Pharmaceutical pollution from healthcare: a systems-based strategy for mitigating risks to public and environmental health

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Summary

Human pharmaceuticals are increasingly being detected in environments around the world, with growing international calls to mitigate the ecological and human health risks posed by these novel entities. Exposure to pharmaceutical pollutants can negatively affect the behaviour, reproduction and health of wildlife, contributing towards declining ecological health and global biodiversity loss. Pharmaceuticals in the environment are also driving rising levels of antimicrobial resistance, a major public health threat. Developing strategies to mitigate these public and environmental health risks has been greatly limited by diverse and often conflicting stakeholder interests and the need to retain the major human health and socioeconomic benefits that pharmaceuticals provide. Here, we propose a multi-stakeholder, systems-based approach for high-income countries to develop transformational national mitigation strategies. Applying this to a UK case study highlighted the growing risks caused by the unsustainability of the current UK healthcare pharmaceutical system and enabled us to identify 37 synergistic intervention points that target both the tangible "easy wins" and the deep-rooted social drivers of the issue. We believe our approach will support high-income countries to minimise the public and environmental health risks associated with pharmaceutical pollution by driving long-term sustainability across the pharmaceutical life cycle, for a positive pharmaceutical future.

Introduction

Pharmaceuticals underpin modern healthcare systems and provide major socioeconomic benefits to societies around the world. In 2022 the pharmaceutical industry contributed a total GDP of USD 2·295 trillion and supported approximately 74·9 million jobs worldwide.[1] Pharmaceutical usage in humans has been rising for many years, driven by ageing populations, the growing incidence of chronic diseases, improving access to medicines, increasing spending on healthcare, the expansion of pharmaceutical manufacturing capacity and the "medicalisation" of society.[2,3] By 2028, the annual global use of pharmaceuticals in human healthcare is predicted to reach 3·778 trillion defined daily doses,[4] with an associated market value of USD 2·3 trillion.[2]

Expanding pharmaceutical production and usage is increasingly being associated with public and ecological health concerns over environmental contamination with active pharmaceutical ingredients (APIs; the biologically active compounds within pharmaceutical products).[5–7] Exposure to pharmaceuticals in the environment can influence the long-term survival, fitness and dynamics of organisms within an ecosystem, contributing to biodiversity loss.[7] For example, oestrogenic compounds including pharmaceuticals from the contraceptive pill and hormone replacement therapies (HRT) can alter fish reproduction,[8] and antidepressant pharmaceuticals can alter fish behaviour, making them less risk-averse and more susceptible to predation.[9,10] Pharmaceutical contamination also has food chain impacts, as tragically illustrated by the almost complete loss of three South Asian *Gyps* vulture populations following the introduction of diclofenac usage in cattle, whose carcasses were subsequently fed upon by the vultures. The loss of the vulture populations in turn had wider negative impacts on local populations, for example in India it led to an estimated 104,386 annual deaths in the following 5-year period, with estimated damages of USD 69.4 billion per year.[11,12]

Antimicrobials and other APIs in the environment also pose a threat to public health through driving environmental selection for antimicrobial resistance (AMR), a major global public health threat and predicted to be one of the leading causes of human deaths worldwide by 2050.[13,14] Humans can be

directly exposed to API pollutants through drinking water[7], ingestion of crops grown in contaminated soils[15] and bathing.[5,16] Where measured, levels of human exposure have mostly been found to be below safe therapeutic dosages, although the long-term public health risks of chronic low-dose exposure remain unclear and underexplored.[7,15] Any risks are likely to be greater in low- and middle-income countries (LMICs) where pharmaceutical pollution levels are reportedly greater[5] and there is typically weaker wastewater management and environmental regulation, fewer policies and infrastructure for safe disposal of pharmaceuticals,[17] and poorer access to sanitation infrastructure.[7]

Most countries do not routinely monitor environmental API levels and where there is such monitoring this is limited to very few pharmaceuticals. Therefore, the scale, distribution and levels of human or wildlife exposure to API pollution remain not well understood. However, research studies are increasingly evidencing extensive contamination of global waterways with pharmaceutical compounds. A 2022 study of 1052 sampling sites across 258 global rivers found that more than a quarter of sites had at least one API at concentrations considered either not safe for aquatic organisms or of risk in terms of driving antimicrobial resistance (AMR).[5] API pollutants are often present in the wastewater effluents from households, manufacturing facilities, hospitals, agriculture and aquaculture, and in some cases leading to very high API concentrations in local environments.[6,7,18,19] In general, API pollutants are found at lower environmental concentrations than other chemical pollutants, however low environmental concentrations do not necessarily equate to lower ecological risk. APIs are designed to be biologically active at very low concentrations, cross biological membranes and be resistant to metabolic breakdown in order to maximise efficacy and reduce side effects in the human body.[7] Human API target sites are also often evolutionarily highly conserved and thus can be active in non-target environmental species.[20] Furthermore, some APIs and their metabolites (products from human metabolism) and/or transformation products (where the parent compound or metabolite has been altered through wastewater treatment) can persist and accumulate in the environment.

A number of international initiatives have now called for action in mitigating the risks that pharmaceutical pollution poses to public and ecological health. This includes the United Nations Environment Programme's Global Chemicals Framework,[21] the International Panel on Chemical Pollution (IPCP),[22] the Intergovernmental Science-Policy Panel (SPP) on Chemicals, Waste, and Pollution Prevention,[23] the Global Leaders Group on Antimicrobial Resistance,[24] the World Health Organisation's (WHO) "Greener Pharmaceuticals' Regulatory Highway"[25] and "Guidance on wastewater and solid waste management for manufacturing of antibiotics",[26] the European Commission's Pharmaceutical Strategy for Europe,[27] and the revised European Urban Wastewater Directive.[28] However, developing mitigation strategies is challenging. The potential ecological and public health risks of pharmaceutical pollution were raised more than 25 years ago, with very little progress made since then.[19,29,30] The issue of pharmaceutical pollution is multifaceted, dynamic and uncertain in nature, with a complex range of interconnected social, economic and environmental drivers. For example, barriers to change have included the need to balance diverging conflicting values and interests across a very broad stakeholder group, the need to find solutions that do not jeopardise the major human health and socioeconomic benefits that pharmaceuticals provide, and the need to overcome huge persistent knowledge gaps surrounding the ecological, health and societal risks and impacts of many pharmaceutical pollutants.[31] Action is further complicated by the fact that the aquatic environment acts as a sink for chemical pollutants from multiple sources, making it difficult to both predict the risk of these mixtures and attribute any impacts to specific causative agents.[32,33] As such, pharmaceutical pollution is an archetypal complex sustainability challenge (also known as a "wicked problem").[34,35] Such challenges are notoriously difficult to address.

Research examining the shortcomings of mitigation strategies for other complex sustainability challenges has suggested that there has been too much focus on short-term technological or behavioural intervention points (so-called "easy wins" or "quick fixes") that have the least propensity for driving large-

scale change. Although these more tangible interventions can help alleviate acute problems and may help pave the way for longer-term change, they typically fail to address the underlying societal drivers and equity-dimensions of environmental fallouts, with the greatest risks of unsustainability often felt by societies' most vulnerable.[36–39] Indeed, studies have shown that poorer disenfranchised communities often bear the greatest burden of risks and impacts from multigenerational chemical and pharmaceutical pollution.[40–42] Thus, strategies seeking to develop long-term sustainable and equitable pharmaceutical pollution mitigation will require greater attention to be paid to the deep-rooted social, economic, policy and regulatory drivers and inequities associated with pharmaceutical usage,[36–39] and should include measures to ensure social justice for past and present pollution fallouts.[43] In line with this, a number of studies examining the issue of pharmaceutical pollution have now called for a systems approach to developing risk mitigation strategies.[44–48]

Systems thinking is a holistic method used for understanding complex issues at multiple societal depths, with a focus on how the system's constituent parts interact and behave as a whole.[49] It is increasingly being applied to complex sustainability issues to create a common language and framework between disciplines and sectors, as well as to identify shared values and priorities for promoting collective and systemic action.[34,39,50,51] In this study, our aim was to use systems thinking methodologies to develop a collective, multi-stakeholder approach for high-income countries (HICs) to create pragmatic strategies to mitigate the public and ecological health risks of pharmaceutical pollution. Herein, we first describe our proposed 7-step approach and then present the outputs of applying the first 4 steps to a case study of the United Kingdom (UK). Our results demonstrate the unsustainability and inequity of the current UK healthcare pharmaceutical system and identify 37 synergistic intervention points that target the "quick fixes" alongside the deep-rooted societal drivers of the system. We believe this work constitutes a foundation for a transformational UK national action plan in which mitigating the risks of pharmaceutical pollution does not detract from and may even enhance the long-term socioeconomic benefits of pharmaceutical supply and use. Our approach also provides a template for other HICs to create similar national strategies that seek long-term, systemic change for a sustainable pharmaceutical future.

Methodological approach

Our overarching approach is presented in **Figure 1**. We use "pharmaceutical system" as a broad term to encompass the societal organisations, processes and factors that shape decisions, impacts and actions across the entire pharmaceutical life cycle. Our approach is based upon the hypothesis that the growing public and ecological risks of pharmaceutical pollution are a consequence of unsustainable complex pharmaceutical systems. The United Nations defines sustainability as "meeting the needs of the present generation without compromising the ability of future generations to meet their own needs"[52] and proposes that there are three interdependent dimensions to this: social, economic and environmental sustainability. Therefore, we surmise that the aim of transformational risk mitigation strategies should be to support the societal evolution of pharmaceutical systems towards long-term social, economic and environmental sustainability.

Central to our approach is working extensively with stakeholders to understand the pharmaceutical system from both a macro (whole system) and micro (individual organisational) level. Strategies targeting system-level change are often criticised for being too abstract, lacking real-world application, and adopting a flawed one-size-fits-all approach. In response, organisations such as the WHO are starting to interlayer governance strategies combining a top-down, systems perspective, with a bottom-up, people-centred and equity-aware perspective grounded in participatory stakeholder design.[35,53–56] Our approach aligns with this by working with stakeholders from across the pharmaceutical life cycle to collectively understand the current situation (step 1), agree on a common goal (step 2) and identify a tangible route to

achieving that goal (steps 3-7). In this study, we applied steps 1-4 to the UK healthcare pharmaceutical system as a specific HIC context.

Scope of the study

The scope for our analyses was defined as encompassing all processes and factors that influence or contribute to the supply, use and waste management of APIs (here referred to as "pharmaceuticals") used in UK healthcare across their entire life cycle.[47] We considered "pharmaceuticals used in human healthcare" to be compounds used primarily to diagnose, prevent, treat or cure human disease; this included both small molecule pharmaceuticals (low molecular weight, chemically-synthesised compounds) and biologics (large, complex molecules derived from living organisms). We did not include personal care products. We took "The environment" to include air, water and soil environments.

Our study did not consider pharmaceuticals used in animal healthcare since although animal use of pharmaceuticals significantly contributes towards the environmental load of pharmaceutical pollution, it is widely believed that urban wastewater is the primary source of total pharmaceuticals entering the environment.[6,57] Of the pharmaceuticals detected in global waterways, those most regularly reported have also been associated with human use.[5,7] Human pharmaceuticals enter urban wastewater through a number of routes, notably from households, healthcare and manufacturing facilities. Up to 90% of orally-administered pharmaceuticals are excreted by patients either as the parent compounds or in a metabolised form.[58] Unused or expired pharmaceuticals are also regularly inappropriately disposed into urban wastewater systems across many countries.[6,57] Further, from a systems perspective, we believe the societal structures and the upstream drivers influencing pharmaceutical use in animal health are sufficiently distinct to warrant a separate analysis.

Our study is focused on HICs as these countries have historically dominated international pharmaceutical trading, income generation, and pharmaceutical usage.[59] In 2023, Western Europe and Japan had per capita pharmaceutical use volumes that were greater than all other global regions and more than double most.[2] HICs generally have well-established healthcare pharmaceutical systems and good access to medicines. Although many HICs also have established manufacturing capacity, the past four decades have seen HICs outsource the manufacturing of APIs to emerging economies. This is reportedly due to the substantial cost differentials and lenient environmental regulations which create a favourable environment for scaling up production and enhancing efficiency in these markets.[4] Thus, HIC pharmaceutical markets have global supply chains, with considerable environmental impacts. However, increasing issues with international pharmaceutical supply chain vulnerability in recent years have raised national security concerns in a number of HICs, leading to increased calls to "reshore" the manufacture of critical pharmaceuticals.[60,61]

Case study: the UK healthcare pharmaceutical system

Like most HICs, the UK population is ageing and suffering from more chronic diseases. A study in 2024 estimated that 14·8% of people in England were living with two or more health conditions (8·88 million people), rising to 68·2% of those aged 80 years and over.[62] Social deprivation is strongly linked with poorer health outcomes, with an estimated 19-year difference in life expectancy between the most deprived and least deprived areas of the UK.[63] In line with other European HICs, the UK has universal healthcare (i.e. free at the point of access) provided through its National Health Service (NHS), and has levels of pharmaceutical research and development expenditure, employment, pharmaceutical production and international trade that have been rising for many years (**Supplementary Table 1; page 2,**

Supplementary Information). As a large, centralised procurement body the NHS also has an unusual degree of collective bargaining power and influence over pharmaceutical pricing, with below-average spending per head compared to other HICs.[64]

In 2022 the NHS became the first healthcare system globally to embed into legislation a target of net zero carbon emissions by 2045.[65] Each of the four devolved UK nations (England, Scotland, Wales and Northern Ireland) are now working to reduce the greenhouse gas emissions of pharmaceuticals throughout healthcare pathways since pharmaceuticals account for 25% of the NHS's annual carbon footprint.[65] Pharmaceutical pollution is mentioned in the sustainability strategy of NHS Scotland[66] but is not part of the NHS strategies of the other three devolved nations.

Stakeholder engagement

We established a transdisciplinary consortium of 48 stakeholders from across the UK pharmaceutical life cycle, including representatives from across the healthcare sector (decision-making, pharmacy, practitioner and public health), academia (biomedicine/health, environmental and social sciences) , industry (pharmaceutical and water), advocacy (environment and sustainable healthcare), policy (environmental and healthcare), finance and the media (**Supplementary Figure 1; page 3, Supplementary Information**). Stakeholder selection across the above-mentioned sectors was based on the snowball method: a core group of initial experts including those who had been involved in our preliminary mapping of the UK healthcare pharmaceutical system[47] identified key stakeholder representatives. Selection was based on expertise and relevant publications regarding the use, management, and treatment of pharmaceutical waste across the UK health systems sectors as well as regarding societal impacts and perceptions of pollution. While our aim was to ensure as diverse and inclusive representation as possible, we were constrained by the need to keep the group size manageable within our resource capacity. The research project's focus on and location in the UK meant that the vast majority (45/48) of consortium members were UK-based (although many work with global partners) with additional European experts invited to reflect on the international dimensions of integrated pharmaceutical supply chains and pollution burdens. Many stakeholders had expertise/experience that spanned multiple sectors and disciplines. Where certain stakeholder groups (e.g. some UK Government departments/agencies) did not accept the invitation to participate, we ensured that we had representation from academics and/or other stakeholder groups that work closely with them and are familiar with their perspectives relating to pharmaceutical pollution.

Within the consortium, we created five interconnected working groups (WGs) that broadly correlated with distinct sectors and stakeholder groups as identified through our preliminary systems mapping work.[47] These covered the topics of: *population health* (WG1); *design, manufacture and licensing* (WG2); *reimbursement, procurement and prescribing* (WG3); *distribution, sales, use and disposal* (WG4); and *environmental monitoring and management* (WG5). Consortium members participated in as many WGs as they wished.

Micro and macro analyses

Our micro analysis comprehensively mapped and detailed the operational and regulatory processes for a typical UK healthcare pharmaceutical product across the entire life cycle, with a focus on those that influence the creation or mitigation of pharmaceutical pollution (step 1, **Figure 1**). Overall, this process helped to create a common language within the consortium by enabling stakeholders to gain a holistic

understanding of the system within areas distant from their own work, and to better understand the activities, needs and constraints of others.

Our macro analysis generated a collective "big picture" perspective across the breadth and depth of the system (step 3). To facilitate this analysis, we adapted a systems thinking tool called the Iceberg Model (**Figure 2A**).[67–69] Based on our previous work and in line with the multi-level perspective framework,[47,48] we identified three distinct depths of the UK healthcare pharmaceutical system that we believed stakeholders could relate to: *structures* (analogous to the micro analysis), *goals*, and *culture* (**Figure 2A**). Each WG used the Iceberg model as a discursive tool for collectively discussing and agreeing on a situational summary at each layer of the iceberg.

Using the information gathered through the micro and macro analyses, the WGs collectively identified leverage points where interventions could be targeted for enabling transformational change (step 4). When considering leverage points, members were asked to focus on those over which UK societal stakeholders have agency, since our aim was to support the development of national mitigation strategies.

An iterative process

Although **Figure 1** depicts an incremental process for the purposes of methodological clarity, in practice the development of outputs for steps 1-4 was an iterative process that took place between October 2023 and December 2024. Through both informal interviews with individual consortium members as well as extensive white and grey literature searching, reports were created for the remit of each WG. These contained: i) maps and descriptions of processes across the UK healthcare pharmaceutical life cycle (micro analysis); and ii) a list of initial leverage points with proposed needs and enablers. WG members provided extensive written input into these reports and then attended online WG workshops to consider the situation and challenges/opportunities for their remit (macro analysis), discuss the draft leverage points and identify any others that had emerged following the macro analysis. Feedback from each WG was then consolidated into the figures and supplementary tables of this manuscript, and further consortium feedback (written and verbal) was integrated to produce the final outputs. In cases where stakeholders had differing interpretations of the situation, this was discussed in more detail and the perspective of the majority was put forward but with alternative viewpoints presented in the more detailed supplementary information.

Case study: the UK healthcare pharmaceutical system

Describing the current system (step 1)

Our micro analysis (summarised in **Figure 3** and described in detail in **Supplementary Table 2; pages 4-18, Supplementary Information**) illustrates the complexity and interconnectivity of the processes across the life cycle of a typical UK healthcare pharmaceutical product. We identified many routes through which pharmaceuticals used in UK healthcare enter the environment across their life cycle (**Figure 4**), although the relative contributions of each source are not clearly understood. Overall, this micro perspective highlights the ever-increasing supply and use of pharmaceuticals in UK healthcare, but also shows that the environmental costs associated with pharmaceutical pollution are currently being externalised and poorly mitigated across the life cycle. As such, we suggest that the existing UK healthcare pharmaceutical system is not environmentally sustainable. This builds upon broader planetary health concerns over the substantial greenhouse gas emission and freshwater usage footprints of UK pharmaceutical usage.[70–72]

Defining the environmental costs and risks of pharmaceutical pollution from UK healthcare is challenging for a number of reasons, a major one being the very limited availability of data on the ecotoxicological risks posed by pharmaceutical pollution exposure to wildlife. A 2018 report estimated that 89% of the 1,912 pharmaceuticals registered for use in UK healthcare did not have available environmental risk data.[73] Of the compounds with available environmental risk data, there are currently (April 2025) twenty which are of sufficient ecological concern to be considered for future UK and EU environmental monitoring lists.[74,75] All of these products are used in UK healthcare. (**Supplementary Table 3; page 19, Supplementary Information**).

Establishing a common goal (step 2)

Our micro analysis highlights important overlaps between the three dimensions of sustainability (social, economic and environmental, **Figure 1**) across the existing UK pharmaceutical system. At both a domestic and global level, poor or marginalised communities who already have reduced access to the healthcare and economic benefits of pharmaceuticals are often disproportionately exposed to negative environmental impacts resulting from pharmaceutical pollution. For example, LMIC populations are typically exposed to higher pharmaceutical pollution levels and greater impacts of AMR.[5,76] Domestically, rising pharmaceutical costs coupled with severely strained NHS budgets pose substantial financial risks to the healthcare sector and are exacerbating the inequalities associated with pharmaceutical and healthcare access. Meanwhile, growing customer, investor and regulator demand for environmental sustainability is providing long-term financial, compliance and reputational corporate risks to the global pharmaceutical sector. These challenges are all being exacerbated by climate change and the loss of biodiversity, which are depleting raw material availability and increasing supply chain volatility.[2,77]

Across our Consortium, there was widespread consensus that the target goal for the UK healthcare pharmaceutical system should be long-term social, economic and environmental sustainability (**Figure 1**). Thus, strategies seeking to mitigate the public and environmental health risks of pharmaceutical pollution from UK healthcare should be aiming for social and economic sustainability as well as mitigating environmental risk.

Understanding challenges and opportunities (step 3)

Our macro analysis (presented in **Table 1**) highlighted some consistencies across the WGs. At the upper *Structures* layer, it was recognised that many operational and regulatory processes to support change in terms of pharmaceutical pollution mitigation were already in place across the system, although this varied between WGs. Where processes already existed, implementation was identified as a major barrier to change, but there were different implementation challenges for different WGs. For example, in WG1 and 5, whose remit was predominantly the public sector (population health and environmental monitoring and management, respectively) the major implementation challenge raised was poor inter- and intra-sectoral collaboration, whereas for WG2 (pharmaceutical design, manufacture and licensing) the implementation challenges listed were the lack of economic/regulatory incentives and physical capacity (for generic manufacturers).

In the middle *Goals* layer there was recognition of the intention to take action but weak governance was a common narrative, either via inadequate policies (WG4), regulations (WG5) and/or the implementation (WG1) of these. Across WG 2, 3 and 4 (which represent the pharmaceutical and healthcare sectors) the consistent prioritisation of acute clinical need and neglect of long-term environmental considerations in favour of short-term economic ones was a major barrier noted. For all WGs, the *Culture* (deepest) layer

summaries highlighted the inherent connectivity of the issue of pharmaceutical pollution with well-established societal sustainability and equity challenges. These included the ongoing medicalisation of care provision,[3,78] the prioritisation of short-term (predominantly health and economic) gains over long-term environmental risks, and the ever-growing challenges of managing a shared resource or limiting a public good (**Table 1**).

Identifying leverage points for transformational change (step 4)

Through an iterative and co-productive engagement process, each WG identified potential leverage points for change at different layers of the Adapted Iceberg Model (**Figure 2A**). These were consolidated into 37 leverage points and grouped according to whether they were focused on *Optimising pharmaceutical supply, use and waste management structures*; *Reforming economic and health sector goals;* or *Evolving societal culture* (corresponding with different depths of the Iceberg Model). The leverage points are outlined in **Table 2** and described further in **Supplementary Table 4; pages 20-35, Supplementary Information**).

WG discussions highlighted the interlinkages and synergies between the leverage points, with each leverage point identified within a WG having needs and enablers that spanned the remit of other WGs. Some leverage points were raised by multiple WGs (e.g. "Better patient pharmaceutical management" came up in WG1, WG3 and WG4 discussions). In contrast, other leverage points initially appeared to be specific to individual WGs but deeper inquiry into the needs and enablers evidenced the need for cross-sectoral collaboration. For example, responsibility for "Greener pharmaceutical design" initially appeared to be within the WG2 remit but further discussions on how to implement this identified the need for pharmaceutical companies to be incentivised through healthcare procurement (WG3 remit) and environmental policies (WG5 remit).

Across all WGs, and particularly when discussing leverage points for the deepest *Culture* layers of the Iceberg Model, there were common themes of needs and enablers that emerged repeatedly. These were grouped into the *Evolve societal culture* category of leverage points. For example, this included raising societal awareness of the issue of pharmaceutical pollution, addressing social and environmental injustice, and improving our knowledge base of the health, socioeconomic and environmental impacts of pharmaceutical pollution. Many of the leverage points at this level were not necessarily UK-specific, highlighting the global nature of identified challenges and demonstrating that leveraging maximal impact will require international collaboration.

According to the Iceberg Model, deeper intervention points have more leverage for transformational change (**Figure 2B**). Therefore, interventions aiming to *Evolve societal culture* would be expected to have the greatest leverage in reducing pharmaceutical pollution from UK healthcare, followed by those targeted at *Reforming economic and health sector goals*, with those aimed at *Optimising pharmaceutical supply, use and waste management structures* having the weakest leverage.

Taking this forward (steps 5-7)

The leverage points identified in **Table 2** represent points within the UK healthcare pharmaceutical system whereby interventions can be targeted to drive change, however the requirements for each one vary considerably in terms of the number of stakeholder groups involved, their location (e.g. some will require more international collaboration than others), cost, timescales, accessibility, acceptability, feasibility, appropriateness and measurability of the interventions required, as well as progress to date (with some leverage points already receiving much attention). In addition to differing requirements, each

leverage point varies in the scale and speed of potential impacts. Key aspects of an action plan (step 5, **Figure 1**) will therefore be to work with the relevant stakeholders to identify short-, medium- and long-term priorities with accompanying tangible targets, in some cases using vector-based targets that aim to incrementally move the system in the direction of an aspirational state rather than setting unfeasible end goals, to allow for adaptation and flexibility.[79] Measuring progress towards these targets will be essential, and this will also require the identification of appropriate qualitative metrics, recognising that not everything that counts can be counted.[80] For example, context, depth and meaning could be added to quantitative indicators (such as reduced API loads) by linking them with qualitative case studies, narratives and rankings (such as optical river assessments via CrowdWater).[81] Following WHO's people-centred approach for AMR,[56] one way of doing so will be to devise regular civil society fora in which regulators, industry, environmental groups, patient advocates, and other civil society actors come together to discuss and reassess targets, feasibility, and prioritisation in view of community feedback.

With the multitude of competing needs and interests across the system, independent facilitation and oversight to co-ordinate implementation (step 6) will be vital for success. This is a system-wide, long-term challenge with strong and deeply-embedded market forces. Therefore, transformative change will be difficult without effective public-policy-practice dialogue across disciplines, sectors and nations, as well as robust governance to define clear roles and responsibilities, ensure compliance with regulatory standards and ethical guidance, and provide transparency and accountability. Core to the success of this will be the use of multiple policy approaches[55] and the interlayering of pollution strategies with other related national action programmes (e.g. AMR, biodiversity targets). Finally, given the dynamic nature of the system, with rapidly evolving regulatory, financial and social incentives for change as public and policy maker awareness and attention on this topic grows, strategies and implementation efforts will need to be flexible and adapt to new information, changing environments and/or market forces (step 7).

How could this approach drive system transformation?

Our UK case study analysis suggests that the technological, institutional and social infrastructures of pharmaceutical supply, use and waste management are entrenched in modern HIC societies in a way that shows some parallels with the "locked-in" theory of our fossil fuel dependence.[82] These are complex adaptive systems that have evolved over centuries and are inherently resilient to rapid change. However, this does not mean that change is impossible. Studies on social system transformation have shown that this process typically features non-linear periods of slow, incremental (evolutionary) change punctuated by infrequent sudden shifts that are catalysed by expected or unexpected events,[83] for example technological innovation, environmental disasters, war, major policy changes, financial market instability or high-profile media affairs.[39] We believe that by targeting action across the breadth and depth of the system, our approach can encourage transformative change by creating systemic conditions that favour and support collective evolution towards greater sustainability, such that it is receptive to positive catalytic events and resilient against negative ones.

Expanding the scope of responsibility and risk

How a problem is framed is key to defining the cause of the problem (who/what is responsible), and the consequences (who/what is impacted).[84] Our UK analysis shows that the stakeholders who are currently allocated responsibility through existing reports and initiatives are those who can directly influence pharmaceutical waste management and environmental fate, for example stakeholders working in pharmaceutical design and manufacture, dispensing, wastewater treatment and environmental regulation (see **Supplementary Table 2; pages 4-18, Supplementary Information**). Expanding the

framing of the issue from a "waste management and environmental fate" problem to a broader "unsustainable system" suggests that the interdependent risks and responsibilities instead lie across the wider publics, industries and governments who have long welcomed the pursuit of scientific innovation to develop new and improved pharmaceuticals, to trade them on international markets for financial gain, and to make them as accessible as possible for human health gain. This is a much broader scope than existing strategies.

Overcoming risk at the individual level

Research into transformational strategies for change has suggested the need for top-down approaches (for example the overarching global strategies aimed at improving manufacturing emissions[26] healthcare wastage[85] and wastewater treatment[28]) to be coupled with local knowledge co-production in order to understand the individual risks, interdependencies, feedback loops and emergent behaviours that exist and vary widely between organisations within complex systems.[53] Our analyses highlight the challenges faced by organisations seeking to take action at the individual level, who often face considerable time, money or resource trade-offs, thus limiting their ability and/or desire to act. For example, the requirement for more staff time and resources are common considerations cited by general practitioners when choosing social prescriptions over pharmaceutical prescriptions,[86] whereas pharmaceuticals can be quick to prescribe and are generally highly cost-effective in terms of healthcare spending.[87] Further, poor coherence between sectors across the system makes it difficult for individual stakeholder groups or sectors to plan, justify and take action, since the their actions are often interdependent upon an array of needs and enablers (e.g. the need for data, resources, social acceptance, tighter regulation, better infrastructure) that are under the control of stakeholders in another part of the system. Our approach aims to encourage positive systematic change by fostering cross-sectoral collaboration and synergistic action at a multitude of leverage points such that the risks and resources required by individual organisations are reduced (and benefits bolstered) across the system.

Identifying win-win opportunities

Our UK case study shows that taking a systems perspective enables the identification of upstream leverage points that offer mutually-beneficial ("win-win") opportunities. These could prevent or reduce the severity of downstream risks associated with pollution whilst optimising the use of limited resources for maximal, long-term progress towards sustainability. For example, strategies focused on health creation and disease prevention (leverage points 25 and 27, **Table 2 and Supplementary Table 4; pages 20-35, Supplementary Information**) are designed to improve long-term human health and socioeconomic benefits to society (e.g. greater quality of life, economic productivity) but could also help to reduce our societal reliance on pharmaceuticals and encourage a reduction in pharmaceutical demand/use. Similarly, developing outcomes-based business models (leverage point 22) and incorporating pharmaceutical pollution targets into sustainable finance incentives within the corporate sector (leverage point 24) could create win-win opportunities by providing a financially-rewarding route for companies who invest in more environmentally sustainable practices.

Conversely, a systems perspective could also help to avoid unintended consequences of well-intentioned solutions which were designed with a narrow problem scope but can have broader negative consequences, as seen in carbon mitigation strategies,[88] one-size-fits-all AMR interventions,[43] or "regrettable substitutions" of hazardous chemicals,[89] where changing practices to mitigate one risk worsened another. In healthcare, the creation of new categories of long-term illness or new cut off points for more established conditions (for example the expansion of the definition of "pre-diabetes")[90] could

play a role in increasing pharmaceutical usage and, in turn, pharmaceutical pollution. Another ongoing example is the shift from gaseous to intravenous general anaesthesia; this has benefits in reducing the greenhouse gas footprint of UK healthcare but there are concerns that it may instead incur broader environmental risks (e.g. greater ecotoxicological risk from increased patient excretion into wastewater).[91]

Potential limitations of our approach

Many of our 48 stakeholder representatives were individuals already actively engaged in pharmaceutical/healthcare sustainability or environmental pollution and may have supported a more positive and optimistic view of opportunities for change. Future steps to transcribe these leverage points into a pragmatic UK national action plan (step 5, **Figure 1**) will therefore need to ensure more inclusive representation. They will also need to consider how to effectively manage the substantial power and political dynamics of this issue, since co-production processes with biases towards more powerful/influential stakeholders have been shown to reproduce or even exacerbate existing inequalities and may jeopardise efforts for system transformation.[53,92] Creating and maintaining such stakeholder collectives is not straightforward. Success depends on transcending academia and traditional knowledge deficit communication as well as addressing power asymmetries and special interests involved in policy formulation.[92] It also entails avoiding disciplinary silos and making policy agendas relevant across multiple domains. These challenges also impacted our own research consortium, for example we faced challenges in engaging some stakeholder groups, particularly those for whom pharmaceutical pollution is not considered to be within their direct remit. Moving forward, the creation and adequate resourcing of a central independent facilitator can be useful to support inclusive, open and fair dialogue between stakeholders, as shown in studies considering how to address AMR as a "super-wicked problem". However, such impartial, pan-sectoral institutions remain rare.[54] In the UK, we have recently established the Pharma Pollution Hub (www.pharmapollution.org) as a new national think tank and charitable organisation aiming to fill such a gap.

Our systems analysis did not include pharmaceuticals used in agriculture, however there are likely to be overlaps in the leverage points between these systems, particularly at the deep-rooted *Evolve societal culture* depth (see **Table 2**). Therefore, the development and implementation of an equivalent strategy for agricultural and domestic veterinary pharmaceutical use would be mutually-beneficial. Our analyses also did not meaningfully consider international pharmaceutical supply and distribution chains, which are intrinsically linked to the UK system but largely outside its regulatory jurisdiction. This is a major limitation to our approach, which uses a defined system scope and boundaries for a challenge whose accountability and impact in reality has no natural geographic or economic borders. The UK is a relatively small pharmaceutical market within the global economy and although UK stakeholders have some agency over the leverage points identified, driving long-term, sustainable action across the UK system will only be possible through meaningful and equitable international collaboration across the global network of national pharmaceutical systems.

Conclusion

Internationally, there is growing recognition and desire for action to reduce pharmaceutical pollution across the public and private sectors, but the challenge lies in how to generate meaningful real-world transformational change. Our UK case study highlights the complexity, resilience and unsustainability of the current UK healthcare pharmaceutical system, and therefore the need for systems-based mitigation

strategies. We believe that this approach could be applied and linked to the development of similar strategies in other HICs which likely face similar macro challenges but may vary in their micro situations. Overall, it provides a template to support stakeholders from across the pharmaceutical life cycle to collectively participate in the Great Transition[93] towards a society that lives within its planetary boundaries.

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Contributions

Kelly Thornber conceptualised the project, acquired funding, designed and facilitated all workshops, led the acquisition, analysis and interpretation of data collected, and co-wrote the draft manuscript. Matthew Bentham and George Kirkham supported the acquisition of data. Charles Tyler conceptualised the project, analysed and interpreted the data, acquired funding and co-wrote the draft manuscript. All authors contributed towards the acquisition, analysis and interpretation of data collected for the UK case study and the refinement of our overall approach. All authors reviewed and edited the manuscript.

Declaration of interests

Stewart Owen is a shareholder and employee of AstraZeneca UK Ltd.

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