

A review of scientific and grey literature on medicine shortages and the need for a research agenda in Operations and Supply Chain Management

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A review of scientific and grey literature on medicine shortages and the need for a research agenda in Operations and Supply Chain Management

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Abstract. High-income countries are facing a significant and worsening drug shortage problem. This position paper argues that operations and supply chain management (OSCM) could (and perhaps should) be used more widely to help address this issue: 1) the problem has significant societal impacts, 2) it poses complex questions for stakeholders and finding answers is challenging due to the complex and dynamic nature of drug supply chains, 3) OSCM scholars are well positioned to provide answers, and 4) the problem introduces fundamentally new research directions for OSCM. To substantiate this, we carried out a review of key stakeholder reports from six European countries and a systematic review of academic literature. These show that there is no real agreement among stakeholders about what causes the shortages and that there are few academic studies that examine this. We also show that stakeholders have suggested many different government measures – ranging from ‘reshoring production’ to revising procurement policies and increasing stock levels – but that there is little research that provides evidence on their comparative cost-effectiveness. Based on our findings, we discuss three promising research directions to which our discipline could contribute.

Keywords: drug shortages, causes, risk management strategies, operations and supply chain management, future research

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1. Introduction

High-income countries are facing significant drug shortages (CNN, 2018). A recent study by the European Association of Hospital Pharmacists (EAHP) revealed that 95% of hospital pharmacies view shortages of medicines as a problem, with antimicrobial agents, oncology drugs, and anesthetic agents being frequently unavailable (EAHP, 2019). The problem emerged before COVID-19 and is worsening in many countries: The Netherlands, for example, reported 1,492 new drug shortages in 2019 compared to 769 in 2018 (Farmanco, 2020). Norway experienced 684 shortages in 2018 compared to 358 in 2017 and 191 in 2016 (NRK, 2019). The US too is facing an “ongoing and worsening drug shortage crisis” (FDA, 2019, p.5).

Drug shortages have significant consequences. In Europe, 42% of hospital pharmacists surveyed report that patients experience delays in treatment, while more than 25% say that shortages lead to suboptimal treatment and cancellation of care (EAHP, 2019). Shortages also have dire economic consequences. Healthcare staff spends considerable time and effort when facing shortages, e.g., by changing prescriptions, identifying alternative suppliers, and sharing the available stock (EAHP, 2019; FDA, 2019). A Dutch pharmacy team spends on average 17.5 hours per week dealing with shortages (KNMP, 2019), which is estimated to cost between 45 and 105 million euros per year (Ministerie van VWS, 2019a).

Government action is generally believed to be crucial in addressing the problem (cf. Bochenek et al., 2018). When deciding on which government measure(s) to implement, two big questions arise. First, what are the causes of shortages, what is their relative importance, and how are they interconnected? It is crucial to understand these issues to assess how effective government measures are in addressing the problem, i.e., to what extent they will reduce the shortages or lessen their impact. We argue that, to improve such understanding, one should first reveal the current gaps in our knowledge regarding the causes. We therefore analyze stakeholder¹ reports from six European countries (Belgium, France, the Netherlands, Norway, Sweden, and the United Kingdom). Our analysis reveals that there is no real agreement among stakeholders about what causes the shortages and there may be factors they have not identified. Second, which measures are likely to be most effective and what would they cost? Our analysis shows that many different government measures are being suggested, ranging from increasing drug prices and ‘reshoring production’ to revising procurement policies and increasing stock levels. However, stakeholders do not have sufficient information about the costs and likely effectiveness of these various approaches.

¹ Relevant government agencies, manufacturers, wholesalers, pharmacists, hospitals, and patient associations.

The main purpose of this position paper is to advocate that operations and supply chain management (OSCM) could (and perhaps should) be used more widely to help answer these questions by presenting an agenda for further research. To substantiate this, we carried out a systematic review of the academic literature on the topic. This shows that research has provided very little empirical evidence or systematic analysis of the root causes of drug shortages, as well as very limited evidence on the cost and effectiveness of the various measures suggested. Particularly, it is unclear whether measures should address the root causes of the shortages (which will be discussed in Section 2) rather than enhancing capacities of the various health systems to deal with their consequences (e.g., by establishing strategic stocks). We also show that research on the topic has come primarily from health science researchers, who understandably may not have used an OSCM toolkit to study the problem. This gives OSCM researchers an excellent opportunity to employ the tools and insights from our discipline and to make a valuable contribution to understanding more about the effectiveness of measures.

Our study primarily focuses on off-patent/ generic prescription drugs that are presently in production. These represent the majority of drug shortages (EAHP, 2019; FDA, 2019) and are subject to one of the key root-causes we discuss: low prices/margins and profits. We do not consider drugs in the R&D phase or orphan drugs, nor do we consider vaccines. We specifically consider *pre*-COVID-19 shortages for two reasons. Firstly, we want to avoid portraying this as a pandemic-related problem. Drug shortages were an issue before the pandemic and are likely to remain so afterwards. Secondly, by focusing on the period before the pandemic, our study provides a baseline for the substantial quantities of upcoming COVID-19-related studies on this topic. This is in line with Ellis (2020) who state 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).

The study is structured as follows. In Section 2, we introduce definitions and provide some important background information on the drug shortage problem. In section 3, we analyze grey literature, providing the evidence for our claims that there is no real agreement among stakeholders about what causes the shortages and that reports suggest a wide range of government measures without providing robust evidence of their cost or effectiveness. In section 4, we argue that there is no strong evidence in the scientific literature on the (root) causes and cost-effectiveness of interventions and show that very few articles on drug shortages have been published in OSCM-related journals. Based on this, in the final section we present an agenda for future OSCM research.

2. Background and definitions

A drug shortage has been defined as a period when the demand or projected demand for the drug exceeds the supply of the drug (cf. FDA, 2019). Shortages arise because of events or conditions adversely affecting part of a supply chain (cf. Ho et al., 2015). In line with other studies on drug shortages (e.g., Jia and Zhao, 2017), we refer to such events or conditions as *causes*. Causes can be classified as either abnormal or normal. Abnormal causes are relatively rare external events, such as pandemics or natural or man-made disasters, that have major adverse consequences. Normal causes are events or situations that occur much more frequently, typically originating within the supply chain, such as fluctuations in demand, production problems, or delays in distribution (cf. Ho et al., 2015; Sodhi and Tang, 2012). A cause is said to be demand-related if the event or situation causing the shortage is due to a change in demand, and supply-related otherwise.

A first-level cause is a delay or disruption (cf. Sodhi and Tang, 2012) that triggers a shortage. Examples include a production problem or discontinuity in production, a transportation delay, an increase in demand, or a product recall. In Section 3 we argue that key stakeholders predominantly report first-level causes, and do not look further back into second- or third-, level causes. To discover where these problems originate, we need to go right back along the causal chain to the root cause². Although systematic root cause analyses and empirical evidence are scarce, scholars seem to agree that recent increases in drug shortages are at least partly driven by several trends (Tucker et al., 2020; Bochenek et al., 2018; Yurukoglu et al., 2017; Gagnon and Volesky, 2017; Heiskanen et al., 2017; Parsons et al., 2016; De Weerd et al., 2015; Pauwels et al., 2014; Birgli, 2013; Schweitzer, 2013; Woodcock et al., 2013). Figure 1 depicts these trends and their interrelationships.

² Realizing that the term “root cause” can be debated (causes typically have even deeper causes and may be part of causal loops), we hereby align with practitioners’ jargon to refer to important causes upstream in the causal chain.

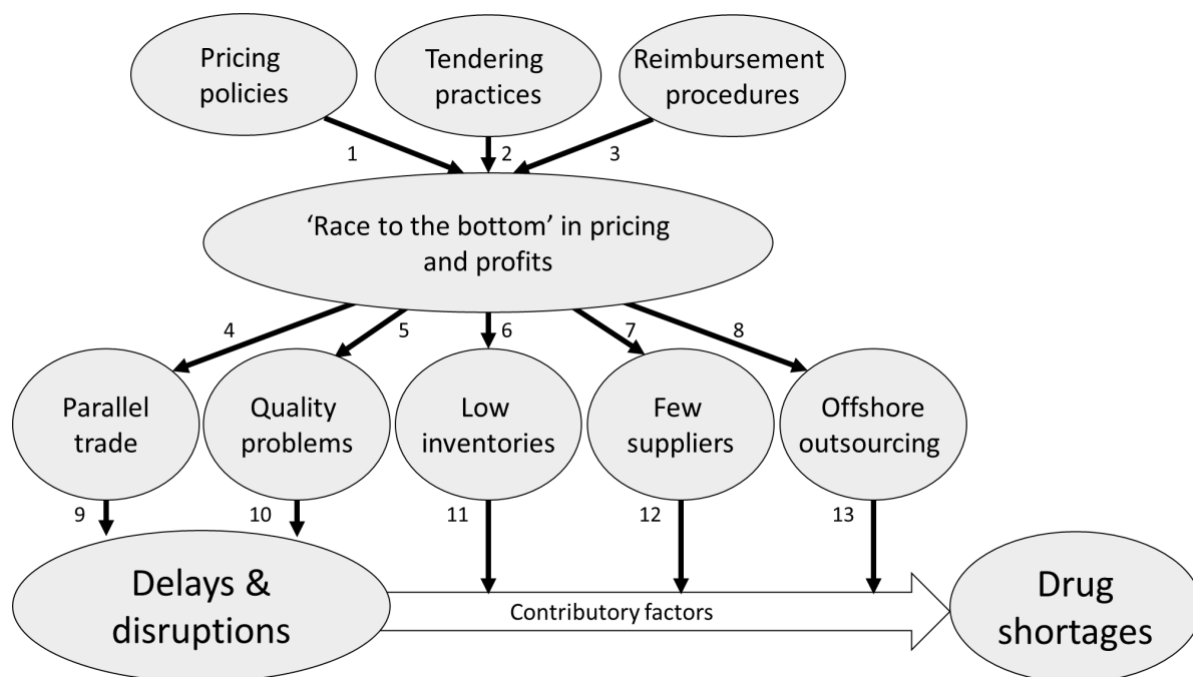


Figure 1. Causes of drug shortages in high-income countries. Adapted from Woodcock and Wosinska (2013). Please note that although this captures key cause-effect relationships, it is a partial and generalized representation of the problem.

Many high-income countries have seen a race to the bottom in pricing and profits in recent years. This is the consequence of pricing policies (e.g., price capping and reference pricing), tendering practices, and reimbursement procedures (see arrows 1–3 in the figure). Low prices have many consequences (see arrows 4–8) that either increase the risk of disruptions or delays (arrows 9–10) or reduce the capacity of supply chains to absorb them (arrows 11–13). Price decreases in one country fuel parallel exports to other countries, leading to artificial disruptions in demand for manufacturers (both in importing and exporting countries) and higher risks of shortages. To avoid losing revenues in importing countries, manufacturers also limit supplies to exporting countries, which also contributes to shortages. Low prices and weak or poorly enforced regulations on inventory levels and manufacturing quality encourage firms in the supply chain to cut costs by maintaining smaller inventories and disincentivize them from investing in manufacturing quality and reliability. Low prices also reduce market attractiveness for manufacturers and can reduce the number of potential suppliers (i.e., manufacturers serving a market) for each drug. Finally, the pressure on prices has led to extensive offshore outsourcing of manufacturing to low-cost economies, making supply chains more vulnerable to disruptions. Many generic drugs are now produced in offshore low-cost production facilities not owned by European and US manufacturers. China and India deliver 80% of the active pharmaceutical ingredients (APIs) for the European and US markets.

We refer to regulations, pricing policies, and tendering practices that emphasize low prices as the *economic root causes* of the drug shortage problem. It should be noted that although Figure 1 reflects the trends believed to explain the recent increases in drug shortages, it is still only a partial,

simplified, and over-generalized representation of the problem. For example, it does not distinguish between issues relating to the specific types of drug such as branded and generic medicines; this second group, for example, are subject to competitive tendering and hence to greater price pressure. To align with the health sciences literature, we use the term *interventions* for measures taken to decrease the likelihood that causes – i.e., adverse events or conditions – occur, the impact these causes have in terms of shortages, or both. In this sense, interventions resemble risk management strategies. For example, efforts to enhance manufacturing quality decrease the *likelihood* of disruptions to production, while holding strategic stocks reduces the *impact* such disruptions may have in terms of creating shortages. We focus not on measures taken by an individual company but on those that *governments* can take to mitigate the risk of shortages, since government action is generally believed to be crucial in addressing the problem (cf. Bochenek et al., 2018). COVID-19 is significantly reinforcing this belief. Tang (2006a), Ho et al. (2015), and Sodhi and Tang (2012) are among the authors who have published detailed overviews of the various types of interventions that organizations could use to mitigate risk in their supply chains. However, these are typically presented from a company perspective and thereby do not capture the variety of government interventions, often in the form of policies, laws, regulations, and economic (dis)incentives. As one of the aims of our analysis is to identify specific types of intervention that may require further study, we divided interventions into three categories. *Market interventions* shape the general market rules and conditions for manufacturers. They represent a generalization of the *economic supply incentives* strategy put forward by Tang (2006a) and are not focused on specific actors in the supply chain. *Supply chain interventions*, in contrast, are government interventions that directly incentivize supply chain actors to strengthen tangible or intangible resources to mitigate shortages. As we detail later, this class of interventions encompasses most of the common supply chain risk management (SCRM) strategies, including those aimed at building in some redundancy or improving flexibility and alignment. Finally, *medical interventions* entail implementing policies or systems to optimize substitution, rationing, and allocation to minimize the health impact of a shortage.

3. Stakeholder perceptions of causes and suggested interventions

The primary objective of this position paper is to advocate that OSCM could be used more widely to address the drug shortages problem. To substantiate this, we now first argue that key stakeholders face significant gaps in evidence and/or knowledge regarding the causes of drug shortages and the government interventions they suggest. We searched the websites of key 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, i.e. pre-COVID. We selected

these six countries because they are representative of the high-income countries we are interested in. Our research group also consists of researchers who speak different languages and can read public reports published in these countries. The search yielded 133 relevant sources (news articles, reports, and government briefs) providing information on the perceived causes, perceived effects, and/or suggested interventions, which we recorded and classified using a data coding scheme. For each country, two researchers were involved in coding and analyzing the data. Further details are provided in Appendix A and B.

3.1 Claim 1: There is no real agreement among stakeholders about what causes shortages

Our analysis of the grey literature reveals three general observations that support this claim. First, many sources report first-level causes only or fail to link those causes to underlying root causes. This seems to be closely related to shortage reporting systems, which (logically) ask the reporter for immediate causes such as production delays or termination, or distribution problems. For example, the Dutch reporting system lists causes such as production delays (58%), increase in demand (21%), and planning or distribution problems (9%) (Ministerie van VWS, 2020a). Similarly, a Norwegian survey study on the “root causes of disruption” lists manufacturing problems (55%) and “other supply chain related problems” (23%) as key causes and includes no mention of underlying economic causes (Norwegian Medicines Agency, 2019).

Second, though dozens of causes can be identified (cf. Bochenek et al., 2018; Heiskanen et al., 2017), individual sources typically only report a small subset of these. This subset differs substantially between countries³. Though it is possible that the relative importance of causes differs for each country⁴, this does not explain the limited overlap between sources or countries in the causes reported. For several causes, it appears to be a consequence of differences in reporting. The Norwegian Association of Pharmaceutical Manufacturers (LMI) lists manufacturing problems (43%) and demand increase (16%) as two key causes (LMI, 2018) whereas the Norwegian Directorate of Health also emphasizes long lead times, just-in-time inventory management, hoarding, and market size (HDir, 2019). One would expect every country in our set to be hit by decreasing prices/margins impacting manufacturing quality, and inventory levels (Section 2). However, we found no mention of these having an impact on inventory levels in sources from Belgium and the UK, and the Netherlands

³ By the set of causes reported for a specific country, we mean all the various causes mentioned in publications from that country.

⁴ The relative importance of causes such as small market size, which tends to mean that the number of suppliers for each drug is limited, and parallel export, which leads to artificial variations in demand, is indeed shown to be country-specific (cf. Bochenek et al., 2018, De Weerd et al., 2015). Our data confirm this to be the case. For example, the impact of parallel export is perceived to be minor in France, whereas it is a major concern for the UK and Belgium, where it has led to strict limits on exports (Fagg, 2019; Department of Health and Social Care, 2019; Sénat République Française, 2018).

and France were the only countries that reported them to be affecting manufacturing quality. We also found France to be the only country reporting that resupply intervals play a role, affecting demand uncertainty and the strength of bullwhip effects, whereas OSCM theory suggests these are rather universal phenomena.

Third, the limited overlap in causes reported for each country and in each source also seems to be the consequence of differences in perception: Stakeholders question or disagree on the validity or relevance of the causes. For example, though several reports point to price policies being an important root cause (cf. Berenschot, 2018), the Dutch Minister of Health, Welfare, and Sport calls this claim “unsubstantiated,” stating that “for most of the shortages, delays in production or distribution are reported as the main cause” (Bruins, 2019a, p. 3) and that “less than 15% of the shortages are reported for drugs subject to the *preferentiebeleid* [i.e., the mostly price-focused reimbursement practice] of Dutch insurance companies” (Bruins, 2019c, p.2). Differences in perception seem to be at least partly related to the role of the stakeholder. For example, while UK’s National Pharmacy Association (2020) highlights the quota systems imposed by manufacturers as an important cause, the manufacturers themselves point to pharmacies and wholesalers exporting medicines intended for use in the UK (ABPI, 2019). Shortages can also be caused by interventions designed to address them (i.e., interventions that backfire). Our data reveal several examples of differing views on such causes. One example is demand pooling for tendering. Norway engages in joint tendering with other Nordic countries and claims this has increased the appeal of markets in those countries and will have a very significant impact on pharmaceutical supplies (Eversana, 2020). France, however, argues that demand pooling and associated tendering practices have *decreased* the number of suppliers per drug and increased vulnerability, and it has therefore considered regionalizing tendering (Sénat République Française, 2018). As a second example, in most of the countries we studied it has been suggested that reporting obligations for potential shortages and penalties for non-availability could be introduced, but these are also believed to have a negative effect on market attractiveness (EFPIA, 2020) and to lead to medicines being delisted (cf. Bochenek et al., 2018). A Dutch report argues that suppliers do indeed “worry about negative impacts on drug supply” whereas other parties “believe strict enforcement can have a positive impact (...)” (Ministerie van VWS, 2019b).

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

Analyzing the country data in terms of suggested interventions reveals four findings that we regard as particularly striking. First, there is vast diversity among the interventions being considered, and many of them resemble supply chain risk management strategies. Initiatives to enhance information sharing (cf. Ho et al., 2015; Christopher and Lee, 2004) during potential or actual shortages are among those

most often suggested. These typically take the form of voluntary or compulsory event notification systems in which manufacturers report potential upcoming shortages or disruptions to supply, wholesalers report low inventory levels, and pharmacies report non-availability of certain drugs at the wholesaler (see, e.g., FAGG, 2020; DHSC, 2019b; Ministerie van VWS, 2017).

Interventions that add redundancy (cf. Sodhi and Tang, 2012) to medicine supply chains are also being considered in each of the countries we studied. European Union Directive 2001/83 requires member states to hold market authorization holders responsible for their obligation to ensure “within the limits of their responsibilities, appropriate and continued supplies of medicinal product[s] to pharmacies and persons authorized to supply medicinal products” (p.73). Member states implement this in different ways, such as placing obligations on pharmacies and others to do this and imposing fines if they do not’. Since such measures have not sufficed in the past years, countries are considering making them stricter and more specific, for example, by introducing stock and lead-time requirements. Belgium, for example, has brought in a law that obliges manufacturers to supply wholesalers within three days (FAGG, 2019). The Netherlands is considering obliging wholesalers and manufacturers to keep a strategic stock of all medicines, covering five months of demand (Bruins, 2019b). Norway has also implemented a “prepositioning duty” for wholesalers (HoD, 2019) and has suggested assessing the notion of keeping common European strategic stocks of drugs and raw materials (HDir, 2019).

Interventions to enhance the flexibility of the supply base (cf. Tang, 2006a) are also frequently suggested. One example would be to award contracts to multiple suppliers. This is believed to counter monopoly formation and ensure a “supply base that that can be drawn upon in the event of a failure” (Sénat République Française, 2018, p.98). Other suggested ways to enhance the flexibility of the supply base through tendering include 1) tendering for “back-up suppliers,” 2) regionalizing the tendering process (to increase the number of suppliers active in a country), and 3) stimulating manufacturers to include multiple suppliers of APIs in their product registration files (Sénat République Française, 2018; Ministerie van VWS, 2017). Supply base flexibility can also be enhanced by disseminating information on back-up supply options during a shortage. The UK, for example, maintains a website with information on “manufacturer contingency arrangements” (PSNC, 2020). In addition, initiatives are underway to eliminate financial barriers to supply base flexibility, as imposed by insurance systems that cover drugs only from a limited set of contracted manufacturers. Several countries are also considering ways of extending the supply base during a shortage. These could include, for example, allowing local contingency manufacturing, expediting the licensing of new suppliers, and temporarily allowing products with packaging that does not conform to standard

requirements (see, for example, Leth et al., 2019; Sénat République Française, 2018; DSB, 2018; Ministerie van VWS, 2017).

The interventions described above are still only a fraction of the total range of interventions suggested in the literature on supply chain risk management (SCRM) (cf. Ho et al., 2015; cf. Sodhi and Tang, 2012; Tang, 2006a). Other interventions emphasized in that literature include enhancing flexibility of transportation (e.g., having multi-modal and multi-route contingency plans for a disruption), postponement (e.g., of packaging and inserting leaflets), using flexible supply contracts (e.g., modifying order volumes based on demand and performance) and flexible manufacturing (e.g., funding technological innovations), and building supplier relationships (e.g., to ensure continuity of access when a manufacturer announces its withdrawal from the market). Other SCRM measures suggested are demand risk mitigation (e.g., preventing hoarding and reducing demand uncertainty by revealing the outcomes of tenders earlier) and manufacturing risk mitigation (e.g., by collaborating with manufacturers to prevent and tackle problems with quality).

The second finding is that stakeholders consider a wide range of risk management strategies that are not easily categorizable in existing SCRM frameworks. Medical interventions are an important example of this. These involve mechanisms and rules or guidelines on substituting medicines that are out of stock and rationing and allocating scarce supplies to minimize negative impacts on patients (see, for example, FAGG, 2020; DHSC, 2019a; Sénat République Française, 2018; Norwegian Ministry of Health and Care Services, 2017). They also include provisions for extending expiry dates and relaxing quality requirements for batches of medicines that are substandard but still safe. Though these interventions are similar in some ways to the risk management strategies of dynamic assortment planning and silent product rollover (see Tang, 2006a), they differ substantially in terms of the objectives (revenue generation as opposed to improvements to health) and approach (influencing demand vs. determining supply).

Market interventions are also difficult to categorize into SCRM frameworks. Although providing economic incentives to encourage additional suppliers is recognized in the SCRM literature as a viable strategy for managing risk (see Tang, 2006a), many of the market interventions suggested go beyond that. The most widely recommended set of market interventions focuses on incentivizing manufacturers to bring production back to Europe, a move that has been explored by French, Dutch, and Norwegian governments and the European Commission (European Commission, 2020; Bruins, 2019b; Ministère des Solidarités et de la Santé, 2019; HDir, 2019). The European Parliament suggests introducing “financial incentives, in line with state aid rules, to persuade producers to make active pharmaceutical ingredients and medicines in Europe” (European Parliament, 2020). Other suggested interventions include revising procurement guidelines to “recognize investments in security of supply

for Europe” (Medicines for Europe, 2019, p.2), investing in business and innovation, and simplifying legislative and administrative procedures (Ministerie van VWS, 2020b). While these interventions resemble the make or buy strategy (see Tang, 2006a), a key difference is that they use government incentives as opposed to direct in-house vs. outsource decisions by manufacturers. Other suggested market interventions include limiting or restricting parallel export (FAGG, 2019), pooling demand from multiple countries to enhance market attractiveness (Eversana, 2020), increasing the duration of contracts with manufacturers (Berenschot, 2018), and implementing revenue guarantees to incentivize the supply of medicines with low expected sales (FHM, 2017). As we argue in Section 5, these market and medical interventions highlight the fact that traditional operations and supply chain knowledge alone will not suffice to address the drug shortage problem and that collaboration with experts in health and economic sciences is key.

The third observation is that little attention has been paid to interventions that tackle the economic root causes (see Section 2). Most of the suggested interventions could be called *reactive*, in that they aim to reduce the likelihood of shortages occurring or to lessen their impact on patients and providers, rather than proactive, namely seeking to address the root causes directly. This has indeed been concluded about the approach taken by the Netherlands: “The current package of measures is focused more on decreasing the effects of shortages or dealing with their consequences than on the underlying causes” (Ministerie van VWS, 2019b, p.19). A similar conclusion has been reached about the UK’s approach: “Currently most shortages are managed reactively instead of proactively” (Miljković et al., 2019, p.64). Other than the few notable exceptions described above, there is little discussion of interventions to tackle economic root causes – through changes to pricing, tendering, and reimbursement – and enhance market attractiveness. As indicated, the proposed interventions could even *decrease* market attractiveness. The European Federation of Pharmaceutical Industries and Associations (EFPIA), for example, advocates that member states should resist “imposing disproportionate requirements in terms of prevention plans, stock piling, reporting and/or penalties, without considering the potential effect of such country requirements on the continued supply of other EU markets” (EFPIA, 2020, p.9).

This brings us to our fourth finding: Stakeholders seem to lack evidence with regard to the cost and effectiveness of interventions. For example, the Norwegian civil protection organization concludes that analyses of the interventions’ effectiveness and efficiency have yet to be conducted (DSB, 2018) and the Swedish civil protection organization states that “It is not clear what the expected effects of the suggested solutions are” (MSB, 2016, p.10). Similarly, the Dutch government analyzed the effects of 27 interventions and concluded that the effects were mostly either difficult to assess or unknown (Ministerie van VWS, 2019b). For the remaining interventions, evidence is provided on

metrics such as the number of times a shortage is reported, the number of times permission is given to import or use non-standard packaging for a drug during a shortage, and the number of times information on stock levels is shared. There seems to be no evidence on the costs and effects of interventions to mitigate drug shortages.

3.3 Summary

In short, stakeholders have suggested a wide range of (predominantly reactive) interventions to address the problem of drug shortages. Many of these interventions share much in common with known supply chain risk management strategies. Several also have clear connections to economics and health sciences. However, evidence on the comparative costs and effectiveness of such interventions is lacking. We specifically note that the measures suggested are largely reactive, and it is not clear whether these are cost-effective in comparison to proactive measures. Our analyses also suggest that stakeholders seem not to be fully aware of the root causes, of their relative importance or of the interrelations between them. Nor are they necessarily aware that government interventions can sometimes be counterproductive, causing problems of their own. These findings suggest that either such knowledge is indeed absent, or that it has not been disseminated to or internalized by stakeholders. The next section discusses what academic research has done to address these knowledge gaps.

4. What research has contributed so far

We included 79 of the 506 articles we identified in our scientific literature review (See Appendix C for details of search terms and inclusion criteria) and read these in depth, using 25 fields to classify each article in terms of:

- Context (countries, medicines, and types of risks studied)
- Purpose (e.g., does the study investigate causes, impacts, and/or interventions?)
- The type of evidence provided (e.g., does it draw upon primary data, secondary data, or on literature alone?)
- The intervention analysis (e.g., type of intervention, analysis of a single intervention or multiple interventions, the outcome metrics used, and the stakeholders considered in the analysis)
- The cause analysis (e.g., the number of causes mentioned and whether a systematic root cause analysis was carried out)
- The research methodology (e.g., qualitative/quantitative data, modeling vs. empirical methods).

Our aim is to highlight areas that are understudied and how existing studies can form a basis for further research. Below we discuss three key findings.

4.1 Claim 1: OSCM has so far played a marginal role in studying the problem of drug shortages

It seems that that the problem of drug shortages has seldom been studied by members of the OSCM community. We identified only ten articles on drug shortages in OSCM-related journals⁵ (Tucker et al.; 2020; Jia and Zhao 2019; Lu and Shi, 2019; Shiau, 2019; Azghandi et al., 2018; Kochan et al., 2018; Jia and Zhao 2017; Dai et al., 2016; Liao et al., 2015; Zadeh et al., 2014). More generally, the use of models, tools, or concepts from our field is scarce. While 44 of the remaining 69 articles in our review do discuss or study supply chain interventions, we did not find references to articles from OSCM-related journals.

4.2 Claim 2: More research is needed that presents a comprehensive view of the causes of shortages

Although many of the articles (63 out of 79) express a view on what causes drug shortages, most of them (44 out of 63) do so by referring to other articles or stakeholder reports; they do not provide *new* evidence. Furthermore, while several studies suggest that there are dozens of causes (see, for example, Heiskanen et al., 2017), the vast majority of the papers (50 out of 63) on possible causes list ten or fewer. Most (36 out of 63) list between one and five, and thus only provide a partial view of the issue. For example, a meta-analysis of shortages in seven European countries groups the causes into five broad categories: Production problems, Economic reasons, Multiple reasons, Other causes, and Unknown cause (Pauwels et al., 2014).

Like many of the stakeholder reports, the academic papers also report primarily on first-level causes. For example, a study on drug shortages among Irish pharmacies distinguishes between Excess demand, Manufacturing/licensing issue, and Unknown (Costelloe et al., 2015). Similarly, a study on Finnish pharmacies identifies the following reasons for shortages: The product had run out in Finland/the product had run out at the supplier, Problem at the manufacturing site, Wholesaler, The owner of the trading license changed, and Shortage of raw materials (Heiskanen et al., 2015). The reason for this focus on first-level causes appears to be the same as we stated earlier: In many of the papers the authors explore specific shortages by eliciting stakeholder views, either directly or indirectly (i.e., via reporting platforms), on the immediate causes. For example, seven of the 19 articles that include data on causes use data on immediate causes drawn from shortage reporting platforms (see, for example, Mazer-Amirshahi, 2018; McLaughlin et al., 2014; Hassig et al., 2014).

⁵ We broadly define this as journals classified by Web of Science 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).

Heiskanen et al. (2017) is a notable exception in trying to develop a comprehensive understanding of the problem. They use semi-structured interviews with manufacturers and wholesalers to elicit expert opinions on the causes of drug shortages. The study reveals several elements included in the framework shown in Figure 1 – long lead times due to offshore production, low inventories, low prices, decrease in the number of suppliers – but no discussion or evidence is provided on how these could be interrelated or impacted by the same cause further up in the chain. The same applies to Pauwels et al. (2015), who ask hospital pharmacists to state their views on the importance of 13 potential causes, including Tendering, Prices too low, Quality issues, Parallel imports/exports, and Non-European production sites. Woodcock and Wosinska (2013), on the other hand, do explore interrelationships. They evaluate disincentives in the pharmaceutical market and use economic theory to argue that these can decrease manufacturing quality, reduce inventories, and ultimately make shortages worse. Similarly, De Weerd et al. (2015) have studied European and national legislation and use inference from economic mechanisms to motivate how they might affect drug shortages or refer to stakeholder reports that make such inference. For example, to argue that tendering can reduce the number of manufacturers serving a market, the study refers to Kanavos et al. (2011) and Kanavos et al. (2009), which use mechanism-based reasoning to suggest this relationship.

Our review revealed three interesting studies that use econometric modeling to study causality. Yurukoglu et al. (2017) studied a policy change in the US that impacted drug prices and showed that shortages went up more for drugs whose prices decreased more significantly. Similarly, Ridley et al. (2016) use longitudinal data on vaccine shortages in the US and reveal that a higher price is associated with a lower likelihood of shortage. Parsons et al. (2016) use data on US drug shortages to show that having a maximum of four suppliers for a drug makes shortages more than twice as likely to occur compared to having five or more suppliers. They also show that shortages of “older” drugs are more likely and suggest this to be the consequence of fewer financial incentives to invest in production and inventories.

In short, most papers that express a view on the causes of drug shortages present either no new evidence or evidence relating to first-level causes only. Most papers that aim to assess the causes comprehensively essentially base their hypotheses on expert opinion and mechanism-based reasoning, which are regarded by health scientists as providing relatively weak evidence (Van de Klundert, 2016; OCEBM, 2011). Studies examining how causes are interrelated are particularly scarce (we return to this in Section 5, where we discuss the needs and opportunities for OSCM research). We found only three papers that use statistical analysis to assess causality. Hence, with a few exceptions, there is a lack of studies presenting strong evidence about the causes and particularly the root causes

of drug shortages. In addition, most of the studies (54 out of 79) focus on the US, and it is uncertain whether the insights are transferable to other countries, given the differences in regulation, parallel export, market size, and pricing and procurement practices, etc. (see Vogler et al. (2017), for example, on differences in tendering systems). This lack of evidence was also noted by Pauwels et al. (2014), who conclude that in Europe “no efforts [have yet been made] to unveil the root causes” (p.7). Similarly, the EFPIA states in its position paper that “despite multiple country reports, there is a lack of sound evidence and knowledge about the key drivers” (EFPIA, 2020, p.4).

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

To assist governments in their decision-making on how to address the problem of drug shortages, there is a need for research that 1) examines the interventions governments are considering implementing (see Section 3.2) but for which it is not clear whether they are cost-effective, 2) provides strong evidence of comparative cost-effectiveness, and 3) assesses the direct and indirect implications of such interventions for all the relevant stakeholders. For example, to assess the impact of changing procurement one should consider not only its direct effect on shortages: This change could also indirectly impact shortages by affecting market attractiveness for suppliers and the number of suppliers serving it. Our review has revealed some academic research that fulfills these three criteria but there is more that could be done.

First, in general, studies providing evidence on the implementation costs and/or the effectiveness of the proposed interventions is scarce; less than a quarter of the articles (18 out of 79) we reviewed did this.

Second, the interventions considered are mostly analyzed from the perspective of a single stakeholder and government interventions are rarely considered. For example, all papers that present *empirical* evidence (7 out of 18) do so in the form of a case study of a specific stakeholder’s response to a specific shortage. These include studies on a single hospital’s experiences of therapeutic substitution (Nystrom et al., 2019; Becker et al., 2013), on rationing/allocation of scarce medicines (Hsueh et al., 2017; Kaur et al., 2013; Rosoff et al., 2012), and on expedited importation from a foreign supplier (Hunnissett-Dritz, 2012). Another study also looks at the way the US Food and Drug Administration (FDA) worked together with manufacturers to take last-minute risk-mitigation actions during a specific shortage (Jensen et al., 2015). More than half (6 out of 11) of the papers presenting evidence obtained using modeling and numerical simulation also consider only one stakeholder. These papers examine the allocation of scarce medicines or vaccines (Russell et al., 2017; Matrajt et al., 2013), the mitigation of shortages through improved sales forecasting (Zadeh et al., 2014), and

inventory management for a manufacturer (Lu and Shi, 2019) and for a hospital (Shiau, 2019; Liao et al., 2015). Two other modelling/simulation papers do look at the implications for multiple stakeholders but do not consider government interventions. Kochan et al. (2018) use a system dynamics model to assess what impact demand and inventory information sharing between hospitals, distributors, and manufacturers has on shortages. Azghandi et al. (2018) simulate the effect of drug recalls on inventory levels for manufacturers, wholesalers, distributors, and health centers, and show how this depends on the amount of safety stock. Finally, Dai et al. (2016) consider one particular government intervention and its implications for multiple stakeholders. They study how the US government could mitigate shortages of an influenza vaccine by constructing a contract that incentivizes a vaccine manufacturer to initiate early production. The nature of the problem here (uncertainty of demand and late decisions on vaccine composition) is, however, rather different from that of the drug shortages problem (see Section 2).

Third, as can be observed from the previous paragraph, many articles (9 out of 18) cover reactive interventions – dealing with shortages through rationing, allocation, or substitution, and last-minute risk mitigation. While this is in line with what is happening in practice, it is difficult to see how such studies can assist governments in moving from a reactive to a more proactive approach. Accordingly, there is a lot of potential for research on proactive interventions that governments could consider: changing tendering practices, limiting parallel trade, introducing stock/lead time requirements, establishing event notification systems, incentivizing relocation of production, pooling demand across countries, etc.

We identified two papers that nicely illustrate the type of research we believe is urgently needed. They consider all the relevant stakeholders, assess the costs and effects of multiple interventions (albeit using data on a small set of drugs and for one specific country), and study interventions that many governments are considering but are hesitant about. The first is a paper by Jia and Zhao (2017), who 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 (% of demand the manufacturer could not meet because of a disruption). They specifically consider changes that are beneficial in terms of the objectives of each stakeholder – the manufacturer, government, group purchasing organization, and healthcare provider – and present general analytical results and specific numerical results for three typical drugs of which there is a critical shortage. Similarly, Tucker et al. (2020) use a multi-stage stochastic model to simulate how government interventions affect a manufacturer's decisions on supply chain design (selection of suppliers, plants, and production lines) and inventories, and they estimate how this affects societal costs and shortages for two generic oncology drugs (% of demand not met from stock). The interventions include

mandatory redundancy (i.e., requiring multiple production lines, suppliers, and/or plants), mandatory inventory (i.e., requiring a safety stock of x months of demand), failure-to-supply penalties (i.e., a penalty for each unit of demand not met from stock), and price changes.

In short, we found little research that fully addresses the important questions governments may have regarding the potential costs and effects of different interventions. Most of the available literature considers reactive interventions or examines interventions from a single stakeholder's perspective. Relying largely on such local optimization is risky, as it does not account for implications for upstream and downstream parts of the supply chain (cf. Settanni et al., 2017). There is huge potential for studies that take a systems perspective.

4.4 Summary

We identified few academic research studies that examine the (root) causes of drug shortages and the comparative cost-effectiveness of important interventions governments are considering. Furthermore, it seems that the problem of drug shortages has seldom been studied by members of the OSCM community. The close link to OSCM, the importance of the problem, and the potential impact of the research results make this a great opportunity for researchers in our field. In the next section we discuss three promising research directions to which our discipline could (and perhaps should) contribute.

5. An agenda for future research

What is clear from the previous discussion is that shortage of drugs is a pressing problem and that to work out suitable ways of tackling it, more research evidence is urgently needed. This section sets out a three-item OSCM research agenda for obtaining such evidence.

5.1 Agenda item 1: Developing an evidence-based system view of the drug shortage problem

Sections 3.1 and 4.2 show that there is limited evidence on the root causes of the shortages, their relative importance, and how they interrelate. Looking at the cause and effect relationships presented in Figure 1, for example, we see that research has explored the link between prices and shortages (Yurukoglu et al., 2017; Ridley et al., 2016). However, with the notable exception of a study on the link between the number of suppliers and shortages (arrow 12: Parsons et al., 2016), we found no studies that quantify the cause and effect relationships that link prices to shortages (i.e., arrows 4-13). This lack of evidence for “the big picture” means that there is risk of stakeholders and academics missing important dynamics and knock-on effects when assessing interventions and studying causes. 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 do so. We therefore advocate further research that can 1) establish sound evidence on understudied cause and effect relationships and 2) combine such evidence with evidence on cause and effect relationships from existing literature to establish a system view of the problem – i.e., research that builds the whole from the parts. OSCM expertise in studying and modeling complex dynamic systems will be paramount in undertaking this type of research, combined with expertise from the health sciences and economics. Particularly, we deem that there is a large potential role for system dynamics modeling and for econometric models that assess causality. These methods would be very suitable for studying, for example, links between prices and manufacturing disruptions, inventories, parallel trade, lead times, and the number of manufacturers. Building on the studies identified in this review, such research could leverage publicly available data sets, including medicine price lists and data on shortages, medicine imports and exports, and the number of market authorization holders for each drug. Direct engagement and collaboration with relevant stakeholders may be necessary to obtain complementary data. For example, data from manufacturers and/or wholesalers are needed to study the impact of prices on stock levels and production disruptions.

5.2 Agenda item 2: Studying the comparative cost-effectiveness of key government interventions

Section 4.3 highlights the paucity of evidence on the cost-effectiveness of many of the interventions being considered by governments. These interventions are very similar to certain supply chain risk management strategies (see Ho et al., 2015; Sodhi and Tang, 2012; Tang, 2006a), but they differ fundamentally from them in various aspects (which we discuss below) and their (cost-) effectiveness has not been estimated for medicine supply chains. We therefore call upon OSCM researchers not only to develop an evidence-based and system view of the causes of drug shortages but in parallel to develop and parametrize models of cost-effectiveness of government interventions. Below we highlight three interventions that have been shown by our review of grey and academic literature to be important and understudied.

Establishing strategic stocks. The first intervention is the imposition of legal requirements for inventory levels (or lead times) and corresponding failure-to-supply penalties, as being considered in several countries. Countries struggle to decide how high such inventory levels should be, where the inventory should be kept (at the manufacturer, wholesaler, or pharmacy), whether and how the levels should differ for different types of medicines, how to finance this, and how these requirements could be enforced (see, for example, Gupta Strategists, 2019). Enforcement is not trivial, as inventory levels are affected by exogenous factors (e.g., increases in demand, parallel export, and disruptions to supply). The challenge of specifying legal requirements differs from traditional inventory management

problems in various ways, one of these being that a policy should not be based on a complex formula or algorithm but 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 of inventory or lead time requirements should take account of the fact that interventions of this type can change the “future state” of the system. For example, the Dutch government has expressed concern that increasing penalties carries the risk that manufacturers of products with small revenues or low prices will decide to withdraw from the market, because the penalties make it less attractive (Ministerie van VWS, 2017). OSCM scholars have the potential to inform this debate by developing models (e.g., stochastic dynamic programming models) that 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. Within the OSCM community there is also much expertise that could inform debates around the reshoring of drug manufacturing. COVID-19 has led to many calls, often ill-informed, for action to be taken, and the comparative cost-effectiveness of possible strategies presents a hugely interesting question. Reshoring of production is most certainly going to significantly increase costs (cf. France24, 2020; Ministerie van VWS, 2020b), and it is questionable to what extent this will resolve the drug shortage problem, partly because upstream supply chains (e.g., for APIs) may remain global. Most importantly, however, it is unclear whether reshoring would be cost-effective *in comparison to* other interventions. For example, in a US House of Representatives hearing Yadav (2020) stated that “we need not frame supply chain security as a zero-sum game. Instead, by focusing on diversification of the supply base of medical product manufacturing, the US would gain supply chain resilience, expanded trade opportunities, and goodwill.” There is a clear need for more OSCM research on the total system cost-effectiveness of reshoring, how it differs for particular drugs and countries, how it depends on other countries’ reshoring decisions, and how it compares to the effects and costs of other interventions. Mixed-method research designs combining case-based research with modeling may be particularly suitable to explore these questions. Case-based research is useful for studying reshoring decisions in context and developing an in-depth understanding of how these decisions impact costs and shortages. For example, our data suggest that reshoring may increase drug prices, as governments may incentivize procurement units to “recognize investments in security of supply for Europe” (Medicines for Europe, 2019, p.2). Information obtained from such case-based research would in turn inform the development of models that estimate cost-effectiveness as a function of location decision variables.

Revising pricing, tendering, and reimbursement practices. Interventions that tackle economic root causes – pricing, tendering, and reimbursement practices – are a third important area

where there is much research potential. Specific examples of such interventions include regionalization of tendering, tendering for back-up suppliers, introducing joint procurement for multiple countries, assigning contracts to multiple suppliers, and making reimbursement dependent on prices. An important reason for the lack of research on such interventions could be that revising pricing, tendering, and reimbursement practices is perceived to conflict with the objective of maximizing affordability (De Weerd et al., 2015; Birgli, 2013). For example, Dutch critique of pricing policies has been countered with by the argument that these have helped save the Dutch government €2.5 billion euros since 2011 (Bruins, 2019a). This trade-off may, however, be a false one as the impact on shortages may depend strongly on the specifics of tendering, pricing, and reimbursement practices. In Denmark, tendering is believed to have led to substantial cost savings and “shortages did not appear to be an issue” (Vogler et al., 2017). The big underlying question is which of the suggested interventions strikes the best balance between affordability and availability (cf. Musazzi et al., 2020). In other words, which will keep prices low while ensuring that sufficient manufacturers remain active in a country to provide ample capacity if one of them experiences a disruption. 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 be very valuable in addressing this question.

5.3 Agenda item 3: Bringing the government perspective and economics into supply chain risk management

As indicated, many of the interventions suggested by stakeholders could be classified using common SCRM frameworks. We nevertheless see two fundamental differences that suggest there is scope for pushing the frontiers of SCRM research. First, interventions could be considered from a government perspective, and thus complement existing SCRM studies (e.g., see Tucker et al., 2020), which typically take the perspective of a particular company or supply chain. As governments are typically not directly engaged in the production and distribution of medicines, government interventions are usually indirect, taking the form of policies, regulations, guidelines, fines, and other forms of financial incentives that influence supply chain actors. COVID-19 shows that governments are increasingly playing this type of role. For example, governments have traditionally not been involved in decisions on production locations, but some are now planning to influence them through economic incentives. Similarly, most governments have traditionally not kept their own stocks of medicines but are planning to influence the stocks kept by firms within the supply chain 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 that arises as a result of

government regulations and fines. The same applies to procurement, distribution, and transportation and to quality and capacity management, and so on. These examples suggest that insights, models, and tools from SCRM may not be directly transferable to the study of government interventions. We therefore submit that there is a great opportunity for SCRM research to expand its scope to consider government policies and regulations⁶.

Second, many interventions can have significant impact on suppliers' decisions to enter or exit a market (see Section 5.2). Although maintaining a diverse supply base is recognized as a valid risk management strategy in SCRM, supply base decisions have typically been regarded as *endogenous* ones – i.e., the supply base is designed by the buying organization. Our context highlights the need to understand how supply base design is impacted by *exogenous* decisions – i.e., suppliers' economic decisions to enter or exit a market. To analyze interventions holistically, it would be very helpful to have models that capture these decisions. There are several supply chain competition or operations economics models that do this (cf. Korpeoglu et al., 2020; Corbett and Karmarkar, 2001), but they include some assumptions that do not hold for medicine supply chains (e.g., demand is affected by price and indirectly by production quantities), analyze outcome variables other than availability, or study interventions/ decision variables that do not necessarily apply in the context of medicine supply chains. We therefore advocate that future researchers should develop models that capture 1) relevant interventions, 2) their impact on entry/exit decisions, and 3) the direct and indirect implications for supply chain risk. Collaboration between economists and OSCM researchers is essential for this.

5.4 Final remarks

In recent years we have seen many calls for operations and supply chain management scholars to increase the relevance of their research (Van Wassenhove, 2019; Tang, 2016; Fisher, 2007) and to do rigorous research that is practice-based and responsible (Lee and Tang, 2018; Gallien et al., 2016). The continuing problem of drug shortages makes it important for the OSCM community to get involved and thereby provides us with a great opportunity: 1) it is a problem that 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 help address these questions, and 4) the problem introduces fundamentally new research directions for OSCM and thereby helps us to push the frontiers of our discipline. COVID-19 has certainly emphasized why such work is urgently needed.

⁶ cf. Pagell et al., (2019) and Tokar and Swink (2019), who argue that sound analyses of the effects of government policies and regulations on supply chains have received limited attention

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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. Through this process 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 below. 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 1 shows the framework and related classification schemes.

Table 1: 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. <i>International Journal of Production Research</i> , 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	Ho, W., Zheng, T., Yildiz, H. and Talluri, S. 2015. Supply chain risk management: a literature review. <i>International Journal of Production Research</i> , 54(16), 5031–5069.

	<p>Production problems</p> <p>Limited information on current and future supply capacity and risk of shortage</p> <p>Small customer</p> <p>Information system failures</p> <p>Deliberate low inventories</p> <p>Few wholesalers</p> <p>Lack of SC transparency</p> <p>Cross-border drug trade</p> <p>Information system failures</p> <p>Deliberate low inventories</p> <p>Epidemic, Natural disaster, War/terrorism, Fires, Political instability, Economic downturns, External legal issues, Regional instability, Government regulations, Social and cultural grievances, Brexit</p>	
Effects of shortages	<p>Effects on patients: does not discuss /analyse (N); simply discusses (D); analyses primary data (P); analyses secondary data (S)</p> <p>Economic /financial effects: does not discuss /analyse (N); simply discusses (D); analyses primary data (P); analyses secondary data (S)</p>	
Market interventions	<p>Economic supply incentives</p> <p>Limit parallel trade</p> <p>Flexible supply termination/ smoothen number of players in the market</p> <p>Law enforcement for: notification of halting/pausing supply</p> <p>Law enforcement: Effort obligation for sufficient inventories</p>	<p>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.</p>
Medical interventions	<p>Silent product rollover ('Prescribe' a different product due to shortages of the original)</p> <p>Allocation rules/ rationing (In case of shortages, no rules on which patients should be prioritized)</p> <p>Flexible quality standards/product characteristics</p>	<p>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.</p>
Supply chain interventions	<p>Centralization</p> <p>Collaboration</p> <p>Flexible supply base</p> <p>Supply contracts</p> <p>Flexible manufacturing process</p> <p>Flexible transport</p> <p>From make to buy and vice versa</p> <p>Postponement</p> <p>Speculation</p> <p>Strategic stock</p> <p>Dynamic assortment planning</p>	<p>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.;</p> <p>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.</p> <p>Tang, C.S. (2006b), "Perspectives in supply chain risk management", International Journal of Production Economics, Vol. 103, pp. 451–488</p> <p>Chopra, S. and Sodhi, M.S. (2004), "Managing Risk to Avoid Supply-Chain Breakdown", MIT Sloan Management Review, Fall 2004, pp. 53–61;</p> <p>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.</p>

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.

Appendix B: Stakeholders & Key Data Sources per Country

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; Regjeringkansliet 2015; 2016; 2018; Socialdept. 2018 https://www.regeringen.se/sveri-ge-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.	Swedish Association of the Pharmaceutical Industry – LIF 2018.	Generics pharma sector: http://www.bogin.nl/ scanned all news articles. association for

	https://www.lmi.no/ 44 hits; 0 hits	https://www.lif.se/ 15 hits	new drugs: https://www.vereniginginnovatiegeneesmiddelen.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 Apoteksforening; 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	Patientförsäkringsforeningen https://www.pff.se/ 11 hits	Patient federation: https://www.patientfederatie.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-legemiddelangel-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 wholesalers: 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	Federaal Agentschap voor Geneesmiddelen	Public Health France: http://www.santepubliquefrance

	t/organisations/public-health-england - 274 hits NHS England website: https://www.england.nhs.uk/ - 216 hits	Gezondheidsproducten: https://www.fagg.be/nl/search?keyword=genesmiddelen+tekort&=Zoeken 40 hits	.fr/ INVS: 31 hits; INPES: 29 hits;
Medicines Agency	Medicine and Healthcare Products Regulatory Agency website: https://www.gov.uk/government/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	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
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.hospitalpharmacistsbelgium.eu/ (no search function)	Orde National des Pharmaciens http://www.ordre.pharmaciens.fr/ 134 hits
Patient	The Patients Association website: https://www.patients-association.org.uk/ - 9 hits	Vlaams patientenplatform http://vlaampatientenplatform.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:	Repertorium van het Belgisch Centrum voor Farmaceutische Informatie (BCFI): http://www.bcfi.be/nl/start 10 hits	

	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	Belgische Vereniging van Artsensyndicaten (BVAS): https://www.absym-bvas.be/ 2 hits	
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Belgium

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Appendix C: 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. Mamani et al., 2013; Pauwells et al. 2014; Dobrzykowski et al., 2014; Jia and Zhao, 2017; Settanni et al., 2017; Duijzer et al., 2018) 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. 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 2 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 2: 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 master file including our coding of each article is available upon request.

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