillomavirus Infections and Related Diseases in the Latin America and Caribbean Region', *Vaccine* 26: L1-L15.
- Perez, G., Lazcano-Ponce, E., Hernandez-Avila, M., Garcia, P. J., Munoz, N., Villa, L. L., Bryan, J., Taddeo, F. J., Lu, S., Esser, M. T., Vuoco, S., Sattler, C. and Barr, E. 2008 'Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 virus-like-particle vaccine in Latin American women', *International Journal of Cancer* 122(6): 1311-1318.
- Pincock, S. 2009 'Nubia Muñoz: defining the role of HPV in cervical cancer', *The Lancet* 374(9701): 1587-1587.
- Rao, P. H., Arias-Pulido, H., Lu, X. Y., Harris, C. P., Vargas, H., Zhang, F. F., Narayan, G., Schneider, A., Terry, M. B. and Murty, V. 2004 'Chromosomal amplifications, 3q gain and deletions of 2q33-q37 are the frequent genetic changes in cervical carcinoma', *Bmc Cancer* 4: 9.
- Reina, J. C., Munoz, N. and Sanchez, G. I. 2008 'State-of-the-art of infections produced by human papillomavirus', *Colombia Medica* 39(2): 189-195.
- Rivera Medina, D. M., Valencia, A., de Velasquez, A., Huang, L.-M., Prymula, R., García-Sicilia, J., Rombo, L., David, M. P. P., Descamps, D., Hardt, K. and Dubin, G. 'Safety and Immunogenicity of the HPV-16/18 AS04-Adjuvanted Vaccine: A Randomized, Controlled Trial in Adolescent Girls', *Journal of Adolescent Health* 46(5): 414-421.
- Rodriguez, J. A., Galeano, L., Palacios, D. M., Gomez, C., Serrano, M. L., Bravo, M. M. and Combita, A. L. 2012 'Altered HLA Class I and HLA-G Expression Is Associated with IL-10 Expression in Patients with Cervical Cancer', *Pathobiology* 79(2): 72-83.
- Sanchez, G. I., Kleter, B., Gheit, T., van Doorn, L. J., De Koning, M. N. C., de Sanjose, S., Alemany, L., Bosch, X. F., Tommasino, M., Munoz, N. and Quint, W. G. V. 2011 'Clinical evaluation of polymerase chain reaction reverse hybridization assay for detection and identification of human papillomavirus type 16 variants', *Journal of Clinical Virology* 51(3): 165-169.
- Sanclemente, G. and Gill, D. K. 2002 'Human papillomavirus molecular biology and pathogenesis', *Journal of the European Academy of Dermatology and Venereology* 16(3): 231-240.
- Sanclemente, G., Herrera, S., Tyring, S. K., Rady, P. L., Zuleta, J. J., Correa, L. A., He, Q. and Wolff, J. C. 2007 'Human papillomavirus (HPV) viral load and HPV type in the clinical outcome of HIV-positive patients treated with imiquimod for anogenital warts and anal intraepithelial neoplasia', *Journal of the European Academy of Dermatology and Venereology* 21(8): 1054-1060.
- Schiffman, M. H., Bauer, H. M., Hoover, R. N., Glass, A. G., Cadell, D. M., Rush, B. B., Scott, D. R., Sherman, M. E., Kurman, R. J., Wacholder, S., Stanton, C. K. and Manos, M. M. 1993 'EPIDEMIOLOGIC EVIDENCE SHOWING THAT HUMAN PAPILOMAVIRUS INFECTION CAUSES MOST CERVICAL INTRAEPITHELIAL NEOPLASIA', *Journal of the National Cancer Institute* 85(12): 958-964.

- Serrano, M. L., Sanchez-Gomez, M., Bravo, M. M., Yakar, S. and LeRoith, D. 2008 'Differential Expression of IGF-I and Insulin Receptor Isoforms in HPV Positive and Negative Human Cervical Cancer Cell Lines', *Hormone and Metabolic Research* 40(10): 661-667.
- Sierra-Torres, C. H., Arboleda-Moreno, Y. Y. and Orejuela-Aristizabal, L. 2006 'Exposure to wood smoke, HPV infection, and genetic susceptibility for cervical neoplasia among women in Colombia', *Environmental and Molecular Mutagenesis* 47(7): 553-561.
- Sierra-Torres, C. H., Au, W. W., Arrastia, C. D., Cajas-Salazar, N., Robazetti, S. C., Payne, D. A. and Tying, S. K. 2003a 'Polymorphisms for chemical metabolizing genes and risk for cervical neoplasia', *Environmental and Molecular Mutagenesis* 41(1): 69-76.
- Sierra-Torres, C. H., Tying, S. K. and Au, W. W. 2003b 'Risk contribution of sexual behavior and cigarette smoking to cervical neoplasia', *International Journal of Gynecological Cancer* 13(5): 617-625.
- Slifka, M. K. and Amanna, I. J. 2007 'State of Immunity: The Politics of Vaccination in Twentieth-Century America', *JAMA: The Journal of the American Medical Association* 297(24): 2769-2770.
- Stoler, M. H., Vichnin, M. D., Ferenczy, A., Ferris, D. G., Perez, G., Paavonen, J., Joura, E. A., Djursing, H., Sigurdsson, K., Jefferson, L., Alvarez, F., Sings, H. L., Lu, S., James, M. K., Saah, A., Haupt, R.I. 2011 'The accuracy of colposcopic biopsy: analyses from the placebo arm of the Gardasil clinical trials', *International Journal of Cancer* 128(6): 1354-1362.
- Urquiza, M., Guevara, T., Espejo, F., Bravo, M. M., Rivera, Z. and Patarroyo, M. E. 2005 'Two L1-peptides are excellent tools for serological detection of HPV-associated cervical carcinoma lesions', *Biochemical and Biophysical Research Communications* 332(1): 224-232.
- Urquiza, M., Guevara, T., Sanchez, R., Vanegas, M. and Patarroyo, M. E. 2008a 'A non-variable L1-peptide displays high sensitivity and specificity for detecting women having human papillomavirus-associated cervical lesions', *Peptides* 29(6): 957-962.
- Urquiza, M., Sanchez, R., Amaya, J., Leon, S., Acosta, J., Patarroyo, M. A., Camargo, M. and Patarroyo, M. E. 2008b 'Specificity of L1 Peptides versus Virus-Like Particles for Detection of Human Papillomavirus-Positive Cervical Lesions in Females Attending Engativa Hospital, Bogota, Colombia', *Journal of Clinical Microbiology* 46(11): 3714-3720.
- Vaccarella, S., Franceschi, S., Herrero, R., Munoz, N., Snijders, P. J. F., Clifford, G. M., Smith, J. S., Lazcano-Ponce, E., Sukvirach, S., Shin, H. R., de Sanjose, S., Molano, M., Matos, E., Ferreccio, C., Anh, P. T. H., Thomas, J. O., Meijer, C. and Study, I. H. P. S. 2006a 'Sexual behavior, condom use, and human papillomavirus: Pooled analysis of the IARC human papillomavirus prevalence surveys', *Cancer Epidemiology Biomarkers & Prevention* 15(2): 326-333.
- Vaccarella, S., Herrero, R., Dai, M., Snijders, P. J. F., Meijer, C., Thomas, J. O., Anh, P. T. H., Ferreccio, C., Matos, E., Posso, H., de Sanjose, S., Shin, H. R., Sukvirach, S., Lazcano-Ponce, E., Ronco, G., Rajkumar, R., Qiao, Y. L., Munoz, N., Franceschi, S. and Surveyst, I. H. P. 2006b 'Reproductive factors, oral contraceptive use, and human papillomavirus infection: Pooled analysis of the IARC HPV prevalence surveys', *Cancer Epidemiology Biomarkers & Prevention* 15(11): 2148-2153.

- Vaccarella, S., Herrero, R., Snijders, P. J. F., Dai, M., Thomas, J. O., Hieu, N. T., Ferreccio, C., Matos, E., Posso, H., de Sanjose, S., Shin, H. R., Sukvirach, S., Lazcano-Ponce, E., Munoz, N., Meijer, C., Franceschi, S. and Grp, I. S. 2008 'Smoking and human papillomavirus infection: pooled analysis of the International Agency for Research on Cancer HPV Prevalence Surveys', *International Journal of Epidemiology* 37(3): 536-546.
- Vera-Bravo, R., Ocampo, M., Urquiza, M., Garcia, J. E., Rodriguez, L. E., Puentes, A., Lopez, R., Curtidor, H., Suarez, J. E., Torres, E., Guzman, F., Diaz, D., Cortes, J., Bravo, M. M., Combata, A. L., Orozco, O. and Patarroyo, M. E. 2003 'Human papillomavirus type 16 and 18 L1 protein peptide binding to vero and hela cells inhibits their VLPS binding', *International Journal of Cancer* 107(3): 416-424.
- Viladiu, P., Bosch, F. X., Castellsague, X., Munoz, N., Escriba, J. M., Hamsikova, E., Hofmannava, V., Guerrero, E., Izquierdo, A., Navarro, C., Moreo, P., Izarzugaza, I., Ascunce, N., Gill, M., Munoz, M. T., Tafur, L., Shah, K. V. and Vonka, V. 1997 'Human papillomavirus DNA and antibodies to human papillomaviruses 16 E2, L2, and E7 peptides as predictors of survival in patients with squamous cell cervical cancer', *Journal of Clinical Oncology* 15(2): 610-619.
- Villa, L. L., et al. 2007b 'Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions', *New England Journal of Medicine* 356(19): 1915-1927.
- Villa, L., Perez, G., Kjaer, S., Lehtinen, M., Paavonen, J., Munoz, N., Sigurdsson, K., Hernandez-Avila, M., Iversen, O. E., Thoresen, S., Garcia, P., Majewski, S., Tay, E. H., Bosch, F. X., Dillner, J., Olsson, S. E., Ault, K., Brown, D., Ferris, D., Giuliano, A., Koutsky, L., Kurman, R., Myers, E., Barr, E., Boslego, J., Bryan, J., Esser, M., Hesley, T., Lupinacci, L., Railkar, R., Sing, H., Taddeo, F., Thornton, A. and Future, I. I. S. G. 2007a 'Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials', *Lancet* 369(9576): 1861-1868.
- Villegas Pinzón, O. 1936 'Resultados inmediatos de la Radioterapia en algunos casos de cáncer de cuello uterino', Bogotá: Universidad Nacional de Colombia.
- Walboomers, J. M. M., Jacobs, M. V., Manos, M. M., Bosch, F. X., Kummer, J. A., Shah, K. V., Snijders, P. J. F., Peto, J., Meijer, C. and Munoz, N. 1999 'Human papillomavirus is a necessary cause of invasive cervical cancer worldwide', *Journal of Pathology* 189(1): 12-19.
- Zhai, Y. L., Hotary, K. B., Nan, B., Bosch, F. X., Munoz, N., Weiss, S. J. and Cho, K. R. 2005. 'Expression of membrane type 1 matrix metalloproteinase is associated with cervical carcinoma progression and invasion', *Cancer Research* 65(15): 6543-6550.
- Zur Hausen, H. 2002 'Papillomaviruses and cancer: From basic studies to clinical application', *Nature Reviews Cancer* 2(5): 342-350.