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Short of Drugs? Call Upon Operations and Supply Chain Management

Abstract

Purpose: This 'impact pathways' paper argues that operations and supply chain management (OSCM) could help address the worsening drug shortage problem in high-income countries. This significant societal problem poses difficult challenges to stakeholders given the complex and dynamic nature of drug supply chains. OSCM scholars are well positioned to provide answers, introducing new research directions for OSCM in the process.

Design/methodology/approach: To substantiate this, we carried out a review of stakeholder reports from six European countries and the academic literature.

Findings: There is little academic research and no fundamental agreement among stakeholders about causes of shortages. Stakeholders have suggested many government measures, but little evidence exists on their comparative cost-effectiveness.

Originality/value: We discuss three pathways of impactful research on drug shortages to which OSCM could contribute: (1) Developing an evidence-based system view of drug shortages; (2) Studying the comparative cost-effectiveness of key government interventions; (3) Bringing supply chain risk management into the government and economics perspectives and vice versa. Our study provides a baseline for future COVID-19-related research on this topic.

Keywords: drug shortages, supply chain risk management, interventions, review, COVID-19

1. Introduction

An *"*ongoing and worsening drug shortage crisis*"* (FDA, 2019, p.5) emerged before COVID-19 in various countries and is aggravating (Farmanco, 2020). Consequences include considerable time and effort confronting shortages, delays in treatment, suboptimal treatment, and cancellation of care (EAHP, 2019; FDA, 2019). In the Netherlands the estimated annual total cost is between 45 and 105 million euros (MvVWS, 2019a).

A drug shortage has been defined as a period when demand or projected demand for a drug exceeds its supply (FDA, 2019). Using SCRM terminology, we see shortages as arising from events or conditions adversely affecting a supply chain (Ho *et al.*, 2015). Following others (e.g., Jia and Zhao, 2017), we refer to such events or conditions as *causes*. Abnormal causes are rare external events, such as pandemics. Normal causes occur frequently, typically originating within the supply chain, such as fluctuations in demand, production problems, or delays in distribution (Ho *et al.*, 2015; Sodhi and Tang, 2012). We use the term interventions for measures taken to decrease the likelihood of adverse events and their impact. Interventions resemble SCRM strategies, typically concerned with how *companies* can mitigate risk in their supply chains (Tang, 2006; Roscoe *et al.*, 2020). In contrast, we focus on *governmental* measures that may mitigate the risk of shortages. Government action is believed to be crucial here (De Weerdt *et al.* 2015), and COVID-19 is reinforcing this belief. When deciding which government intervention(s) to implement, several questions arise: What are the causes? What is their relative importance? How are they interconnected? Which interventions are likely to be most effective, and at what cost?

This impact pathways paper argues that OSCM could help answer these questions. We present an agenda for further research, based on a review of the academic literature on drug shortages combined with an analysis of secondary data pre-COVID from six European countries.

Our study focuses on off patent and generic prescription drugs, which represent most drug shortages (EAHP, 2019; FDA, 2019) and provides a baseline for future COVID-19-related research on this topic.

Both supply chain risk management (SCRM) (Sodhi and Tang, 2012) and resilience (van Hoek, 2021) provide useful perspectives, where some see the first as an enabler of the latter. Research on resilient medicine supply chains has been very scant (c.f. Lücker and Seifert, 2017; Tucker et al. 2020). We agree with Ellis (2020) that risk management in pharmaceutical supply chains should be a *"*strategically imperative exercise that is regularly revisited, not one to dust off when a disruption occurs*"* (p.8).

2. Stakeholder perceptions of causes and interventions

We searched websites of stakeholder organizations in Belgium, France, the Netherlands, Norway, Sweden, and the United Kingdom for material on drug shortages published between January 1st 2010 and December 31st 2019 resulting in 134 relevant sources. For each country, two researchers were involved in coding and analyzing the data. Further details are provided in link to online-addendum], section A.

2.1 Claim 1: There is no real agreement among stakeholders about causes of drug shortages

Firstly, many sources report first-level causes and do not link them to underlying issues. Typically, manufacturing problems, and "other supply chain related problems" are listed as key causes, with no mention of possible underlying economic causes (NoMA, 2019), for example price, tendering, and reimbursement policies. Such policies can affect supply bases, inventories, production quality and capacity, and lead times, but there is little evidence. It has been shown in other sectors that pressure on prices results in outsourcing manufacturing to low-cost economies, making supply chains more vulnerable to disruptions (van Hoek, 2020).

Secondly, though dozens of causes can be identified, sources typically report a small subset which differs substantially *between* countries. For example, Belgian and UK sources make no reference to impacts of prices and margins on inventories, and only the Netherlands and France report effects of quality issues. Sources also differ *within* countries. Norwegian pharmaceutical manufacturers list

manufacturing problems and demand increases as key causes (LMI, 2018) whereas the Directorate of Health emphasizes long lead times, just-in-time inventory management, hoarding, and market size (HDir, 2019). Similarly, the UK's National Pharmacy Association (2020) highlights quota systems imposed by manufacturers as an important cause, while manufacturers point to pharmacies and wholesalers exporting medicines intended for the UK (ABPI, 2019).

2.2 Claim 2: Many suggested interventions but little evidence or knowledge of what works

Most shortages are managed reactively instead of proactively, focusing "more on decreasing the effects of shortages or dealing with their consequences than on the underlying causes" (MvVWS, 2019, p.19). There is vast diversity among additional interventions considered, many resembling SCRM-strategies, such as better information sharing and adding *redundancy* through emergency stock. Interventions to enhance the *flexibility* (Tang, 2006) are also frequently suggested, such as awarding contracts to multiple suppliers to counter monopoly formation and ensure a "supply base that can be drawn upon in the event of a failure" (SFR 2018, p.98). Stakeholders also consider numerous interventions not easily categorizable in SCRM frameworks such as substituting medicines that are out of stock and rationing and allocating scarce supplies. Widely recommended is bringing production back to Europe. This resembles the make or buy SCRM strategy (Tang, 2006), but uses government incentives as opposed to in-house vs. outsourcing decisions by manufacturers.

However, stakeholders provide little evidence on cost effectiveness. For example, the Dutch government analyzed the effects of 27 interventions and concluded they were mostly difficult to assess or unknown (MvVWS, 2019). We found no analysis of which interventions are more cost-effective than others.

3. What research has contributed so far

We identified 506 articles in our scientific literature review and read 79 in depth, and classified each article in terms of context, purpose, type of evidence provided, intervention analysis, cause analysis and research methodology. Three of the authors were involved in coding to secure inter-rater reliability. See [link to online-addendum], section B for details of search terms and inclusion criteria.

3.1 Claim 1: OSCM has so far played a marginal role in studying the drug shortage problem

We identified only ten articles on drug shortages in OSCM-related journals (Azghandi *et al.*, 2018; Chang et al. 2019; Dai *et al.*, 2016; Jia and Zhao 2017; Kochan *et al.*, 2018; Liao *et al.*, 2015; Lu and Shi, 2019; Shiau, 2019; Tucker *et al.*; 2020; Zadeh *et al.*, 2014). The remaining identified articles make little use of models, tools, or concepts from our field.

3.2 Claim 2: More research presenting a comprehensive view on shortage causes is necessary

Scholars agree that recent increases in drug shortages are driven by several trends (De Weerdt *et al.*, 2015; Heiskanen *et al.*, 2017; Pauwels *et al.*, 2014; Tucker *et al.*, 2020; Yurukoglu *et al.*, 2017). However, most papers that express a view on the causes present either no new evidence or evidence relating to first level causes only. Papers aiming to assess the causes comprehensively use mainly expert opinion and mechanism-based reasoning, regarded by health scientists as relatively weak evidence (Van de Klundert, 2016). Studies examining causal interrelations are particularly scarce.

Like stakeholder reports, academic papers report primarily on first-level causes. Indeed, Pauwels *et al.* (2014) conclude that "no efforts [have yet been made] to unveil the root causes" (p.7). This may be the consequence of eliciting stakeholder views on causes of *specific* shortages, directly or via reporting platforms.

Heiskanen *et al.* (2017) and Pauwels *et al.* (2015) do reveal several underlying causes but provide no new evidence on how these factors could be interrelated or impacted further upstream. Woodcock and Wosinska (2013) explore such interrelationships with economic theory to argue that disincentives

in the pharmaceutical market can worsen shortages. De Weerdt *et al.* (2015) use inference from economic mechanisms and stakeholder reports to indicate how European and national laws might affect drug shortages. We found only three studies that apply econometric modeling to study causality between shortage and pricing. Yurukoglu *et al.* (2017) showed that shortages rose for drugs whose prices decreased most significantly. Ridley *et al.* (2016) revealed that a higher price is associated with a lower likelihood of shortage. Parsons *et al.* (2016) show that having maximum four suppliers makes shortages more than twice as likely to occur compared to having five or more suppliers.

3.3 Claim 3: More work is needed to assess holistically the cost-effectiveness of suggested government interventions

To assist governmental decision-making, there is a need for research that 1) examines proposed interventions for which cost-effectiveness is unclear, 2) provides strong evidence of comparative cost-effectiveness, and 3) assesses the direct and indirect implications for all relevant stakeholders. For example, to assess the impact of changes in procurement one should consider effects on market attractiveness and the number of suppliers. Only 18 studies provide any evidence on implementation costs and/or effectiveness of proposed interventions. All papers that present *empirical* evidence (7 of the 18) comprise case studies of a specific stakeholder's response to a shortage. Similarly, more than half of the papers that present evidence from *modeling* and numerical simulation consider a single stakeholder and a single intervention (cf. Zadeh *et al.*, 2014). Reliance on such local optimization can miss implications for upstream and downstream parts of the supply chain (Settanni *et al.*, 2017). Two modelling/simulation papers (Azghandi *et al.*, 2018; Kochan *et al.*, 2018) account for multiple stakeholders but do not consider the government. Dai *et al.* (2016) study how the US government could mitigate shortages of an influenza vaccine through incentivizing a manufacturer to initiate early production, and Jensen *et al.* (2015) investigate how the US Food and Drug Administration (FDA) collaborated with manufacturers to take last-minute risk-mitigation actions. Half the articles cover reactive interventions, like rationing, allocation, or substitution, and last-minute risk mitigation.

Accordingly, there is great potential for research on proactive interventions that governments *could* consider.

We identified two papers that illustrate urgently needed research taking a systems perspective (capturing multiple stakeholders, causes beyond first-order ones, interdependencies of causes). Jia and Zhao (2017) model the impact of increasing prices and failure-to-supply penalties on manufacturers' inventory and capacity decisions, and the subsequent effect of those decisions on shortages. Tucker *et al.* (2020) use a multi-stage stochastic model to simulate how government interventions affect a manufacturer's decisions on supply chain design and inventories and estimate how this affects societal costs and shortages.

4. Pathways for future research

4.1 *Pathway item 1: Develop an evidence-based system view*

Sections 2.1 and 3.2 describe limited evidence on the causes of shortages, their relative importance, and how they interrelate. With the notable exception of a study on the link between the number of suppliers and shortages (Parsons *et al.*, 2016), we found no studies that quantify the cause-and-effect relationships linking causes related to pricing, tendering and reimbursement to shortages. That means a serious risk of stakeholders and academics missing important dynamics and knock-on effects. For example, we did not identify any modeling studies that capture how interventions impact the number of suppliers, even though it is widely believed that they may. Furthermore, research on how interventions can backfire is needed. For example, joint tendering is claimed to increase appeal for their markets (Eversana, 2020), while France argues that it could *decrease* the number of suppliers and increase vulnerability (SRF, 2018).

We therefore advocate further research that can 1) establish sound evidence on understudied cause and effect relationships and 2) combine it with evidence from existing literature to establish a system

view of the problem. We need research that builds the whole from the parts. OSCM expertise in studying and modeling complex dynamic systems will be paramount here, combined with expertise from the health sciences and economics. We see a large potential role for system dynamics modeling and econometric models that assess causality. These methods would be very suitable for studying links between prices and other underlying causes and manufacturing disruptions, inventories, parallel trade, lead times, and the number of manufacturers. Building on the leading studies identified in this review, such research could complement publicly available data sets, with direct engagement with relevant stakeholders.

4.2 Pathway item 2: Studying the comparative cost-effectiveness of key government interventions

Section 3.3 highlights the paucity of evidence on the cost-effectiveness of proposed governmental interventions. We therefore call upon OSCM researchers to develop and parametrize models for this:

Establishing strategic stocks. Legal requirements for inventory levels (or lead times) and corresponding failure-to-supply penalties have been considered in several countries. Countries struggle to decide how high such inventory levels should be, where the inventory should be kept, whether and how to differentiate by medicine, how to finance, and how to enforce. The challenge of specifying legal requirements differs from traditional inventory management, notably that a policy should be expressed in relatively simple language – e.g., keep a safety stock of x months of demand for medicines with characteristics y and z. Furthermore, evaluations should take into consideration that such interventions can change the "future state" of the system. For example, there are concerns that increasing penalties carries the risk that manufacturers with small revenues or low prices will withdraw from the market. OSCM scholars have the potential to inform this debate by developing models to optimize market-wide inventory policies and failure-to-supply penalties and account for market withdrawals. Such models can be parametrized using publicly available data on drug demand, prices, market authorization holders, and shortages.

Reshoring of drug manufacturing. The OSCM community possesses much expertise that could inform debates around reshoring of drug manufacturing. COVID-19 has led to many calls for action and the comparative cost-effectiveness of possible strategies is hugely interesting. Reshoring will certainly increase costs (France24, 2020), and it is questionable to what extent it will resolve problems, partly because upstream supply chains (e.g., for Active Pharmaceutical Ingredients) may remain global. There is a clear need for more OSCM research on the total system cost-effectiveness of reshoring, how it differs for specific drugs and countries, how it depends on other countries' reshoring decisions, and how it compares to the effects and costs of other interventions.

Revising pricing, tendering, and reimbursement practices. Interventions that tackle economic causes – pricing, tendering, and reimbursement practices – are a third important research area. Since tackling these practices is perceived to conflict with the objective of maximizing affordability, a delicate balance needs to be struck (cf. Musazzi *et al.*, 2020). OSCM expertise on game theoretic modeling and mechanism design, parametrized using data on shortages, prices, numbers of market authorization holders, and expertise on procurement practices could help address this question.

Future research in this area would also benefit from a behavioral OSCM perspective (Bendoly et al., 2010) to examine how cognitive and psychological factors impact contractual relationships in drug supply chains. For instance, *framing bias* is relevant to consider when designing tenders and contracts (Selviaridis and van der Valk, 2019), e.g. whether switching from a predominant 'prevention' contract framing (emphasizing control and penalties to suppliers) to a 'promotion' (stressing supplier rewards) could help instigate collaboration and flexibility in supplier relationships. Studying how *perceptions* of fairness (e.g. regarding pricing), trust and power influence contractual negotiations would also be a fruitful avenue for further research.

4.3 Pathway item 3: Bringing the government perspective and economics into supply chain risk management

Many interventions suggested by stakeholders could be classified using common SCRM frameworks. We nevertheless see two fundamental differences that can push the frontiers of SCRM research. First, interventions could be addressed from a government perspective, and thus complement existing SCRM studies. Governments and their policies have a critical role in mitigating supply chain disruptions (Scholten et al. 2020). As they are rarely directly engaged in the production and distribution of medicines, interventions are usually indirect. COVID-19 shows that governments are increasingly intervening to avoid or minimize shortages. For example, they have traditionally not been involved in decisions on production locations, but some plan to influence them through economic incentives. Similarly, most governments have not stocked medicines but are now planning to influence stocks kept by firms by introducing regulations and fines. Studying inventory management and facility location from a company perspective can hence be fundamentally different from studying stockpiling and production reshoring resulting from government regulations. The same applies to procurement, distribution, quality and capacity management, and so on. Sound analyses of government policies' effect on supply chains have received limited attention (Scholten *et al.* 2020). Second, although maintaining a diverse supply base is recognized as a SCRM strategy, supply base decisions have typically been made by existing supply chain members*,* i.e. the buying organization. Our context highlights the need to understand how supply base design is impacted by other actors' decisions to enter or exit a market.

It would be very helpful to have models that capture these decisions. Several general supply chain economics models are available (Corbett and Karmarkar, 2001; Korpeoglu *et al.*, 2020), but they include some assumptions that do not hold for medicine supply chains. They also analyze outcome variables other than availability, or study interventions and decision variables that may not apply. We therefore advocate that researchers should develop models that capture 1) relevant interventions, 2) their impact on entry/exit decisions, 3) the direct and indirect implications for supply chain risk. Collaboration between economists and OSCM researchers is essential here.

To summarize, our suggested pathways are graphically depicted in Figure 1.

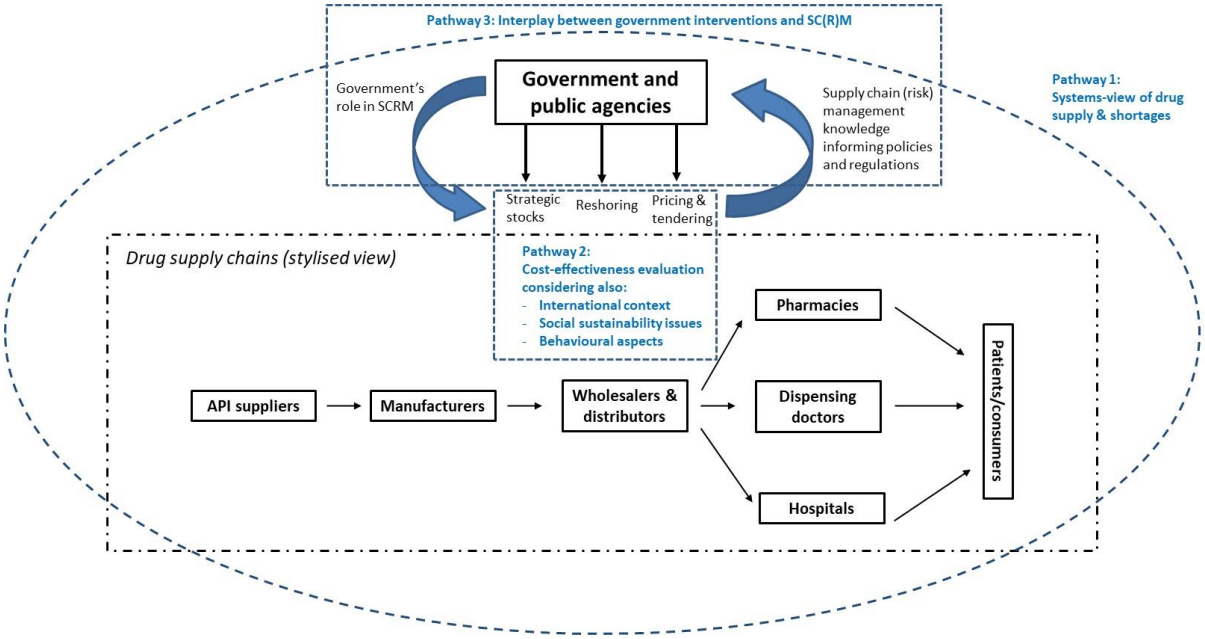

Figure 1: Visualizing the suggested pathways

4.4 Final remarks

We have seen many calls for OSCM scholars to increase the relevance of their research (Van Wassenhove, 2019) and undertake studies that are practice-based and responsible (Lee and Tang, 2018), contributing towards more sustainable and resilient supply chains (Sarkis, 2021), but accounting for difficult trade-offs (Matos et al. 2020). The continuing problem of drug shortages demands that the OSCM community gets more involved and provides us with a great opportunity: (1) the problem has substantial patient and economic impacts; (2) it poses complex questions for stakeholders to which there is no obvious answer; (3) OSCM scholars are well positioned to address these questions; and (4) the problem introduces fundamentally new research directions for OSCM and pushes the frontiers of our discipline. COVID-19 has amply demonstrated why such work is urgently needed. The pandemic has substantially worsened the situation, not only for COVID-related medicines and vaccines, but also in terms of strong knock-on effects on regular drug supply, particularly in low- and middle-income countries. More resilient and sustainable drug supply chains will provide better global long-term access.

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Appendix A: Review and analysis of the grey literature

We conducted an analysis of publicly available secondary data (including policy reports, governmental communications, and press articles) on drug shortages in six European countries: Belgium, France, the Netherlands, Norway, Sweden, and the United Kingdom. We selected these six because they are representative of the high-income country settings we are focusing on. Our research group consists of researchers who speak different languages and can read public reports published in these countries.

For each country, we searched for drug shortages-related issues, causes of shortages and (ongoing) interventions pursued to tackle these shortages following four key steps. First, we consulted the latest risk analysis documents published by ministries/governmental agencies, or other equivalent publications to get an overview of the drug shortages problem, and to identify additional sources referred to in these documents (through snowballing). Second, we researched the website of the Ministry of Health (or equivalent) in each of the six countries. This step also helped to identify additional key stakeholders: public health agencies, healthcare providers, manufacturers, wholesalers and distributors, and patient representative organisations. Third, and based also on inputs from the two previous steps, we researched in detail the websites of all key stakeholders in each country. Fourth, we complemented these results by searching online for any press articles focusing on drug shortages. The stakeholders and key data sources per country we studied are shown in Table 1.

Table 1: Stakeholders and key data sources per country for the grey literature analysis

Country Stakeholder	**Norway***: search for "legemiddelmangel"; "vaksinemangel" on website of the stakeholders*	**Sweden** *search for* "brist läkemedel" *on website of the stakeholders*	**Netherlands** *search for "geneesmiddelen tekort" on website of the stakeholders*
Agency for Risk Analysis	The Norwegian Directorate for Civil Protection - DSB 2018. https://www.dsb.no/ 14 hits; 0 hits	Swedish Civil Contingencies Agency - MSB 2013; 2017; 2018 https://www.msb.se/ 244 hits	No such thing in NL
Ministry of Health	Ministry of Health and Care Services - HoD 2018; Meld. St.28. 2014–2015; Meld. St.10. 22016-2017; Meld. St.34. 2015-2016; IS-2635 2017. https://www.regjeringen.no/no/dep/hod/id421/ : 27 hits; 2 hits;	Ministry of Health and Social Affairs - SOU 2013; 2017; Regjeringskansliet 2015; 2016; 2018; Socialdept. 2018 https://www.regeringen.se/sveriges-regering/socialdepartementet/ 226 hits	Government website: https://www.rijksoverheid.nl 369 hits
Health regulator/ directorate	Norwegian Directorate of Health - HDir 2018a; b. https://helsedirektoratet.no/: 14 hits; 0 hits	Socialstyrelsen 2016a; b http://www.socialstyrelsen.se/ 692 hits	Website assessment body for drugs: https://www.cbg-meb.nl/ 285 hits
Public Health Agency	Norwegian Institute of Public Health – FHI Johansen et al. 2017. https://www.fhi.no/ 0 hits; 1 hit;	Public Health Agency of Sweden – FHM 2017. https://www.folkhalsomyndigheten.se/ 331 hits	Public health institute: https://www.rivm.nl 585 hits
Medicines Agency	Norwegian Medicines Agency – LMV; Harborg 2017. https://legemiddelverket.no/ 367 hits; 0 hits	Swedish Medical Products Agency – LMV 2017; 2018. https://lakemedelsverket.se/ 889 hits	Assessment body for drugs: https://www.cbg-meb.nl/ 285 hits
Hospital	Sykehusinnkjøp – HF 2018. https://sykehusinnkjop.no/ 5 hits; 0 hits	Landstingen - SKL 2014. https://skl.se/ 12 hits	Hospital association: https://www.nvz-ziekenhuizen.nl 23 hits
Manufacturer	Association of the Pharmaceutical Industry in Norway - LMI 2016. https://www.lmi.no/ 44 hits; 0 hits	Swedish Association of the Pharmaceutical Industry – LIF 2018. https://www.lif.se/ 15 hits	Generics pharma sector: http://www.bogin.nl/ scanned all news articles. association for new drugs: https://www.verenigginginnovatievegeneesmiddelen.nl/ 208hits

Wholesaler	Norwegian Pharmacy Association – NPA 2017. https://www.apotek.no/ 22 hits; 0 hits		Association of pharma wholesalers: https://vno-ncw.nl/content/bond-van-groothandelaren-het-pharmaceutische-bedrijf-bg-pharma 0 hits; 115 hits
Retailer		Sveriges Apoteksförening; http://www.sverigesapoteksforening.se/ 41 hits	Pharmacists association: https://www.knmp.nl/ 156 hits
Patient	Pasientforeningen https://www.pasient.no/ Kreftforeningen https://kreftforeningen.no/ 1hit	Patientförsäkringsföreningen https://www.pff.se/ 11 hits	Patient federation: https://www.patientenfederatie.nl/zoeken?q=geneesmiddelen+tekort&Search= 28 hits
Other	National Center for Medicine Shortages and Preparedness in Specialist Health Service https://oslo-universitetssykehus.no/avdelinger/klinikk-for-laboratoriemedisin/avdeling-for-farmakologi/nasjonalt-senter-for-legemiddelmangel-og-legemiddelberedskap 75 hits	Riksrevisionen 2018 https://www.riksrevisionen.se/ 0 hits Generikaforeningen http://www.generikaforeningen.se/ (no search function) https://www.apotekarsocieteten.se/ 4 hits	Statistics body for pharma sector: https://www.sfk.nl/ 137 hits Insurance companies association: https://www.zn.nl 54 hits Website monitoring body for pharmacists: https://farmanco.knmp.nl/tekorten-in-cijfers Website monitoring body for drug wholesales: https://www3.sfk.nl/tekorten/ Website statistics on Dutch pharmacy: https://www.sfk.nl/
Country Stakeholder	**United Kingdom** – search for "medicine shortages" and "vaccines shortages" on the website of the relevant stakeholders; also search for "Brexit and medicines supply", "Brexit and vaccines supply".	**Belgium –** *search strategy: search for "geneesmiddelen tekort" on website of the stakeholders*	**France –** *search strategy: search for "penurie medicaments"*
Agency for Risk Analysis	The Civil Contingencies Secretariat (part of the UK Cabinet Office) website: https://www.gov.uk/government/emergency-preparation-reponse-and-recovery - 8 hits	Not found for Belgium	Agence Nationale de Securite du Medicament et des produits de sante https://www.ansm.sante.fr/ 280 hits
Ministry of Health	Department of Health and Social Care website: https://www.gov.uk/government/organisations/department-of-health-and-social-care - 724 hits	Government website (Federale Overheidsdienst Volksgezondheid): https://www.health.belgium.be 329 hits	Ministry of Health and Solidarity: https://solidarites-sante.gouv.fr/ 59 hits
Health regulator/ directorate	Medicine and Healthcare Products Regulatory Agency website: https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency - 245 hits National Institute for Health and Care Excellence website: https://www.nice.org.uk/ - 0 hits	Government website (Federale Overheidsdienst Volksgezondheid): https://www.health.belgium.be 338 hits	Haute autorite de sante (HAS) https://www.has-sante.fr/portail/ 365 hits
Public Health Agency	Public Health England website: https://www.gov.uk/government/organisations/public-health-england - 274 hits NHS England website: https://www.england.nhs.uk/ - 216 hits	Federaal Agentschap voor Geneesmiddelen Gezondheidsproducten: https://www.fagg.be/nl/search?keyword=geneesmiddelen+tekort&=Zoeken 40 hits	Public Health France: http://www.santepubliquefrance.fr/ INVS: 31 hits; INPES: 29 hits;
Medicines Agency	Medicine and Healthcare Products Regulatory Agency website: https://www.gov.uk/government/	Agentschap Zorg en Gezondheid https://www.zorg-en-gezondheid.be/ 2 hits	Agence Generale des Equipements et Produits de Sante http://ageps.aphp.fr/ 4 hits

	organisations/medicines-and-healthcare-products-regulatory-agency - 244 hits (same hits as above, see "Health regulator" category) (NHS) Specialist Pharmacy Service: https://www.sps.nhs.uk/ -733 hits		
Hospital	Community Hospitals Association website: http://www.communityhospitals.org.uk/ - 0 hits	Belgische Vereniging der Ziekenhuizen: http://www.hospitals.be	Federation Hospitaliere de France https://www.fhf.fr/gestion-hospitaliere/association-hopital.html 804 hits
Manufacturer	Association of the British Pharmaceutical Industry website: https://www.abpi.org.uk/ - 53 hits UK Bio Industry Association website: https://www.bioindustry.org/ - 90 hits	Algemene Vereniging van de Geneesmiddelenindustrie: https://pharma.be/nl/ 4 hits Medaxes: Association for accessible medicines: https://www.medaxes.be/nl (no search function) Bachi: http://www.bachi.be/nl/ 0 hits	Les Entreprises du Medicament https://www.leem.org/ 43 hits
Wholesaler	Healthcare Distribution Association website: https://www.hdauk.com/who-we-are - 17 hits	Algemene Vereniging van de Geneesmiddelenindustrie: https://pharma.be/nl/ 4 hits	
Retailer	The Pharmaceutical Services Negotiating Committee website: https://psnc.org.uk/dispensing-supply/supply-chain/ - 52 hits National Pharmacy Association website: https://www.npa.co.uk/the-npa/ - 41 hits Company Chemists' Association website: https://www.thecca.org.uk/ - 3 hits Association of Independent Multiple Pharmacies website: https://www.aimp.co.uk/ [no search function]	Apothekersbond: https://www.apb.be/ 15 hits Koninklijke Apothekers Vereniging Antwerpen (KAVA) https://www.kava.be/ (no search function) Belgische/Vlaamse Vereniging van Ziekenhuis Apothekers (BVZA or VZA): http://www.vza.be/nl/default/6579/BVZA-ABPH.aspx 24 hits Hospital Pharmacists of Belgium (terrible website): http://www.hospitalpharmacistbelgium.eu/ (no search function)	Orde National des Pharmaciens http://www.ordre.pharmacien.fr/ 134 hits
Patient	The Patients Association website: https://www.patients-association.org.uk/ - 9 hits	Vlaams patientenplatform http://vlaamspatientenplatform.be/ 13 hits	France Assos Sante http://www.france-assos-sante.org/ 1 hit
Other	Royal Pharmaceutical Society website: https://www.rpharms.com/ - 64 hits British Medical Association website: https://www.bma.org.uk/ - 354 hits Dispensing Doctors' Association website: https://www.dispensingdoctor.org/ - 26 hits Department for Exiting the European Union website: https://www.gov.uk/government/organisations/department-for-exiting-the-european-union - 23 hits	Repertorium van het Belgisch Centrum voor Farmaceutische Informatie (BCFI): http://www.bcfi.be/nl/start 10 hits Belgische Vereniging van Artsensyndicaten (BVAS): https://www.absym-bvas.be/ 2 hits	

Through the process described above we identified a total of 133 documents that the key stakeholders produced across the six countries. The full list of the documents we analysed is provided at the end of this appendix. It is noted that we carried out a second wave of data collection in August 2020 to ensure that we had covered all relevant documents up until the end of December 2019. We intentionally excluded 2020 documents from our sample because our focus was on drug shortages pre-COVID-19.

We downloaded all the documents and stored them into a common database (Dropbox folder) that we created for this purpose. We fully read the documents and analysed their contents in an excel sheet based on a simple coding framework we designed for analytical purposes. This framework included the following classification schemes: observed shortages; causes of shortages; and interventions to address shortages. Table 2 shows the framework and related classification schemes.

Table 2: Scheme for classification of grey literature on drug shortages

Classification scheme	Related categories	Initial Scientific Sources
Demand Related Causes of Shortage – normal and abnormal	Gaming Domino effect Little demand flexibility Limited information on demand evolution Changing Demand Pattern Epidemic, Natural disaster, War/terrorism, Fires, Political instability, Economic downturns, External legal issues, Regional instability, Government regulations, Social and cultural grievances Logistical problems Geographic concentration Lack of raw materials Manufacturer quotas Few manufacturers - specify root causes Inflexible manufacturing capacity	Ho, W., Zheng, T., Yildiz, H. and Talluri, S. 2015. Supply chain risk management: a literature review. *International Journal of Production Research*, 54(16), 5031–5069.
Supply Related Causes of Shortage – normal and abnormal	Entry barriers Mergers and acquisitions Decisions based on product and market attractiveness Local production Market strategies Complex and long production processes and quality controls Tight production planning Geographic concentration Counterfeits demanding recalls Lack of raw materials Deliberate low inventories Production problems Limited information on current and future supply capacity and risk of shortage Small customer Information system failures Deliberate low inventories Few wholesalers Lack of SC transparency Cross-border drug trade Information system failures Deliberate low inventories Epidemic, Natural disaster, War/terrorism, Fires, Political instability, Economic downturns, External legal issues, Regional instability, Government regulations, Social and cultural grievances, Brexit	Ho, W., Zheng, T., Yildiz, H. and Talluri, S. 2015. Supply chain risk management: a literature review. *International Journal of Production Research*, 54(16), 5031–5069.
Effects of shortages	Effects on patients: does not discuss /analyse (N); simply discusses (D); analyses primary data (P); analyses secondary data (S)	

	Economic /financial effects: does not discuss /analyse (N); simply discusses (D); analyses primary data (P); analyses secondary data (S)	
Market interventions	Economic supply incentives Limit parallel trade Flexible supply termination/ smoothen number of players in the market Law enforcement for: notification of halting/pausing supply Law enforcement: Effort obligation for sufficient inventories	Tang, C.S. (2006a), "Robust Strategies for mitigating supply chain disruptions", International Journal of Logistics: Research and Applications, Vol. 9 No. 1, pp. 33–45.
Medical interventions	Silent product rollover ('Prescribe' a different product due to shortages of the original) Allocation rules/ rationing (In case of shortages, no rules on which patients should be prioritized) Flexible quality standards/product characteristics	Tang, C.S. (2006a), "Robust Strategies for mitigating supply chain disruptions", International Journal of Logistics: Research and Applications, Vol. 9 No. 1, pp. 33–45.
Supply chain interventions	Centralization Collaboration Flexible supply base Supply contracts Flexible manufacturing process Flexible transport From make to buy and vice versa Postponement Speculation Strategic stock Dynamic assortment planning	Jahre, M. 2017. Supply Chain Strategies in Humanitarian Logistics: A Review of how Actors Mitigate Supply Chain Risks. Journal of Humanitarian Logistics and Supply Chain Management, 7(2), 82-101.; Lavastre, O., Gunasekaran, A. and Spalanzi, A. (2014), "Effect of firm characteristics, supplier relationships and techniques used on supply chain risk management (SCRM): an empirical investigation on French industrial firms", International Journal of Production Research, Vol. 52 No. 11, pp. 3381–3403. Tang, C.S. (2006b), "Perspectives in supply chain risk management", International Journal of Production Economics, Vol. 103, pp. 451–488 Chopra, S. and Sodhi, M.S. (2004), "Managing Risk to Avoid Supply-Chain Breakdown", MIT Sloan Management Review, Fall 2004, pp. 53□61; Manuj, I. and Mentzer, J.T. (2008), "Global supply chain risk management strategies", International Journal of Physical Distribution and Logistics management, Vol. 38 No. 3, pp. 192–223.

We inductively coded observed shortages in terms of medicines and /or vaccines in short supply, and any associated details. Regarding causes of shortages, our coding framework drew a distinction between demand- and supply-related causes, and between normal and abnormal causes following prior research on supply chain risk management (Ho et al., 2015). Based on these classification schemes, observed causes of shortages were coded into one the four categories: "demand-related, normal cause" (e.g. changing demand patterns), demand-oriented, abnormal cause" (e.g. epidemic outbreak), "supply-related, normal cause" (e.g. single sourcing and limited manufacturing capacity),

and “supply-related, abnormal cause” (e.g. import /export bans). Regarding interventions, our coding scheme identified three key categories based on Tang (2006), Sodhi and Tang (2012), and Ho et al. (2015): “market” (e.g. economic supply incentives), “supply chain” (e.g. flexible supply base), and “medical” interventions (e.g. rationing or allocation rules).

Coding and analysis of the country-specific reports was conducted by a team of twelve researchers (including four of the authors). For each country, two researchers were assigned to code the secondary data to ensure bias-free analysis and assessment of the document sources. Specifically, for each country we selected a small sample of documents that both researchers coded, and then compared our within-country coding. All coding disagreements were discussed and eventually adjudicated. In addition, during the data coding process, we held lengthy discussions, and made iterations, to ensure a standardized approach to our coding across the six countries. All these steps increased our confidence regarding the reliability of our coding and analysis. Further details regarding the steps taken to ensure inter-coder reliability are available upon request.

List of documents we analysed in the six countries

Belgium

1. FAGG. 2019. Nieuwe maatregelen om onbeschikbaarheden van geneesmiddelen te beperken. Accessed 5.09.2020. https://www.fagg.be/nl/news/nieuwe_maatregelen_om_onbeschikbaarheden_van_geneesmiddelen_voor_menselijk_gebruik_te_beperken#:~:text=van%20het%20FAGG-,Nieuwe%20maatregelen%20om%20onbeschikbaarheden%20van%20geneesmiddelen%20voor%20menselijk%20gebruik%20te,professionele%20stakeholders%20van%20het%20FAGG&text=Op%2018%20mei%202019%20treedt,van%20geneesmiddelen%20betreft%20in%20werking.
2. FAGG. 2020. Onbeschikbaarheid van geneesmiddelen. Accessed 5.09.2020. https://www.fagg-afmps.be/nl/items-HOME/Onbeschikbaarheid_van_geneesmiddelen
3. Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten. 2018. Beschikbaarheid van geneesmiddelen: herinnering aan de wettelijke verplichtingen. https://www.fagg.be/nl/news/news_disponibilite
4. Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten. 2018. Stappenplan voor concrete oplossingen en aanbevelingen bij onbeschikbaarheid van een geneesmiddel. https://www.fagg.be/nl/news/stappenplan_voor_concrete_oplossingen_en_aanbevelingen_bij_tijdelijke_onbeschikbaarheid_van_een
5. Federale Overheidsdienst FINANCIEN. n.d. Het FAGG verfijnde de maatregelen om tekorten aan geneesmiddelen te vermijden. Accessed 5.09.2020. https://financien.belgium.be/nl/douane_accijnzen/ondernemingen/corona-informatie-en-maatregelen/uitvoer/het-fagg-verfijnde-de
6. Geneesmiddelentekorten in de openbare apotheek. 2015. (Master’s Thesis) Eline Moors. https://docplayer.nl/17572645-Geneesmiddelentekorten-in-de-openbare-apotheek.html
7. Onbeschikbaarheid van geneesmiddelen in het ziekenhuis: beheer, oorzaken en budgetimpact. 2015. Claus, B. et al. Farmaceutisch Tijdschrift voor België.
8. Time Investment in Drug Supply Problems by Flemish Community Pharmacies. 2017. Elfi De Weerdt, Steven Simoens, Minne Casteels and Isabelle Huys. Frontiers in Pharmacology. doi: 10.3389/fphar.2017.00568
9. Wetsvoorstel tot wijziging van de wet van 25 maart 1964 op de geneesmiddelen wat de tekorten van geneesmiddelen betreft (door Yoleen Van Camp). 27 april 2017. http://www.dekamer.be/FLWB/PDF/54/2440/54K2440001.pdf

France

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2. Rapport publique au Premier ministre et au Ministères des Solidarités et de la Santé. Juin 2020. Mission stratégique visant à réduire les pénuries de médicaments essentiels. Accessed 1st of September 2020 at : https://www.vie-publique.fr/rapport/274702-mission-strategique-pour-reduire-les-penuries-de-medicaments-essentiels
3. Sénat République Francaise. 2018. Pénuries de medicaments et de vaccins: Renforcer l’ethique de santé publiques dans la chaîne du médicament. Note de synthèse. 2 Octobre. Accessed 4th October at: https://www.senat.fr/notice-rapport/2017/r17-737-notice.html.

Netherlands

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9. Ministerie van Volksgezondheid Welzijn & Sport. 2016a. Stand van zaken werkgroep geneesmiddelentekorten. Accessed 30.11.2018. https://www.rijksoverheid.nl/binaries/rijksoverheid/documenten/kamerstukken/2016/12/14/kamerbrief-over-stand-van-zaken-werkgroep-geneesmiddelentekorten/kamerbrief-over-stand-van-zaken-werkgroep-geneesmiddelentekorten.pdf
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Appendix B: Review and analysis of the academic literature

To ensure rigour and replicability of our survey of the academic literature, we followed a systematic literature review approach (Tranfield, Denyer and Smart, 2003). The process commenced with reviewing key articles on shortages of medicines and vaccines in pharmaceutical supply chains. Specifically, we selected thirteen articles that we deemed important (e.g. Dobrzykowski et al., 2014; Duijzer et al., 2018; Jia and Zhao, 2017; Mamani et al., 2013; Pauwells et al. 2014; Settanni et al., 2017;) based on our expert judgement and familiarity with key authorities in this research field. This research scoping exercise informed our subsequent definition of literature search terms and the design of a classification framework we used to code and analyse the research articles we reviewed.

The initial scoping study also confirmed our expectation that the topic of drug shortages spans across disciplines, notably health and life sciences, biomedical sciences, and operations and supply chain management (OSCM). Accordingly, we decided to devise a rather broad literature search strategy relying on the Web of Science (WoS) database and the PubMed database, which is maintained by the US National Library of Medicine at the National Institutes of Health. The WoS database was selected because it is broad in its coverage of peer-reviewed journals across fields of study, including OSCM, operations research and healthcare services. Specifically, as part of our preparatory work we confirmed that the WoS database includes all major OSCM journals, broadly define as journals classified by WoS as Operations Research and Management Sciences, Mathematics (and related categories such as Mathematics and Computational Biology), or Engineering (and related categories such as Computer Science and Engineering).The PubMed database was chosen as a complementary source of scientific literature given its emphasis on health science- and medicine science-related outlets. An additional reason for using both databases was our intention to identify any similarities and differences between health sciences outlets and OSCM journals with respect to their relative focus on the shortages topic, and the approaches they use to study drug shortages.

We conducted a keyword-based search in both databases. We jointly defined our search terms considering also the findings of our initial scoping study. We used the following search terms in combination: "medicin* shortage*", "drug* shortage*", "medicinal* shortage*", and vaccine* shortage*. We restricted our search to peer-reviewed articles (i.e., we excluded conference proceedings, books, and other document types) written in English. We also decided to restrict our literature review to articles published from January 2009 to December 2019 (inclusive). We opted for setting 2009 as our starting year given that the drug shortages topic attracted increasing interest in practitioner and academic circles alike during the 2010s, as also reflected by the organisation of the First International Summit on Medicines Shortages in June 2013, which was hosted by the International Pharmaceutical Federation.

This first search step produced 397 hits for the WoS database, and 256 hits for the PubMed. After merging the two searches and removing duplicates, we arrived at a set of 514 articles. Next, two of the authors read the abstracts of all 514 articles to evaluate their relevance, and to decide whether

they should be included in our subsequent detailed analysis. During this step, we excluded many articles because these addressed none of the following aspects of interest: shortages observed, causes of shortages, effects of shortages, interventions to tackle shortages, or impact of interventions. This assessment and elimination process resulted in a set of 83 articles that qualified for our detailed analysis and classification. We downloaded and stored all these articles into a scientific literature database we jointly maintain. We also noted the publication details of each article: authors, year, title, and journal.

Next, we developed a comprehensive file for data extraction (Tranfield et al., 2003) based on a spreadsheet which we used to classify the chosen articles. Table 3 presents all the classification schemes we developed, and their respective categories. For our literature analysis we used the following classification schemes: shortages studied, country in focus, medicines/vaccines in focus, type of situation (normal vs. extreme), causes of shortages, effects of shortages on patients and healthcare costs, types of interventions to address shortages, impact of interventions, and explicit reference of study to OSCM scholarship. For the classification of observed shortages, causes and impacts of shortages, and interventions to address shortages, we were interested to know whether the articles simply discussed those, or provided analysis based on primary or /and secondary data. Regarding the classification according to whether an article studies causes of shortages (yes /no), we defined the content of additional related schemes in terms of number of causes identified (low=1-5; medium=6-15; high=16-plus), the level of analysis (first-level vs. root-cause) and (non)linearity of analysis (linear vs. causal loop analysis).

With respect to interventions, we defined three types (medical, supply chain, and market interventions) based on our early consultation of key studies and our expert knowledge. In addition, we wanted to know whether the articles we reviewed provided any evidence (either empirical or modelling-based; or both) on the impact of interventions. Amongst other categories, we defined interventions in terms of scope (one vs. multiple interventions), their proactivity extent (reactive; proactive; both), and any impact metric used to quantify the effects of an intervention. In total, we used 20 classification fields to code the data.

Table 3: Schemes for classification of academic literature on drug shortages

Classification scheme	Related categories
Shortages observed	Does not present data on shortages (N); Presents /analyses primary data (P); Presents /analyses secondary data (S)
Country /countries in focus	Open-ended categories (inductively derived)
Medicines /vaccines studied	Open-ended categories (inductively derived)
Type of situation	Normal situations vs extreme situations
Causes of shortages	Does not discuss /analyse shortages (N); Discusses causes (D); analyses primary data on causes (P); analyses secondary data (S) Number of causes (low, medium, high) Systematic root-cause analysis (yes /no) Linear cause analysis vs. causal loop analysis
Effects of shortages	Effects on patients: does not discuss /analyse (N); simply discusses (D); analyses primary data (P); analyses secondary data (S) Economic /financial effects: does not discuss /analyse (N); simply discusses (D); analyses primary data (P); analyses secondary data (S)
Interventions to tackle shortages	Medical interventions: does not discuss /analyse (N); simply discusses (D); analyses primary data (P); analyses secondary data (S)

	Supply chain interventions: does not discuss /analyse (N); simply discusses (D); analyses primary data (P); analyses secondary data (S) Market interventions: does not discuss /analyse (N); simply discusses (D); analyses primary data (P); analyses secondary data (S)
Impact of interventions	Evidence on impact of intervention: empirical; modelling; both; None (if the study does not provide evidence of impact) Reactive interventions; proactive interventions; both; None (if no impact evidence provided) One intervention vs. multiple interventions; None (if no impact evidence provided) Research method (if empirical evidence provided): open-ended categories, derived inductively Impact metric used (if impact evidence provided): open-ended categories, derived inductively Optimisation /scenario analysis (if impact evidence provided): yes /no
Reference to OSCM studies	Uses concepts /approaches from OSCM literature: yes /no

Three of the authors were involved in reading, evaluating, and classifying the set of 83 articles we included in our detailed review. To ensure high level of interrater reliability, we initially identified a common subset of 13 articles (15% of the total number of studies) that each author assessed independently. The three authors then met to compare and discuss their respective classifications and coding. This step resulted in an interrater agreement of 91% - out of 260 classification fields in total (20 fields x13 articles), there were 24 disagreements in our coding. We discussed all disagreements to identify possible sources of misinterpretation regarding the definition and application of the classification schemes. All disagreements were subsequently adjudicated.

Based on such discussions and given the high rate of inter-coder reliability, we decided to divide the remaining 70 articles equally between the three authors. During this last step of our detailed reading and coding, we decide to exclude a further four articles from our final sample (n=79). These articles were excluded because they only superficially referred to shortages and focused on other topics e.g. clinical research on doses of critical ingredients to be included in a vaccine. The list below presents the OSCM-oriented papers focusing on drug shortages, as a sample of the articles we coded. The full list of the 79 articles we coded and the accompanying master file including our coding of each article are available upon request.

List of OSCM-oriented articles on drug shortages

Azghandi, R., Griffin, J. and Jalali, M. S. (2018), "Minimization of drug shortages in pharmaceutical supply chains: A simulation-based analysis of drug recall patterns and inventory policies*", Complexity*, doi.org/10.1155/2018/6348413.

Chang, J., Lu, H. and Shi, J. (2019), "Stock out risk of production-inventory systems with compound Poisson demands, *Omega*, Vol. 83, pp. 181-198.

Dai, T., Cho, S-H. and Zhang, F. (2016), "Contracting for on-time delivery in the US influenza vaccine supply chain", *Manufacturing & Service Operations Management*, Vol. 18 No. 3, pp. 332–346.

Jia, J., and Zhao, H. (2017), “Mitigating the U.S. drug shortages with Pareto-improving contracts”, *Production and Operations Management*, Vol. 26 No. 8, pp.1463–1480.

Kochan, C. G., Nowicki, D. R., Sauser, B., and Randall, W. S. (2018), “Impact of cloud-based information sharing on hospital supply chain performance: A system dynamics framework”, *International Journal of Production Economics*, Vol. 195, pp. 168185.

Liao, H. C., Chen, Y. K., and Wang, Y. H. (2015), “The study of an optimal robust design and adjustable ordering strategies in the HSCM”, *Computational and Mathematical Methods in Medicine*, /doi.org/10.1155/2015/517245.

Lu, H., and Shi, J. J. (2019), “Stockout risk of production-inventory systems with compound Poisson demands”, *Omega*, Vol. 83, pp. 181-198.

Shiau, J. Y. 2019. A drug association based inventory control system for ambulatory care. *Journal of Information and Optimization Sciences*, 40(6), 1351-1365.

Tucker, E. L., Daskin, M. S., Sweet, B. V. and Hopp, W. J. (2020), “Incentivizing resilient supply chain design to prevent drug shortages: policy analysis using two-and multi-stage stochastic programs”, *IISE Transactions*, Vol. 52 No. 4, pp. 394-412.

Zadeh, N. K., Sepehri, M. M. and Farvaresh, H. (2014), “Intelligent sales prediction for pharmaceutical distribution companies: A data mining based approach”, *Mathematical Problems in Engineering*, doi.org/10.1155/2014/420310.