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COMMENTARY

Managing medication supply chains: Lessons learned from Taiwan during the COVID-19 pandemic and preparedness planning for the future

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ABSTRACT

Coronavirus disease 2019 (COVID-19) has posed unprecedented challenges for nations worldwide, among which medication shortages can cause a devastatingly negative impact on global health. Using Taiwan as an example, this report describes the sources of potential medication shortages, discusses the preparedness and contingency strategies to address medication shortages, and outlines the evidence-based recommendations on ensuring a stable medication supply and improving the quality and security of medicines.

Many drug shortages have focused on shortfalls of overseas manufacturing, but the effect of the COVID-19 crisis on misallocation of medications within the nation's internal supply chains is also a great concern. A wide range of stakeholders are involved in pharmaceutical supply chains, including government regulators, health care insurers, pharmaceutical companies, frontline physicians and pharmacists, patients and families, professional and patient associations or unions, and even individuals who acquire medications from abroad. Collaborative inputs and efforts from all these interdependent stakeholders are critical for establishing transparent preparedness and contingency plans to address drug shortages affected by disruptions of overseas manufacturing or stockouts in pharmacies owing to medication misallocation. Strategies have been documented and recommended in Taiwan and the United States to mitigate drug shortages and ensure the long-term quality and security of medicines.

Barriers to accessing medicines are nothing new, but the COVID-19 pandemic poses urgent and even novel challenges to the stability and integrity of medication supply, which urges for a need to reconsider and reinforce effective management strategies for pharmaceuticals. Active management, transparent information, and timely communications are essential to ensure a stable supply of key therapeutic medications, especially during a pandemic.

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The novel coronavirus disease 2019 (COVID-19) has posed unprecedented challenges for nations worldwide, among which medication shortages can cause a devastatingly negative impact on global morbidity and mortality.¹ As the COVID-19 pandemic disrupts factories, many countries have placed restrictions on shipping or exporting pharmaceuticals.² Taiwan has emerged as a global model in the battle against COVID-19 by effectively containing the large-scale community spread of infection through a combination of efforts by public

and private sectors of the society.^{3–6} These include the use of big data analytics, innovative health information technology, smart contact tracing, proactive testing, and quarantine or isolation-treatment; the activation of Taiwan's strong health care, public health, and social care systems and of advance pandemic preparations and planning made through experiencing the severe acute respiratory syndrome epidemic in 2003; and the prevalent awareness and collaborative efforts of the general public.^{3–6} As of September 4, 2020, Taiwan has fewer than 500 confirmed cases with only 7 deaths among its roughly 23.8 million residents. Despite its early success, as the COVID-19 pandemic continues and probably recurs, all countries, including Taiwan, need to reconsider and reinforce their pharmaceutical management strategies to prevent medication shortages that may loom ahead. Failure to do so can lead to unnecessary and preventable deaths, particularly among individuals with chronic diseases.

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Key Points**Background:**

- The coronavirus disease 2019 (COVID-19) pandemic has posed unprecedented challenges for nations worldwide, among which medication supply shortages can cause a devastatingly negative impact on global morbidity and mortality.
- Even though many of medication supply chain disruptions have focused on shortfalls of overseas manufacturing, the impact on misallocation of medications within the nation's internal supply chains is also a great concern.
- Taiwan has emerged as a global model in the battle against COVID-19 by effectively containing the large-scale community spread of infection through a combination of efforts by public and private sectors of the society.

Findings:

- Collaborative inputs and efforts from all interdependent stakeholders in pharmaceutical supply chains are critical for establishing transparent preparedness and contingency plans to address drug shortages affected by disruptions of overseas manufacturing or stock-outs in pharmacies due to medication misallocation.
- Strategies have been documented and recommended in Taiwan and the United States to mitigate drug shortages and ensure the long-term quality and security of medicines.
- Active management, transparent information, and timely communications are critical to ensure a stable supply of essential therapeutic medications, especially during a pandemic.

COVID-19 crisis, hospital pharmacies may pose an increased risk of viral transmission owing to a large influx of crowds seeking health services and filling their prescriptions in hospitals. Therefore, patients would be advised to have their prescriptions filled in community pharmacies, which could increase dispensing services in community pharmacies. This could exacerbate the shortage of medications in community pharmacies owing to misallocation of medications. To address this, the government considers relaxing the typical refill policies, so patients with chronic illnesses do not have to pick up medications as often during the COVID-19 epidemic. To avoid medication hoarding by patients, the real-time Taiwan National Health Insurance (NHI) reimbursement database could be used to track unusual reimbursement or demand surges for medications.

A wide range of stakeholders are involved in the pharmaceutical supply chains, including government regulators (e.g., Taiwan FDA), NHI administration, pharmaceutical companies, frontline physicians and pharmacists, patients and families, professional and patient associations or unions, and even individuals who acquire medications from abroad. Inputs from all these interdependent stakeholders are important for establishing transparent preparedness and contingency plans to address drug shortages affected by disruptions of overseas manufacturing or stockouts in pharmacies owing to medication misallocation.^{8,9}

Early preparedness and contingency plans to address potential medication shortages

Before the COVID-19 crisis, in 2012, Taiwan FDA had already set up a drug supply and shortage information network in which an online platform is provided for the public to report cases of medication shortages.⁷ Once a case is filed, Taiwan FDA will immediately activate an evaluation and management protocol to identify alternative drugs or therapeutic approaches, confirm stockpile volumes, estimate the time duration of shortages, and, when necessary, initiate nationwide integration and mobilization to start the case-specific manufacture or import procedure. In addition, the frontline clinicians will be officially advised that writing “no alternative drugs allowed” on a prescription is prohibited unless the specific drug or formulation is a must necessity and non-replaceable for the individual patients.

As early as late January 2020, Taiwan FDA has held joint meetings with pharmaceutical manufacturers and commercial associations and initiated multiple strategies as early and proactive measures in response to potential pharmaceutical shortages due to the COVID-19 crisis, including (1) inventory checking for identifying and tracking medications likely to have shortages, (2) identification of alternative sources of APIs or medications, (3) expedited review of applications for relevant APIs, (4) establishment of financial stimulus and reimbursement plans to relieve the cost burden of identifying and using alternative sources, and (5) reinforcement of the supply-demand balance ruling to ensure the rational distribution, allocation, and stockpile of medications.⁷ The government has been strengthening risk communications about medication shortages by providing updated information through multiple channels, releasing news reports and announcements, holding press conferences, and continuously tracking public opinions

Sources of potential medication shortages

Similar to many countries, up to 40% of medications in Taiwan rely on active pharmaceutical ingredients (APIs) produced in China.⁷ In mid-March 2020, to reassure the public, Taiwan Food and Drug Administration (FDA) announced that medications are not under a threat of sudden shortages or supply chain disruptions because pharmaceutical companies have up to 6-month stockpiles of ingredients, most of which can be obtained from alternative sources. However, if the COVID-19 pandemic persists, certain medications may be in short supply, such as antihyperthyroid, cardiovascular, anti-epileptic, and antidiabetic agents, and the costs may increase substantially by 30% or more for alternatives.

Although many drug shortages have focused on shortfalls of overseas manufacturing, the impact of the COVID-19 crisis on misallocation of medications within Taiwan's internal supply chains is also a great concern. With a consideration of pharmaceutical arbitrage, drug companies have thus tended to distribute a much higher proportion of medications to hospital pharmacies than to community pharmacies. During the

Table 1
Recommended strategies to mitigate drug shortages, avoid medication misallocation, and ensure the long-term quality and security of medicines

Strategy	Description
Strategies to ensure the adequate pharmaceutical supply and improve the long-term quality and security of medicines	<ul style="list-style-type: none"> • Consider medicines and their components as a strategic asset instead of a commodity • Improve tracking and forecasting of the antimicrobial supply chain • Create an Essential to National Security drug supply list that includes medications for which a supply interruption could cause an immediate risk to public health • Provide economic and policy incentives for the immediate restitution of pharmaceutical manufacturing capability to the nation • Strengthen the government oversight of drug manufacturers and overseas facilities • Improve testing of imported medications • Establish and maintain certain vulnerable pharmaceutical agents within the strategic national stockpile • Improve inventory management along supply chains
Strategies to mitigate drug shortages and avoid medication misallocation recommended by THRF-TAPO, Taiwan FDA, and Taiwan pharmacist professionals and associations	<ul style="list-style-type: none"> • For governmental agencies: <ul style="list-style-type: none"> - Establish appeal and referral pathways for patients who cannot fill the prescriptions - Establish the reporting and counseling system for adverse effects resulting from alternative drugs or therapeutics - Display a warning for medications being of a shortage concern on i-Cloud/electronic prescription records to inform clinicians and pharmacists - Implement a real-time, open tracking system for the supply-demand status to timely adjust distribution and allocation of medications - Reinforce the audit procedure to ensure the supply-demand balance of medications - Broaden the supply chains of essential medicines instead of having the pharmaceutical industry be dependent on only 1 or 2 countries - Increase domestic production of medicines to protect the supply chain and product availability from unpredictable global crisis events - Continue refining pharmaceutical administration and laws to perfect the systems of the distribution, allocation and dispensing of medications • For pharmaceutical companies: Recognize and strictly follow the rational drug allocation guidelines issued by Taiwan FDA • For hospital pharmacies: Avoid excess stockpiles of medications and serve as the satellite pharmacies between pharmaceutical companies and community pharmacies to enhance sufficient medications allocated to community pharmacies • For pharmacists and their associations: Step up to the plate and work more closely with relevant stakeholders to address misallocation of medications

Abbreviations used: THRF, Taiwan Healthcare Reform Foundation; TAPO, Taiwan Alliance of Patients' Organizations; FDA, Food and Drug Administration.

to proactively respond or clarify when necessary. These actions serve to increase public awareness of issues related to drug supply, fight against disinformation, and respond to public opinions in a timely manner.

Furthermore, to avoid misallocation and excess stockpiles of medications among health care facilities (i.e., hospitals, community pharmacies, and primary care clinics), Taiwan FDA has successively issued 2 official guidelines specific for managing drug supply and misallocation during the COVID-19 crisis.^{10,11} The guidelines clearly define principles of how pharmaceutical companies should supply and distribute medications as well as how health care facilities should purchase and stockpile medications. Per these guidelines, central health authorities can inspect and track the status of medication management by pharmaceutical companies and impose legal liability by laws if a violation is found, and in addition, an official e-mail address is provided to the public for reporting cases of misallocation and irrational stockpiles of pharmaceutical products.

Yet, there may be demand surges for specific medications based on emerging evidence or hearsay of benefits for fighting COVID-19, such as remdesivir and hydroxychloroquine. Recent data have suggested that remdesivir not only shortens time to recovery but reduces the likelihood of dying of COVID-19 in adults hospitalized with moderate-to-severe COVID-19 disease and can halt replication of COVID-19 virus growth in human lung cells and mice.¹² Hydroxychloroquine, however, does not reduce symptom severity or improve clinical status among outpatient adults who are symptomatic with early COVID-19 or adults hospitalized with mild-to-moderate

COVID-19, and it may produce a higher rate of cardiac and liver adverse effects.^{13,14} Nevertheless, Taiwan's government has been preparing for production of these 2 drugs. Two Taiwanese research teams have successfully synthesized remdesivir and can help with mass production of the drug through technical transfer in support of the nation's epidemic prevention and control.¹⁵ In addition, Taiwan is among the world's top manufacturers of the API for hydroxychloroquine, and with an agreement with Taiwan's government, the manufacturer can step up production to prioritize the offer of sufficient drugs to people in Taiwan and then export to help other countries if the drug is in short supply.

Recommended strategies to ensure access to medications and improve management of medication supply chains

To address the root causes of drug shortages, the inter-agency Drug Shortage Task Force led by U.S. FDA offered 3 recommendations.¹ First, there is a need of creating a shared understanding of the impact of medication shortages on patient outcomes, health care delivery, and health care costs and of the contracting practices that may contribute to shortages. Second, the government should develop a rating system to incentivize pharmaceutical manufacturers to invest in achieving a mature quality management system for their facilities. A basic quality management system focuses on current good manufacturing practice (CGMP) compliance; however, adherence to CGMP standards is only foundational and not sufficient. A mature quality management system builds in the

following elements: vigilant attention to upgrading facilities and equipment; training of employees to promote their understanding and contributions to the quality, product, and manufacturing process; ongoing monitoring of manufacturing processes and laboratories using statistical-based methods; and use of risk management practices, all of which exceed the explicit requirements currently stated in the CGMP. Third, there is a need of promoting sustainable private sector contracts (e.g., with payers, purchasers, and group purchasing organizations) to ensure that there is a reliable supply of medically important drugs. Moreover, several strategies^{8,16} can be adopted to mitigate drug shortages, avoid medication misallocation, and ensure the long-term quality and security of medicines (Table 1). The government must also create pathways for health care facilities, especially community pharmacies, to obtain sufficient medications because leaving it to the free market would cause price gouging that is immoral and puts health care workers and patients at risk. The government can consider invoking the legal act with the involvement of health care, industry, and economics experts and set profit limits on medications. Furthermore, as in any preparedness plan, it is essential to perform regular inventory checks of medications and run drills on distributing and allocating medications.

Conclusion

As of September 4, there is no known nationwide essential shortage of medications in Taiwan. There are local stockout events occurring mostly in community pharmacies owing to long-standing distribution issues resulting from nontransparent price negotiation and strong profit competition among stakeholders, etc. Implementing additional recommended measures may be necessary to prevent worsening of local shortages.

As General Dwight D. Eisenhower states, “Plans are useless, but planning is indispensable.” During this unprecedented global health crisis, countries should take actions to understand their pharmaceutical supply chains and develop comprehensive preparedness and contingency plans to allow a rapid response for managing unforeseen medication shortages. In the United States, pharmaceutical benefits managers (e.g., CVS Health/Caremark, OptumRx, IngenioRx, Express Scripts, Humana Pharmacy Solutions) who serve as intermediaries between drug manufacturers and pharmacies, may have significant behind-the-scene functions in determining drug costs for insurers and access of medications for patients. Active management, transparent information, and timely communications are critical to ensure a stable supply of essential and key therapeutic medications, especially during a pandemic.

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