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INVITED REVIEW

Drug shortages. Part 1. Definitions and harms

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Abstract

Drug shortages are repeatedly in the news. The earliest drug shortages were reported during the First World War, but the numbers of shortages have increased in recent years. In the first part of this two-part review, we discuss definitions of drug shortages and so-called stockouts, which are localized shortages, and the harms that they can cause. Drug shortages make it difficult or impossible to meet the therapeutic needs of individual patients or populations, but we lack an adequate definition. The problems are too complicated to be encompassed in a brief intensional dictionary-style definition, and that is reflected in the many different attempts at definition that have been proposed. We therefore propose an extensional operational definition that incorporates the processes by which products are manufactured, the causes of shortages and the contributory factors. A definition of this sort allows one to identify the main causes of a particular drug shortage and therefore the remedies that might prevent, mitigate or manage it. In the second part of the review we discuss the causes and solutions in more detail. Adverse drug reactions and medication errors attributable to shortages occur but are not often reported. Adverse reactions to substitute medicines are possible, and errors can occur because of unfamiliarity or unnecessary treatment with replacement medicines. Other harmful outcomes include withdrawal reactions, undertreatment, treatment delays and cancellations, failure of alternatives and disruption of clinical trials.

KEYWORDS
adverse reactions, medication errors, pharmaceutical preparations, prescription drugs, shortages

1 | INTRODUCTION

Drug shortages are often in the news[1] and are often looked on as a recent phenomenon. However, drug shortages have been with us for a long time. For example, fears of shortages were expressed in the USA as early as 1914, in view of the 'crisis in Europe', and shortages of salvarsan were reported soon after.[2] During the Second World War, there were shortages of potassium salts and squill in the UK in 1941,[3] quinine and mepacrine in India in 1942,[4] and ointment bases, phenol, alcohol, glycerin, liquid paraffin and ascorbic acid in the UK in 1942 and 1943.[5,6] However, shortages have become more common in recent years.

In the first part of this two-part review we discuss how drug shortages are defined and the harms, including medication errors,

which can result. In the second part, we shall discuss the trends in drug shortages, their causes and potential solutions.

2 | METHODS

We consulted three published lists of definitions of drug shortages: the World Health Organization's report of a meeting held on 5 October 2016,[7] an OECD review,[8] and a review based on a literature search.[9] We found 79 English-language definitions, some of which may be variant translations from languages other than English; however, for the purposes of analysis we have treated these as separate definitions.

We searched PubMed, Medline and EMBASE to the end of 2022, initially using the term 'shortage*'. In PubMed, for example, this resulted in over 45 000 hits, many of them nothing to do with drug shortages, too many to review. We therefore limited our search to titles of papers, which resulted in about 6700 hits in PubMed. Searching for 'stockout*' in the same way increased the number by 69 hits. We then used the titles of the papers and their associated MeSH terms to distinguish drug shortages of medications from other types of shortages, such as shortages of food and water, transplant organs, staff, beds or equipment. We also excluded shortages of blood products, radiocontrast media and radionuclides. This resulted in 1297 hits, of which 526 (41%) were about drug shortages in general and the rest about shortage of types of drugs (e.g. antibiotics) or specific drugs. Vaccines accounted for 208 (16%).

Our approach to definition has been published previously[10] and used extensively. It has led to definitions that have been accepted internationally.[11] The method involves analysing how definienda, the terms to be defined, have been used in technical publications, analysing previous definitions for their important contents, choosing terms that have been repeatedly used by others, and the Ramsay–Lewis method, in which the meaning of a term is given implicitly by the relevant scientific theory, including all the assertions that it makes about the term. In this case we have produced an operational definition by using reports of actual cases of drug shortages, extracting their stated causes and the factors associated with them and linking them to the processes of marketing a medicine.

3 | DEFINING DRUG SHORTAGES

There is no general agreement as to what constitutes a drug shortage. Our analysis is based on 79 previously published definitions. Of these, 29 were included in national legislations or were supranational (e.g. from the EU or WHO), 28 were institutional (governmental, e.g. The Food and Drug Administration [FDA], or professional non-governmental, e.g. the International Society for Pharmaceutical Engineering [ISPE]), and 22 were included in various publications on drug shortages.

3.1 | Usage and previous definitions

3.1.1 | Local and general shortages

The term 'drug shortage' is generally used in two ways, in reference to a local shortage of a medication, usually in a pharmacy, when it is also known as a stockout, and to general shortage, either nationally or internationally. These two types of shortage have different implications, since a local shortage may often be overcome by going, for example, to a different pharmacy. Here we are concerned primarily with general shortages.

3.1.2 | Supply and demand

Shortages can be viewed from either the supply side or the demand side. The word 'supply' was included in 45 previous definitions, of which 17 also included the word 'demand'; two included the word 'demand' without mentioning supply. Clearly both are important in any definition.

3.1.3 | Stockout

Of the 79 definitions we surveyed, 14 were actually definitions of a stockout. We regard this term as denoting the complete absence of a medicine from the shelves of any pharmacy that would be expected to stock it. It is variously defined as an inability of a pharmacy to deliver a drug to a patient, zero usable stock, complete absence of a medicine in stock, no 'medicine facility shelf', and absence of a medicine at a health facility level. In at least one specific case it has been defined as either a complete absence or a certain minimum level of stock for a given duration. But a local absence of stock in a pharmacy need not imply a general shortage.

3.1.4 | Pharmacy

Some definitions referred to pharmacies where there is a stockout, but different authors used different terms to qualify the term 'pharmacy' (e.g. 'community', 'hospital', 'dispensary internal use', and 'health facility pharmacy'). Presumably any pharmacy that habitually stocks an item is susceptible to a stockout.

3.1.5 | Patients

Of the 79 definitions, 33 specifically mentioned patients or patient care: none mentioned carers and only one referred to possible effects on public health. Phrases used included: problems with continued treatment; detrimental consequences; affecting patients' ability to access required treatment; compromising or influencing or impacting on patient care; [failure to] meet/comply with patients' needs; [failure

to] meet current projected demand at the patient/user level; and [failure to] meet expected patient volumes. In these paraphrases, we have added the bracketed word 'failure', since no definition mentioned it, even though shortages are often due to failures of some sort, resulting in a failure to meet patients' therapeutic needs.

3.1.6 | Duration

Different definitions offer different time courses over which a medicine is unobtainable in order to define a shortage—at least 1, 3, 4, 14, 20 days, or at least 1 month. Some are vaguer still—'every delay in monthly supply' or 'within a few days'. However, different delays affect different medicines differently, a concept that has been referred to as 'forgiveness', a measure of the length of time a medicine can be omitted without loss of benefit, defined as 'the difference between the medicine's post-dose duration of beneficial action and the prescribed dosing interval'.[12] For example, missing a few doses of insulin may be life-threatening; missing a few doses of a contraceptive pill may result in an unwanted pregnancy; missing treatment with a statin for a few days will not increase the risk of a myocardial infarction or stroke; statins are more forgiving than insulin or oral contraceptives. The significance of duration will therefore differ according to the forgiveness of the drug in short supply.

3.1.7 | Scope

Some definitions, particularly those included in forms of legislation, were framed for the benefit of legal systems and regulators. Some referred to a specific country. Some referred to specific diseases. Few took in a wider purview; only two referred to local, national and international shortages.

In Box 1 we have listed some of the general problems with previously published definitions.

BOX 1 Some general problems with published definitions of a drug shortage.

- Interchangeability of terms meaning different things: shortage, [un]availability, supply disruption/interruption/issue, stockout
- Varying definitions depending on different aspects of the supply chain being addressed—manufacture, distribution, dispensing
- Varying specificity, e.g. in reference to locality, different types of pharmacy, or specific medicines
- Varying timeframes or durations specified or timeframes not specified at all
- The contrast between definitions relating to supply and those relating to demand
- Failure to reflect the importance to the patient
- Varying definitions describing what a shortage is, what a stockout is, and how to recognize a shortage, rather than defining what a shortage is
- Lexicographical problems; for example, many of the statements describe when a drug shortage occurs rather than defining a drug shortage itself (e.g. [a drug shortage] 'occurs when', 'happens when', 'is a situation when')

3.2 | An operational definition

Ideally, a drug shortage would be defined in a single sentence, perhaps with explanatory notes. However, given all the problems discussed above, we believe that it is not possible to frame a satisfactory dictionary definition that could be used to indicate when a shortage has occurred. Consider, for example, the dictionary definitions of 'drug' and 'shortage', both taken from the *Oxford English Dictionary* (*OED*)

> drug, *n.* a natural or synthetic substance used in the prevention or treatment of disease
> shortage, *n.* deficiency in quantity

A definition of a drug shortage could be crafted directly from these two definitions, but such a definition would omit all the major associated details discussed above.

An alternative approach to the problem is via an operational definition, as shown in Figure 1. This definition was constructed in three steps:

(a) by enumerating the main processes whereby a medicinal product is manufactured to an acceptable standard and finally delivered to the patient: obtaining the raw materials, synthesis or extraction of the active ingredients, formulation of the authorized pharmaceutical product, and delivery to a pharmacy, either directly or via a distributor;
(b) by adding the main causes of shortages that have been described and related factors;
(c) by indicating the two main outcomes of failure in the system: stockouts and shortages:
   (i) stockouts, caused by failure at any level, if they affect availability only locally;
   (ii) shortages, caused by national or international failure at any level, leading to an inability to meet the therapeutic needs of a population or individual patients.

This operational definition does not contain the kinds of restrictive stipulations that some other definitions include. For example, a WHO definition[9] stipulated that a medicine must be essential for a shortage to be declared, but did not define 'essential', although elsewhere the WHO has defined an essential medicine as one 'that satisfies the priority health care needs of the population'.[13] And

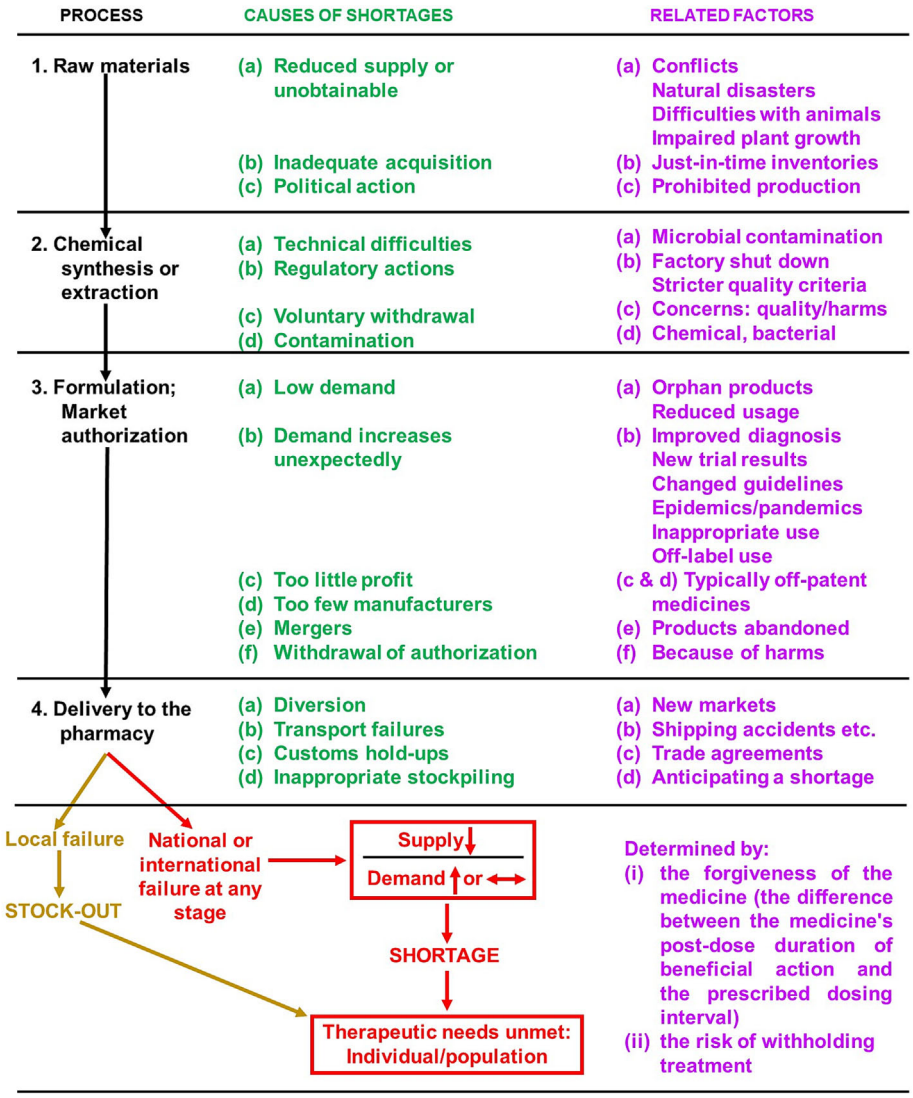

FIGURE 1 The processes are in the left-hand column (black print), causes are in the middle column (green), and related factors are in the right-hand column (purple). Failure at any stage, nationally or internationally, to make a medicine available for longer than the forgiveness of the medicine, thus failing to meet the therapeutic needs of individuals or the population (e.g. vaccination) constitutes a shortage (red). Local failure leads to a stockout (orange). 'Therapeutic' includes the use of medicines in prevention, diagnostic tests, symptomatic relief, replacement therapy, control of disease and cure.

although such medicines are included in the WHO's essential medicines list, their definition of a shortage cannot apply to individual countries, whose essential medicines lists are widely different from each other.[14]

Similarly, the 2012 US Food and Drug Administration Safety and Innovation Act (FDASIA[15]) stipulates that for a shortage to be declared, a medicine should be 'life-supporting', or 'life-sustaining', or 'intended for use in the prevention or treatment of a debilitating disease or condition'. The first two terms have been described as follows[16]: 'Life supporting or life sustaining means a product that is essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life'.

This stipulation serves the purposes of the Act and reflects actions that the regulator and manufacturers should take (e.g. giving advance warning of an expected shortage), but patients might be forgiven for thinking that the definition of a shortage should not be limited to such medicines. A medicine that was useful for treating say, attacks of migraine, would not be encompassed by this definition, but patients who suffer severe frequent attacks and find themselves unable to obtain an effective medicine during a shortage would be entitled to feel that their medicine ought to be included and dealt with in the same way as other medicines.

Note that the operational definition illustrated in Figure 1 does not stipulate the time after which a shortage should be declared. That will depend partly on the forgiveness of the medicine and will differ from medicine to medicine.

4 | HARMS AND ERRORS RESULTING FROM SHORTAGES

It is striking how infrequently clinical harms attributed to drug shortages have been reported, until relatively recently. In illustration of this, consider three papers, published by the American Society of Health-System Pharmacists.

TABLE 1 A summary of 66 unwanted outcomes selectively reported from a database of over 1000 cases reported to the Institute for Safe Medication Practices in 2010.[25]

Type of outcome	Number of cases (%)	Example
Adverse reactions to substitute medicines (dosage error)	16 (24)	During a shortage of propofol, dexmedetomidine was given at a rate of μg/kg/min instead of μg/kg/h
Medication errors (wrong dosage of drugs in short supply)	13 (20)	Wrong dose of morphine given because of a switch in strengths
Adverse reactions to substitute medicines (correct dosage)	8 (12)	Gastrointestinal perforation associated with indometacin during shortage of Ibuprofen
Delays in treatment	6 (9.1)	A patient with viral meningitis had to be transported by helicopter from one hospital to another because aciclovir was not available
Medication errors (wrong formulation of drugs in short supply)	6 (9.1)	Bags of heparin, stocked against shortages, were dispensed instead of plain intravenous solutions
Medication errors (wrong drugs replacing drugs in short supply)	5 (7.6)	Hydralazine was given instead of look-alike ondansetron in vials, during shortage of prefilled ondansetron syringes
Undertreatment (drug unavailable)	4 (6.1)	A paralysed, ventilated patient received no sedation during shortage of propofol; no alternative was offered
Undertreatment (use of low dosages for conservation of drugs in short supply)	3 (4.5)	A patient had intraoperative awareness when given too little propofol
Failure of alternatives	3 (4.5)	Inadequate sedation with benzodiazepines during a shortage of propofol
Cancellations	1 (1.5)	Unspecified cancellation of operations and procedures
Unnecessary treatment with alternatives	1 (1.5)	General anaesthesia was used when alternatives to propofol failed to produce adequate sedation

- The first, 'ASHP Guidelines on Managing Drug Product Shortages' (2001), discussed the causes of shortages under 11 headings and actions that might be taken under 13 headings.[17]
- The second, 'ASHP Guidelines on Managing Drug Product Shortages in Hospitals and Health Systems' (2009), introduced only minor changes and added a diagram detailing processes for decision-making in the management of shortages.[18]
- In the third, 'ASHP Guidelines on Managing Drug Product Shortages' (2018), there were more major headline changes, and this time a completely new section, titled 'Patient safety', with references from 2010 onwards.[19]

In our review of the literature published since the year 2000, 1297 papers in all, we found that, in addition to frustration and anxieties, drug shortages can cause four types of clinical harm:

- failure to treat conditions properly, with delays and suboptimal treatment or none;
- withdrawal effects (e.g. during shortage of heroin)[20];
- adverse effects of substitute medications;
- medication errors, particularly when the substitutes are unfamiliar.

In addition, extra monitoring[21] and referrals to other facilities[22] may be required, clinical trials may be disrupted because of reduced recruitment,[23] and drug expenditure may increase.[24]

In some cases authors have reported observing few if any harms as a result of shortages. Publication bias, in the form of failure to publish studies that show harms, leading to underestimation of harms, may have affected studies of drug shortages. However, harms do occur, as the examples in Table 1 show.[25]

Occasionally drug shortages might prove beneficial, through unavailability of ineffective or harmful treatments. For example, during a shortage of noradrenaline, 214 patients with severe sepsis or septic shock were either given noradrenaline ($n = 106$) or not ($n = 108$).[26] A retrospective analysis showed that there was no difference in ICU length of stay after controlling for differences in intensity of the illness (APACHE II score), age, weight and sex; however, those who were *not* given noradrenaline were more likely to survive (odds ratio [OR] = 5.9; 95% confidence interval [CI] = 3.1, 11). But perhaps the difference was accounted for by the higher serum lactate concentrations in the treated group, which were not controlled for. In another study of septic shock, noradrenaline shortage was associated with increased mortality.[27]

5 | CONCLUSIONS

Shortages of medicines harm and worry patients, increase the risk of medication errors and impose administrative and financial burdens on healthcare.

The overall costs to patients and healthcare systems cannot be quantified without clear definitions and good data.

Because it is hard to provide a clear definition of a drug shortage, one that would clearly specify the circumstances in which a shortage could be recognized as having occurred, we have proposed an

operational definition that could be used to do that, without imposing regulatory restrictions that fail to take the needs of individual patients into account. This definition also allows potential solutions to be mapped onto likely causes.

The causes of drug shortages are complex, and some—such as natural disasters—cannot be predicted. When they can be predicted (for example, because a manufacturer plans to cease production), they could and should be mitigated.

When drugs are, in some sense, essential, there is a strong argument for increasing stocks, and possibly for assuring domestic manufacture, especially if there are no suitable alternatives. The definition of 'essential' will vary according to local healthcare requirements and individual patients' views of their needs for treatment.

AUTHOR CONTRIBUTIONS

Jeffrey K. Aronson and Robin E. Ferner performed literature searches; Jeffrey K. Aronson wrote the first draft; all authors contributed to the writing of the final paper.

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- Explaining drug shortages. 18 October 2019. https://blogs.bmj.com/bmj/2019/10/18/jeffrey-aronson-when-i-use-a-word-explaining-drug-shortages
- Drug shortages: harms and errors. 25 October 2019. https://blogs.bmj.com/bmj/2019/10/25/jeffrey-aronson-when-i-use-a-word-drug-shortages-harms-and-errors
- Drug shortages: solutions. 1 November 2019. https://blogs.bmj.com/bmj/2019/11/01/jeffrey-aronson-when-i-use-a-word-drug-shortages-solutions
- Defining drug shortages. 8 November 2019. https://blogs.bmj.com/bmj/2019/11/08/jeffrey-aronson-when-i-use-a-word-defining-drug-shortages
- Drug shortages: an operational definition. 15 November 2019. https://blogs.bmj.com/bmj/2019/11/15/jeffrey-aronson-when-i-use-a-word-defining-drug-shortages-operational-definition
- Expiry dates of medicines. 29 November 2019. https://blogs.bmj.com/bmj/2019/11/29/jeffrey-aronson-when-i-use-a-word-expiry-dates-of-medicines
- Problems with expiry dates of medicines. 6 December 2019. https://blogs.bmj.com/bmj/2019/12/06/jeffrey-aronson-when-i-use-a-word-problems-with-expiry-dates-of-medicines

CONFLICT OF INTEREST STATEMENT

JKA and REF have no direct competing interests; they have both written articles and edited textbooks on adverse drug reactions and have acted as expert witnesses in civil and coroners' cases involving such reactions. CH holds grant funding from the NIHR, and the NIHR School of Primary Care Research; he has received financial remuneration for legal advice and has received expenses and fees for his media work.

DATA AVAILABILITY STATEMENT

The results of searches used in this review are available on request from the corresponding author.

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