Commentary

Sum of the parts: Ensuring a resilient global drug supply chain

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Drugs are a cornerstone of disease treatment and prevention. Worldwide, most people use medications, a mean of 1.6 medications daily.[1] However, most countries do not produce drugs domestically; they depend on a global supply chain. A single pill taken by a patient in country A, was likely produced in country B with the raw active ingredients (ie, active pharmaceutical ingredients or APIs) produced in country C, using nonmedical components from country D and chemical components from even more countries. Thus, the availability of 1 pill may be influenced by events occurring in many different countries. Of drugs consumed in most developed countries, 90% of the APIs are made in foreign facilities (80% in China and India).[2] Concerningly, for 90% of drugs, all the APIs are manufactured at a single facility where a single event can disrupt production. Manufacturers then produce finished dosage forms (FDFs) from this API (eg, tablets), and 60% of FDFs are made in foreign facilities.[2]

Due to this complexity of drug supply, the disruptions that lead to drug shortages are a complex global issue that can be affected by a variety of factors from geopolitical issues, trade, civil unrest, weather, and pandemics.[3] Drug shortages are increasingly common. Over the last decade, the number of drug shortages has increased dramatically, especially in outpatient settings.[2] A drug shortage is defined as a situation where a patient is unable to access an interchangeable version of a medication due to supply limitations.[2] Drug shortages can present in a variety of ways, ranging from temporary disruptions to permanent discontinuances. Shortages may arise from several causes, including manufacturing problems, sole-source contracts, and demand increases. Between 2015 and 2017, there were >1,000 drug shortages in the United States, and the annual number is increasing.[3] Treatment discontinuation or alteration due to shortages can have clinical consequences. Thus, studies have raised concerns that shortages might be associated with worsening illness and death.[4] Because drug shortages may alter therapy by forcing discontinuation or switching, there is a high potential that these shortages may lead to negative outcomes. Indeed, drug discontinuation (often due to nonadherence) is associated with increases in therapy failure, hospitalization, and death.[5,6]

Coronavirus disease 2019 (COVID-19) has significantly influenced drug manufacturing; Chinese API manufacturers closed and the European Union and Indian governments prohibited drug export as a result of the pandemic.[7,8] These issues combined with news of patients and organizations stockpiling drugs may have worsened the already strained drug supply chain.[9] Prior to COVID-19, drug shortages disproportionately affected antimicrobials, central nervous system medications, and cardiovascular medications.[2] Many of these drugs are included in the World Health Organization list of essential medicines.

To tackle this problem, we need to understand and account for the risk. Much of the discourse in the literature of developing essential medicines lists has been focused on clinical risk but little attention has been given to supply chain risk. Importantly, solutions for this problem will have to account for both. Recent work in the United States has suggested that the development of parteo-improving contracts (ie, contracts that account for supply chain quality) may lessen the incidence of drug shortages.[10] For example, the Veterans' Health Administration, the largest health system in the United States, has attempted to account for supply-chain quality in the drug formulary (uncommon practice in US health systems).[10] Additionally, recent European guidelines suggest the development of risk measurements on the potential impact of shortages for all formulary-listed drugs.[11] Better understanding our supply chain and the potential weaknesses should be the cornerstone of all strategies to tackle this problem.

Several steps are involved in the drug supply chain, from drug manufacturing through distribution, ending with prescription dispensing (Fig. 1). Internal and external supply-chain factors can lead to shortages and ultimately impact outcomes.[4,12,13] Supply factors drive the supply chain to provide medications to patients while demand factors influence production. There are 2 main types of drug supply-chain uncertainty and risk: internal risks (eg, quality) and external risks (eg, the pandemic). The ability (or resilience) of the supply chain to manage and provide a timely response to both internal and external risks may ameliorate negative outcomes (eg, patient harm) of unanticipated events.[3,14]

Drug shortages are a global issue, and considering and accounting for the coordination of global drug distribution systems will be essential for any relevant solutions. Our current pandemic has shown us even more the potential flaws in our current distribution systems. An international unified approach is critically needed to mitigate drug shortages.

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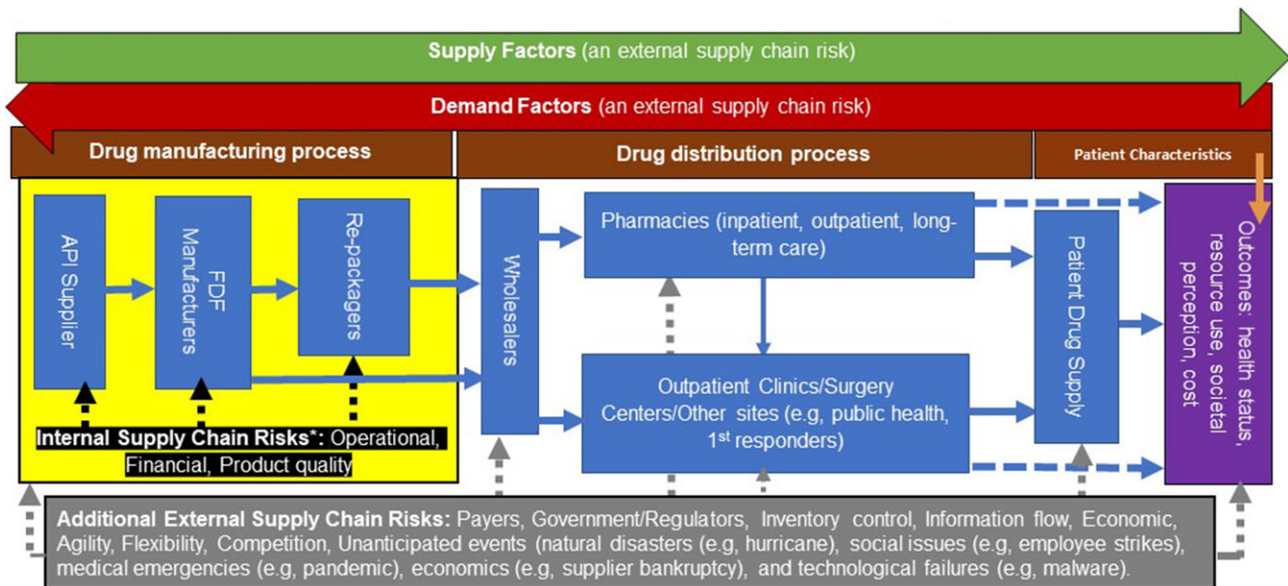**Fig. 1.** Factors associated with drug supply disruption, association with patient characteristics, and impact on outcomes.

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