Doctopic: Analysis and Interpretation

12_09 Essay Duffin

PII

# The art of medicine

## An activist history of drug shortages and its silos

Her pale green eyes expressed utter fear, but she was adamant that her chemotherapy must stop. At 50 years old, Heather was a widow with two daughters and metastatic breast cancer. The prochlorperazine controlling her nausea, was unavailable, and nothing else seemed to work for her. Doubting that such an old drug could be unavailable, I rang her pharmacist, demanding an explanation. "That's right, doctor", the harried man replied. "There's none in our city, but you can prescribe...", and he listed other, pricier drugs, all ineffective for Heather. It was 2010, and Heather had just introduced me to one aspect of drug shortages. The historian in me wanted to uncover what caused these shortages; the physician wanted to fix it. Those motives coalesced into my activist efforts on this issue; however, despite a decade of hot pursuit, neither goal has been reached.

A decade later, we face the COVID-19 pandemic, and drug shortages are in the news for various reasons. Demand increase is one cause: the slightest hint that a drug might work causes panic buying and dwindling stocks, depriving those who need it for other conditions: hydroxychloroquine, remdesivir, and agents used in the intensive care unit. Shortages of raw materials or active pharmaceutical ingredients disrupt manufacturing downstream. Border closures interfere with shipping. But drug shortages have been raging for a decade or more. The COVID-19 pandemic has amplified and exposed a long-standing problem.

Back in 2010, staff in our cancer clinic wrote to alert Canadian health ministers about the problem of drug shortages. No replies came. I kept pulling on the thread. By 2011, I had so much information that a local politician suggested that I make an information website. The website became a filing cabinet for compiled evidence. Mostly it is ignored, except by random journalists or frustrated patients who blog their experiences. But, I still update it every morning. Maintaining my website illustrated the global dimensions of the problem. Initially planning to focus on Canada, I soon realised that the problem did not originate there and could not be solved there. Now it tracks news from 110 countries.

**Further reading**

Bruhn WE, Fracica EA, Makary MA. Group purchasing organizations, health care costs, and drug shortages. *JAMA* 2018; **320:** 1859–60

Burki T. Brexit and medicine shortages in the UK. *Lancet* 2018; **394:** 1218

Ashraf Shazly/AFP/Getty Images

Drugs in shortage vary by country. COVID-19 has its own array. Last year, in North America, there were, among others, shortages of vincristine for childhood leukaemia, of tamoxifen, etoposide, and BCG immunotherapy for other malignancies, and of drugs for hypertension, heart disease, arthritis, allergies, and epilepsy. During 2019, there were also shortages of some vaccines in India, of antidepressants in South Africa, and of drugs for tuberculosis and HIV in Kenya. A leaked document in November, 2019, from the UK Department of Health and Social Care described "unprecedented" shortages of medications for some cancers, arthritis, Parkinson's disease, and certain mental illnesses. In short, the drugs that become intermittently unavailable in any given country are the drugs that it needs; many of the drugs are generic.

Noticeable silos exist in relation to drug shortages. The silos extend beyond borders. Shortages are defined, explained by, or blamed on the latest, local issue—all probably true to some extent, but confined in another kind of silo, built of politics, economics, and perceived morality. In different countries different issues have been raised to explain drug shortages, ranging from pharmaceutical company practices, mismanagement, corruption, poverty, and political contexts and sanctions. In the UK, among the factors raised to explain drug shortages have been uncertainties and stockpiling related to Brexit and post-Brexit events. Moral sanctions have featured in debates about the scarcity of lethal drugs for executions in the USA; here alone, shortages save lives as executions are deferred. In retaliation, some US states consider reviving old methods of killing rather than bend to the objective of reconsidering the death penalty.

Silos are also constructed by professions as they seek to explain drug shortages. Doctors may blame pharmacists and the pharmaceutical industry. Pharmacists may blame governments. Industry may also blame government for too stringent regulations, and a 2012 US Congressional report blamed Food and Drug Administration (FDA) inspections of factories. But by 2019 an FDA report on root causes of drug shortages, largely blamed the global trading system and the too-low prices of generics that prompt drop-out of manufacturers, leading to the precarious situation of single supplier, which an inspection or a hurricane can quickly turn into a severe shortage. Some business journalists blame the anti-trust practices of US group purchasing organisations. It is also fashionable in some quarters to blame China or India for increasingly being the providers of raw materials

of sometimes questionable quality. Well intentioned doctors and their embrace of clinical practice guidelines might also have a role. For example, as physicians stopped prescribing β blockers for first-line antihypertensive therapy, prescriptions and sales plummeted, which could have contributed to subsequent shortages in Canada.

Vexingly, interest groups, including physicians, incensed over one shortage or another, can lose interest when their own issue is resolved. They may overlook connections underlying shortages between specialties and jurisdictions. My website lists many potential causes of drug shortages, including those seen in the COVID-19 pandemic. Among these potential causes are market increase; absence or contamination of raw materials; import–expert pressures; drug pricing; moral sanctions; natural disasters; declining numbers of manufacturers; and manufacturing difficulties, such as deviation from industry norms identified by government inspectors. Each element is capable of producing or aggravating a drug shortage; most shortages probably result from permutations and combinations of several causes.

Pharmacists explain that temporary shortages have always occurred, but numbers seem to have increased in the past decade. To confirm that impression, I examined a century of reports on drug shortages in a few newspapers of record: *The Times*, *The New York Times*, and *The Globe and Mail*. There were some sparse reports of drug shortages during wars, embargoes, or economic recessions, but in 2009–10 such reports began to soar. This observation raises as yet unanswered questions about the possible role of the economic crisis of 2008–09.

Drug shortages are unlikely to be solved by or within individual countries. To help build a stronger global dialogue on drug shortages, I suggest four steps that could help.

First, increased efforts are needed to measure drug shortages. Exceptionally, since 2012, the USA releases annual reports through the FDA and occasionally its Government Accountability Office. The two agencies track annual drug shortages and efficiency in managing them. Since March, 2017, Canada requires companies to list drug shortages on a website, without yet publicly analysing the nature or rate of shortages. Since 2018, the European Medicines Agency and the Heads of Medicines Agencies collaborate through a joint taskforce as a clearing house for information about shortages in the EU; national reports were released in 2019, with a centralised list, built as an EU non-profit project. In early 2020, China too promised a state catalogue of drug shortages. Regular analyses of these reports are vital for characterising drug shortages and locating similarities and differences between nations.

Second, every nation should define an essential medicines list. According to WHO, about 120 countries have such lists, dominated by low-income and middle-income countries. Wealthy countries often have formularies generated by smaller jurisdictions or institutions, such as hospitals or distributors, but rarely do they generate lists at the national level based on need. Although essential medicines lists cannot solve shortages, they help manage them, bringing order to the chaos of each sudden absence. They allow for advanced contingency planning and identifying drugs most vulnerable to shortage and by locating substitutes for a future crisis.

Third, we also need to consider why shortages have not resulted in ramped up manufacture of less profitable but effective drugs where they are needed. The response to the COVID-19 pandemic might be starting to have that effect. Aiming to control costs and incentivise neglected innovation, some experts and politicians have called for the creation of nationalised pharmaceutical entities, often spouting protectionist rhetoric. A main objective of the private pharmaceutical industry is to make money; altruism and professional reputation might motivate the industry to sustain or maintain profit loss. But most drug shortages are in off-patent generic drugs without barriers to new producers. Surely some money can be made in satisfying demand, and benefits would include a more stable drug supply. Others have decided to strike out on their own. For example, the US non-profit Civica Rx generic drug and pharmaceutical company, owned by a coalition of health systems, released its first product, an antibiotic, in 2019 and now has about 40 more in the pipeline. Similarly, the “public benefit pharmaceutical manufacturing corporation” Phlow promises to use innovative manufacturing exclusively in and for the USA. This is good news for the owners and US clients, but a drop in the bucket for the rest of us, even as such initiatives suggest one path forward for advocates of domestic drug-making. Canada’s pharmaceutical industry has declined since the 1980s, and it currently reports about 1600 drug shortages, many of which are not related to the pandemic.

Above all, concerted efforts are needed to identify and examine the causes of drug shortages from before and beyond the COVID-19 pandemic. The mystery surrounding the origin of drug shortages is what motivated my project from its inception. Just as physicians cannot treat diseases without first diagnosing them, all actors need to talk openly, without recrimination, across the boundaries of those national, international, and professional silos to expose the reasons for drug shortages wherever they may be.

Heather died with brain metastases in 2012. Perhaps her death was inevitable, but her tremendous suffering was not. It is for her memory and for so many patients like her that I keep tilting against what seems like an inexplicably impenetrable wall.

*Jacalyn Duffin*
Queen’s University, Kingston, ON K7L 3N, Canada
duffinj@queensu.ca

Canadian Drug Shortage. http://www.canadadrugshortage.com/ (accessed Sept 4, 2020)

Donelle J, Duffin J, Pipitone J, White-Guay B. Assessing Canada’s drug shortage problem. Toronto: C D Howe Institute, 2018

Drug Shortages Task Force. Drug shortages: root causes and potential solutions. Washington, DC: US Food and Drug Administration, 2019

Duffin J. Do practice guidelines cause drug shortages? The historical example of beta-blockers. *CMAJ* 2019: **191:** e1029–31

European Medicines Agency. Shortages catalogue. 2020. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/availability-medicines/shortages-catalogue#ema-shortages-catalogue-section (accessed Sept 2, 2020)

Gibson R, Singh JR. China Rx: exposing the risks of America’s dependence on China for medicine. Amherst, NY: Prometheus Books, 2018

Heads of Medicines Agencies, European Medicines Agency. HMA/EMA Task Force on availability of authorized medicines for human and veterinary use. 2020. https://www.hma.eu/522.html#c5765 (accessed Sept 2, 2020)

The Economist. The parrots eat ‘em all; drug shortages. *The Economist*, Sept 14, 2019

Persaud N, Jiang M, Shaikh R, et al. Comparison of essential medicines lists in 137 countries. *Bull World Health Organ* 2019; **97:** 394–404C

Quigley, F. Tell me how it ends: the path to nationalizing the US pharmaceutical industry. *SSRN* 2019; published online Nov 30. http://dx.doi.org/10.2139/ssrn.3496795 (preprint)

Rees V. Leaked document reveals “unprecedented” medicine shortages in the NHS. *European Pharmaceutical Review, News*, Nov 19, 2019

US House of Representatives, Committee on Oversight and Reform. The FDA’s contribution to the drug shortage. Washington, DC: Committee on Oversight and Reform, 2012

Zizhuo C, China to establish state catalog for medicines in short supply, *ECNS News*, Jan 16, 2020