Canada's Drug and Health Technology Agency

CADTH Health Technology Review

Drug Shortages and Patient Harms

Technology Review

Authors: Lindsay Ritchie, Jennifer Horton

Contributors: Chris Kamel, Anusree Subramonian, Kendra Brett

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to **requests@cadth.ca**

Key Messages

What Is the Issue?

- Drug shortages are a global issue with complex dynamics. Shortages can occur due to disruption at any point along the drug supply chain. Several strategies are used in Canada to prevent or alleviate the effects of drug shortages, including mandatory reporting by drug manufacturers.
- An understanding of the amount and types of real or potential harm caused to patients can inform policy decisions around drug shortage management and prevention.

What Did We Do?

- We searched for literature providing evidence on patient outcomes associated with supply chain disruptions of pharmaceuticals and vaccines. An information specialist conducted a search of peer-reviewed literature sources published between January 1, 2003, and September 13, 2023.
- Documents were excluded if the objective was to investigate the potential effects of a drug shortage in the absence of an actual drug shortage or if the outcomes were not direct patient harms.

What Did We Find?

- One scoping review and 33 non-randomized studies were identified that evaluated patient outcomes associated with supply chain disruptions of pharmaceuticals and vaccines.
- We identified a wide variety of drug classes experiencing shortages. The most frequently reported shortages were anesthetics, oncology drugs, vaccines, drugs for the treatment of COVID-19, antimicrobials, and small-volume parenteral solutions.
- Most of the included primary studies concluded that the replacement drug or protocol was a safe or acceptable alternative to the shortage drug. The subset of primary studies that concluded that the replacement drug or protocol was not a safe or acceptable alternative to the shortage drug reported worse outcomes in health system usage (including length of hospital stay), adverse events, disease progression, and mortality.

What Does this Mean?

- Drug shortages have the potential to cause harm to patients and some drug shortages may have a greater impact on patients than others. The ability to predict which drugs could cause the greatest harm during a supply disruption would be a great benefit for future planning.
- The diversity of drugs experiencing shortages and their associated harms emphasizes that decision-makers may need to take a case-by-case approach when developing policies meant to lessen the impact of drug shortages.

Context and Policy Issues

What Is the Problem?

Drug shortages are a global issue with complex dynamics. Between 2022 and 2023, over 2700 drug shortages were reported to Health Canada, lasting an average of 98 days.[1] Of these, 34 were considered high impact: shortages with the greatest potential consequences to people and healthcare systems (e.g., no therapeutic alternatives available).[1,2]

There are multiple steps along the drug supply chain, including:

- Drug development and regulatory approval
- Manufacturing
- Purchase and distribution
- Delivery to hospitals, pharmacies, and patients[3]

Interruptions to any of these phases can cause a shortage. For example:

- Good Manufacturing Practice non-compliance leading to recalls
- Non-profitable drugs leading to decisions to cease production
- Stockpiling of medication
- External factors, such as a natural disaster[3,4]

In addition, weak points in the supply chain, such as relying on the supply of drugs from a single source or not having protocols in place to respond to increases in demand, can also cause or worsen existing drug shortages.[3,4]

What Is the Current Practice?

Strategies currently used in Canada to attempt to prevent or alleviate drug shortages include:

- An expedited drug review process to accelerate Health Canada approval of substitute drugs in urgent circumstances
- Quality assurance protocols in drug manufacturing
- Development of ethical frameworks for resource allocation
- Compounding drugs
- Rationing protocols at the hospital and pharmacy level[3]

Furthermore, in 2017, mandated reporting of drug shortages went into effect.[2] Drug manufacturers are required to report anticipated shortages or discontinuations, ideally 6 months in advance, to allow time to put into place mitigation plans. Manufacturers are also required to report actual shortages as soon as they are aware of them.[2]

Why Is It Important to Do This Review?

People can experience clinical harm resulting from drug shortages. This can take several forms:

- Inadequate treatment or management of health conditions
- Withdrawal-related side effects
- Adverse or safety events associated with replacement drugs
- Medication errors[4]

Some drugs have the potential for much greater patient harm if they become difficult to obtain. For example, shortages of drugs with life-saving benefits or strict dosing schedules might have more impact on patient outcomes, especially if there are no alternative options available.[2,4]

This report is the first in a series of CADTH-published initiatives that aims to emphasize potential priority medications and to ultimately support decision-making during drug shortages.

Objective

The purpose of this report is to summarize the evidence on patient outcomes associated with supply chain disruptions of pharmaceuticals and vaccines.

Research Question

What is the evidence on patient outcomes associated with supply chain disruptions of pharmaceuticals and vaccines?

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources including MEDLINE and the Cochrane Database of Systematic Reviews. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concept was drug shortages. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or indirect treatment comparisons; any types of clinical trials or observational studies; real-world evidence using routinely collected data; or to the Canadian context. The search was completed on September 13, 2023 and limited to documents published since January 1, 2003.

Selection Criteria and Summary Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1. Information from the relevant studies was extracted into summary tables and organized by broad clinical indication categories by 1 reviewer. Data were extracted on the study characteristics, shortage drug and its substitute, if applicable, findings that related to direct patient harms, and overall conclusion. Outcome results and their direction of effect were briefly summarized as reported by the study's authors and categorized into the following: no difference, worse, improved, or mixed between groups (e.g., in studies with multiple comparator groups, an outcome may improve in one group but worsen in another). No formal critical appraisal (e.g., risk of bias assessment) of the included studies was conducted.

Table 1: Selection Criteria

Criteria	Description
Population	General population
Concept	Supply chain disruptions of pharmaceuticals and vaccines
Outcomes	Patient harms (e.g., mortality, emergency department visits, hospitalization rates, adverse events)
Study designs	Health technology assessments, systematic reviews, scoping reviews, non-randomized studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2003.

Studies were excluded if:

- the natural effects of a drug shortage could not be observed due to the study design (e.g., randomized controlled trial)
- the shortage product was a multivitamin, supplement, homeopathic medication, or device
- the purpose of the study was to investigate the potential effects of a drug shortage in the absence of an actual drug shortage (e.g., anticipatory)
- the primary or secondary outcomes were not direct patient harms (e.g., studies that reported treatment delays without describing a direct measurable effect to patients were excluded)

Due to the large volume of potentially relevant articles identified for full-text review, those published prior to January 1, 2018, were excluded. A list of the articles published prior to 2018 that were identified for full-text review, but not screened for inclusion and exclusion criteria, can be found in Appendix 2.

Overall Summary

Quantity of Research Available

A total of 1871 citations were identified in the literature search. Following screening of titles and abstracts, 1742 citations were excluded and 129 potentially relevant reports from the electronic search were retrieved for full-text review. Of these potentially relevant articles, 95 publications were excluded for various reasons, and 34 publications met the inclusion criteria and were included in this report. These comprised 1 scoping review and 33 non-randomized studies.

Appendix 1 presents the PRISMA[5] flowchart of the study selection. Additional references of potential interest are provided in Appendix 2.

Summary of Study Characteristics

The scoping review by Phuong et al. (2019)[6] included 40 studies. Sixteen primary studies published between 2006 and 2017 met the inclusion criteria for this report. Of these, 3 were prospective cohorts and 13 were retrospective cohorts. The authors of the scoping review were from Australia.[6]

Of the 16 relevant primary studies in the scoping review, 4 were conducted in a surgical setting, 2 in a nonspecific hospital setting, 1 in the intensive care unit, 1 in an air medical setting, and 8 did not specify a setting.[6]

The 33 included primary clinical studies comprised 1 registry study,[7] 5 prospective cohort studies,[8-12] and 27 retrospective cohort studies.[13-39] Two studies were published as research letters.[8,30] The studies were published between 2018 and 2023. The primary clinical studies were conducted by authors from the US,[9,10,15-19,21,22,24-26,28,29,31,32,34-37] Canada,[13,20,30,33] France,[7,14,27] Australia,[11,12] Brazil,[23] Democratic Republic of the Congo,[38] Japan,[8] and the Netherlands.[39]

Twenty of the included primary studies compared outcomes between the shortage drug and its substitute before and during a drug shortage period.[13-22,24,26,27,31-35,37,39] Of these, 3 studies had at least one substitute drug group that had a supply disruption and was further compared to an additional substitute drug group.[14,34,39] In Cole et al. (2021), the intervention and comparator groups flipped partway through when supply of the shortage drug resumed, and the substitute drug went into shortage.[10] In Li and Cimino (2020), the study occurred during the drug shortage period and compared patients who continued taking the shortage drug to those who switched to a substitute drug.[28] In van Langenberg et al. (2020), for long-term outcomes, the intervention group was the substitute drug and compared to patients who switched back to the shortage drug when supplied resumed.[11] In this same study, there was no comparator group for short-term outcomes.[11] Nine studies did not have a comparator group.[8,9,12,23,25,29,30,36,38] The registry study aimed to identify adverse drug reactions related to drug shortages and describe the types of drugs and harms involved.[7]

Nine of the included primary studies were conducted in a nonspecific hospital setting,[13,18,22,24,25,29,35,36,39] 6 in the emergency department,[10,15,26,32-34] 5 in the intensive care unit,[17,20,21,27,31] 5 in the community,[8,9,12,30,38] 3 in a surgical setting,[16,19,37] 3 in a hospital outpatient setting,[11,14,28] and 1 in dialysis clinics.[23]

Summary of Findings

The 16 relevant primary studies from the scoping review (SR) are summarized in Table 2. The registry study and 32 non-randomized studies (NRS) are summarized in Table 3.

There was considerable variability in the types of drugs experiencing shortages. Broadly defined categories by clinical indication were identified as follows:

- Anesthetic, analgesic, or sedative medications (SR: 3 studies; NRS: 7 studies)[6,10,17-19,26,34,37]
- Oncology drugs and drugs used in conjunction with oncology drugs (SR: 4 studies; NRS: 5 studies)[6,13,14,28,35,36]
- Vaccines (NRS: 4 studies)[8,9,12,38]
- Antimicrobials, including antibiotics and antivirals, and drugs used in conjunction with antimicrobials (SR: 3 studies; NRS: 3 studies)[6,22,31,33]
- Drugs specific to the treatment or management of COVID-19 (NRS: 3 studies)[20,27,39]
- Drugs that did not fit into the above categories (SR: 6 studies; NRS: 6 studies)[6,11,16,21,23,30,32]
- Non-drug, specifically, small-volume parenteral solutions, which are used to administer intravenous drugs (NRS: 4 studies)[15,24,25,29]

Strategies used to manage drug shortages:

- Alternative drug (SR: 13 studies; NRS: 14 studies)[6,8-14,16,26,30-32,34,37]
- Dose-sparing strategies (e.g., fixed dose) (SR: 1 study; NRS: 3 studies)[6,20,22,38]
- Alternative route of administration (e.g., oral formulations) (NRS: 4 studies)[18,21,35,36]
- Alternative method of administration (e.g., infusion technique) (SR: 1 study; NRS: 4 studies)[6,15,24,25,29]
- None (e.g., no suitable replacement available) (SR: 1 study; NRS: 2 studies)[6,23,33]

- A combination of above, either at the same time or in sequence (NRS: 5 studies)[17,19,27,28,39]

Outcomes relating to patient harms and the direction of effect during a drug shortage period:

- Mortality: No difference (SR: 5 studies; NRS: 9 studies);[6,11,15-17,21,22,24,27,31] Worse (SR: 1 study; NRS: 1 study);[6,20] Improved (NRS: 1 study);[13] Mixed results between groups (NRS: 1 study)[39]
- Hospital admission: No difference (NRS: 1 study);[30] Worse (NRS: 1 study);[11] Mixed results between groups (NRS: 1 study)[34]
- Intensive care unit (ICU) admission: No difference (SR: 1 study; NRS 1 study);[6,34] Worse (NRS: 2 studies)[13,39]
- Emergency department (ED) visit: No difference (NRS: 2 studies);[18,37] Worse (NRS: 1 study)[30]
- Hospital readmission: No difference (NRS: 1 study);[33] Improved (NRS: 2 studies)[18,24]
- Hospital length of stay (LOS): No difference (SR: 3 studies; NRS: 7 studies);[6,17,18,20,22,24,31,35] Worse (NRS: 1 study);[13] Mixed results between groups (NRS: 2 studies)[34,39]
- ICU LOS: No difference (NRS: 4 studies)[17,20,21,34]
- ED LOS: Mixed results between groups (NRS: 2 studies)[10,34]
- Post-anesthetic care unit LOS: Worse (NRS: 1 study)[37]
- Adverse events: No difference (SR: 8 studies; NRS: 17 studies);[6,8,9,12,14-16,25-29,31,33-36,38] Worse in at least one safety outcome (SR: 2 studies; NRS: 5 studies);[6,11,13,19,24,37] Improved in at least one safety outcome (SR: 2 studies; NRS: 1 study);[6,32] Mixed results between groups (NRS: 1 study)[10]
- Disease progression: No difference (SR: 1 study; NRS: 2 studies);[6,27,28] Worse (SR: 2 studies; NRS: 3 studies);[6,11,23,31] Improved (NRS: 1 study)[13]
- Duration of mechanical ventilation: No difference (SR: 1 study; NRS: 2 studies);[6,17,20] Worse (SR: 1 study);[6] Improved (NRS: 1 study)[21]
- Pain: No difference (NRS: 1 study)[17]

Primary study author's conclusions:

- The replacement drug or protocol was a safe or acceptable alternative to the shortage drug (NRS: 26 studies)[8-10,12-18,20-22,24-30,32-36,38]
- The replacement drug or protocol was considered not safe or at increased risk of harmful outcomes (NRS: 6 studies)[11,19,23,31,37,39] The shortage drug class differed for all 6 studies[11,19,23,31,37,39] and was compared to an alternative drug or protocol in 5 studies.[11,19,31,37,39] There was no suitable replacement therapy available in 1 study.[23] For these 6 studies, worsening direct patient harms were reported for the following outcome categories: Health system usage (3 studies),[11,37,39] adverse events (3 studies),[11,19,37] and disease progression (3 studies).[11,23,31] Swets et al. (2023) reported lower survival in 2 of the 3 replacement drug groups compared to the shortage drug.[39]

Canadian Context

Four primary studies investigated drug shortages occurring in Canada.[13,20,30,33] The shortage drugs were carmustine, tocilizumab, probenecid (in conjunction with an antibiotic), and generic valsartan.[13,20,30,33] Lachance et al. (2023) reported the alternative drug, bendamustine, had worse outcomes in adverse events and ICU admissions and better outcomes in survival and disease progression.[13] Stukas et al. (2022) reported the decreased dose of tocilizumab had worse outcomes in mortality, but no difference in

hospital LOS, ICU LOS, or duration of mechanical ventilation.[20] Landry et al. (2019) reported that using the antibiotic without addition of the shortage drug had no difference in readmissions or adverse events.[33] McAlister and Youngson (2020) reported worse outcomes for ED and outpatient visits, but no difference in hospital admissions.[30] Three studies concluded that the replacement drug or protocol was an acceptable alternative to the shortage drug.[13,20,33] The fourth study concluded that there were no long-term adverse effects due to the shortage.[30]

Table 2: Summary of Included Scoping Review

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
Phuong et al. (2019)[6]				
Anesthetics				
Romito B, et al. Hosp Pharm. 2015;50(9) :798–805. USA	**Study design**: Retrospective cohort **Population:** NR **Setting:** Surgery	**Drug Class:** General anesthetic, systemic Shortage: Propofol Replacement: Alternative agents	Mortality	No difference
Price B, et al. Am J Emerg Med. 2013;31(7) :1124–32. USA	**Study design**: Retrospective cohort **Population:** People requiring endotracheal intubation **Setting:** Air medical	**Drug Class:** General anesthetic, systemic Shortage: Etomidate Replacement: Ketamine	Adverse drug reaction	No difference
			Hemodynamics	No difference
Roberts R, et al. Crit Care Med. 2012;40(2) :406–11. USA	**Study design**: Retrospective cohort **Population:** Non-cardiac ICU patients **Setting:** ICU	**Drug Class:** General anesthetic, systemic Shortage: Propofol Replacement: Alternative anesthetic agents	Duration of mechanical ventilation	Increased with alternative anesthetic agents (NSS)
Oncology Drugs and Adjuncts				
Duan F, et al. Radiology. 2016;278(2):612-21. USA	**Study design**: Prospective cohort **Population:** People undergoing transcatheter arterial chemoembolization of hepatocellular carcinoma **Setting:** NR	**Drug Class:** NR Shortage: NR Replacement: Alternative vehicles of oncology medications	Adverse drug reaction	No difference

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
Berger JL, et al. Onco Targets Ther. 2014;7:1409–13. USA	**Study design**: Retrospective cohort **Population:** People with recurrent epithelial ovarian carcinoma **Setting:** NR	**Drug Class:** Antineoplastic Shortage: Pegylated liposomal doxorubicin (Doxil) Replacement: Non-FDA-approved second-generation liposomal doxorubicin (Lipo-Dox)	Treatment response	No patients had a complete or partial response with alternative therapy
Nickel RS, et al. Pediatr Blood Cancer. 2014;61(5):810–4. USA	**Study design**: Retrospective cohort **Population:** People with newly diagnosed lymphoblastic leukemia and lymphoma **Setting:** Hospital	**Drug Class:** Antineoplastic Shortage: Daunorubicin Replacement: Mitoxantrone	Mortality	No difference
			ICU admission	No difference
			Adverse event: fever, bacteremia, invasive fungal disease	No difference
			Hospital LOS	No difference
Trifilio S, et al. Leuk Res. 2013;37(8):868–71. USA	**Study design**: Retrospective cohort **Population:** People with acute myeloid leukemia **Setting:** NR	**Drug Class:** Antineoplastic Shortage: Daunorubicin Replacement: Idarubicin	Mortality	No difference
			Adverse drug reaction	No difference
			Complete remission	No difference
Antimicrobials and Adjuncts				
McLaughlin MM, et al. Infect Dis Ther. 2017;6(2):259–64. USA	**Study design:** Retrospective cohort **Population:** NR **Setting:** NR	**Drug Class:** Antiviral Shortage: IV acyclovir Replacement: High-dose oral valacyclovir	Adverse drug reaction	40% of patients experienced at least one adverse drug reaction to high-dose oral valacyclovir

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
Dilworth TJ, et al. J Manag Care Pharm. 2014;20(12):1246–54. USA	**Study design**: Retrospective cohort **Population:** People with HIV *Pneumocystis jirovecii* pneumonia **Setting:** Hospital	**Drug Class:** Sulfonamide Shortage: IV trimethoprim-sulfamethoxazole Replacement: Alternative agents	Mortality	Equal number of deaths in both groups
			Clinical status	Worsened in the shortage group
			Treatment failure	No difference
			Adverse events	No difference
			Hospital LOS	No difference
Mendez MN, et al. Pharmacotherapy. 2006;26(1):61–7. USA	**Study design**: Retrospective cohort **Population:** NR **Setting:** NR	**Drug Class:** Penicillin; Beta-lactamase inhibitor Shortage: Piperacillin-tazobactam Replacement: Alternative antimicrobials	Adverse drug reaction	No difference in vancomycin-resistant enterococci rates Decrease in *Clostridium difficile* infections with alternative antimicrobials
Other				
Vail E, et al. JAMA. 2017;317(14):1433–42. USA	**Study design**: Retrospective cohort **Population:** People with septic shock **Setting:** NR	**Drug Class:** Vasopressor Shortage: Norepinephrine Replacement: Alternative vasopressors	Mortality	Increased with alternative vasopressors
Blaine KP, et al. Clin Anesth. 2016;35:516–23. USA	**Study design**: Retrospective cohort **Population:** People undergoing cardiac surgery **Setting:** Surgery	**Drug Class:** Antifibrinolytic Shortage: Epsilon-aminocaproic acid Replacement: Tranexamic acid	Adverse drug reaction	Decreased with tranexamic acid
Cho S, et al. nn	**Study design**: Retrospective cohort	**Drug Class:** Calcium channel blocker	Mortality	No difference

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
Pharmacother. 2016;50(9):718–24. USA	**Population:** People with acute subarachnoid hemorrhage **Setting:** NR	Shortage: Nimodipine Replacement: Shortened course of treatment	Adverse drug reaction	No difference
			Hospital LOS	No difference
			Duration of mechanical ventilation	No difference
			Neurological outcomes	No difference
Malone C, et al. Ulster Med J. 2016;85(3):174–7. UK	**Study design**: Prospective cohort **Population:** People undergoing non-emergent caesarean section **Setting:** Surgery	**Drug Class:** Uterotonic Shortage: IV oxytocin Replacement: Syntometrine	Transfusions, blood loss	No difference
			Adverse drug reaction	Increased intra-operative antiemetics with Syntometrine
Ladha KS, et al. Anesth Analg. 2015;121(2):404–9. USA	**Study design**: Retrospective cohort **Population:** NR **Setting:** Surgery	**Drug Class:** Vasopressor Shortage: Pharmacy-prepared ephedrine syringes Replacement: Alternative vasopressors	Hemodynamics	No difference
Goldblatt J, et al. Blood Cells Mol Dis. 2011;46(1):107–10. Australia	**Study design**: Prospective cohort **Population:** People with Gaucher's disease **Setting:** NR	**Drug Class:** Metabolic enzyme Shortage: Imiglucerase Replacement: None	Clinical complications	Most patients had no significant clinical complications

FDA = United States Food and Drug Administration; ICU = intensive care unit; IV = intravenous; LOS = length of stay; NR = not reported; NSS = not statistically significant.

Table 3: Summary of Included Non-Randomized Studies by Clinical Indication

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
General				
Borneau-Martin et al. (2023)[7] France	**Study design**: Registry **Population**: Drug shortage related ADRs reported to a pharmacovigilance database N = 462 **Setting:** Any	**Drug Class:** Any Most frequently reported: nervous system drugs, cardiovascular drugs, anti-infectives for systemic use Replacement drug used in 96% of reported ADR cases	Number of ADR cases related to drug shortages	Increased at a greater rate than total reported ADRs over the study period
			ADRs	84% of cases related to drug shortages
			Serious ADRs: hospitalization, medically significant or life-threatening events, death	46% of cases related to drug shortages
			Death	2% of cases related to drug shortages
			Disease worsening	16% of cases related to drug shortages
			Medication errors	11% of cases related to drug shortages
Anesthetics, Analgesics, and Sedatives				
John et al. (2022)[17] USA	**Study design**: Retrospective cohort **Population**: Mechanically ventilated adults N = 100 **Setting:** ICU	**Drug Class:** Opioid analgesic Shortage: IV opioids Replacement: Oral opioids or alternative non-opioid agents	Hospital LOS	No difference
			ICU LOS	No difference
			Mortality	No difference
			Duration of mechanical ventilation	No difference
			Pain level	No difference
Katsivalis et al. (2022)[18] USA	**Study design**: Retrospective cohort **Population**: Adults with sickle cell disease	**Drug Class:** Opioid analgesic Shortage: IV opioid medications	Hospital LOS	No difference
			Readmission	Fewer 30-day readmissions during the shortage period

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
	N = 89 **Setting:** Hospital	Replacement: Oral opioids	ED visits	No difference
Rodriguez-Monguio et al. (2022)[19] USA	**Study design**: Retrospective cohort **Population**: Adults with cancer N = 3906 **Setting:** Surgery	**Drug Class:** Opioid analgesic Shortage: Any opioid analgesic in shortage during study period Replacement: Any, including drug substitutions, dose conversions, and alternative administration routes	Adverse event: post-operative hypoxemia	Increased in patients exposed to opioid shortages (NSS)
			Adverse event: post-operative hypoxemia reversed by IV naloxone	Increased in patients exposed to opioid shortages (NSS)
Cole et al. (2021)[10] USA	**Study design**: Prospective cohort **Population**: Patients with acute agitation N = 1257 **Setting:** ED	**Drug Class:** Antipsychotic Shortage: Droperidol; Olanzapine Replacement: Droperidol; Olanzapine	ED LOS	Longer ED LOS in the olanzapine group
			Adverse event: extrapyramidal	Extrapyramidal adverse events were more common with droperidol
			Adverse events: cardiovascular, respiratory, intubation	No difference
Farrell et al. (2020)[26] USA	**Study design**: Retrospective cohort **Population**: Adults requiring rapid sequence intubation N = 82 **Setting:** ED	**Drug Class:** General anesthetic, systemic Shortage: Etomidate Replacement: Ketamine; Methohexital	Complications: dental trauma, airway trauma, esophageal intubation, new-onset seizures	No occurrences in either group
			Complications: aspiration	Two aspirations occurred in the etomidate group
Nelson et al. (2019)[34]	**Study design**: Retrospective cohort	**Drug Class:** Benzodiazepine	ICU admission	No difference

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
USA	**Population**: Adults with acute alcohol withdrawal syndrome N = 300 **Setting:** ED	Shortage: IV diazepam; IV lorazepam Replacement: IV lorazepam and IV phenobarbital; IV phenobarbital	Overall admission	Increased admission rates with phenobarbital only compared to diazepam No difference between the other groups
			LOS, total	LOS was shortest with lorazepam + phenobarbital compared to diazepam and phenobarbital only
			LOS, ED	ED LOS was shortest with diazepam compared to lorazepam + phenobarbital and phenobarbital only
			LOS, floor and ICU	No difference
			Intubation	No difference
Neff et al. (2018)[37] USA	**Study design**: Retrospective cohort **Population**: Adults undergoing general anesthesia N = 2090 **Setting:** Surgery	**Drug Class:** General anesthetic, systemic Shortage: Propofol Replacement: Inhaled volatile agents	Post-operative nausea and vomiting	Greater incidence of post-operative nausea and vomiting during the propofol shortage period
			PACU LOS	Longer duration of stay in the PACU during the propofol shortage period
			Readmit to ED	No difference
Oncology Drugs and Adjuncts				
Lachance et al. (2023)[13] Canada	**Study design**: Retrospective cohort **Population**: Patients undergoing autologous stem cell transplantation for	**Drug Class:** Antineoplastic Shortage: Carmustine Replacement: Bendamustine	Febrile neutropenia	No difference
			Mucositis	Increased development of grade ≥ 3 mucositis with bendamustine

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
	relapsed-refractory lymphoma N = 227 **Setting:** Hospital		Toxicity: cardiac, pulmonary, liver	No difference
			Toxicity: renal	Increased with bendamustine
			ICU admission	Increased with bendamustine
			Transfusion	Increased need for platelet transfusion with bendamustine Decreased need for red blood cell transfusion with bendamustine
			Hospital LOS	Increased with bendamustine
			Mortality	No early treatment-related deaths associated with bendamustine Better overall survival with bendamustine
			Disease progression	Better progression-free survival with bendamustine
Strobbe et al. (2023)[14] France	**Study design**: Retrospective cohort **Population**: Patients receiving paclitaxel-based chemotherapy N = 831 **Setting:** Outpatient	**Drug Class:** H2A Shortage: Ranitidine; Famotidine Replacement: Alternative H2A (famotidine); No H2A (H1A, corticosteroid, or combined H1A/corticosteroid)	Hypersensitivity reactions	No difference
Li and Cimino (2020)[28] USA	**Study design**: Retrospective cohort **Population**: Patients receiving chemotherapy N = 22	**Drug Class:** Antineoplastic Shortage: Etoposide injection Replacement: Alternative therapy (e.g., oral	Adverse drug events	No difference
			Disease progression	No difference

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
	Setting: Outpatient	etopisode or etopophos injection)	Medication errors	None recorded
Roy et al. (2019)[35] USA	**Study design**: Retrospective cohort **Population**: Adults receiving HDTMX as inpatients N = 18 **Setting:** Hospital	**Drug Class:** Alkalinizing agent Shortage: IV sodium bicarbonate/IV sodium acetate Replacement: Oral sodium bicarbonate with oral or IV acetazolamide as needed	Hospital LOS	No difference
			Adverse events: acute kidney injury, hepatotoxicity, myelosuppression	No difference
			Adverse events: pneumonitis, mucositis, rash	No occurrences in either group
Visage et al. (2019)[36] USA	**Study design**: Retrospective cohort, uncontrolled **Population**: Pediatric patients receiving HDTMX N = 102 (HDTMX cycles) **Setting:** Hospital	**Drug Class:** Alkalinizing agent Shortage: IV sodium bicarbonate Replacement: Oral sodium bicarbonate/oral sodium citrate-citric acid	GI side effects	The incidence of GI side effects was not drastically impacted by use of an oral alkalinizing agent
Vaccines				
Miyazato et al. (2023)[8] Japan	**Study design**: Prospective cohort, uncontrolled **Population**: People at risk of yellow fever N = 11279 **Setting:** Community	**Drug Class:** Live vaccine, viral Shortage: YF-Vax Replacement: Alternative 17D-204 yellow fever vaccine (Stamaril)	Adverse events	The alternative vaccination was shown to be generally safe.
			Serious adverse events	Three participants developed serious adverse events that may have been related to vaccination
Rojas et al. (2023)[9] USA	**Study design**: Prospective cohort, uncontrolled	**Drug Class:** Live vaccine, viral Shortage: YF-Vax	Adverse events	No safety issues were identified

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
	Population: People at high risk of yellow fever N = 627079 **Setting:** Community	Replacement: Stamaril	Serious adverse events	Serious adverse events were very rare and consistent with the known safety profile
Wong et al. (2020)[12] Australia	**Study design**: Prospective cohort, uncontrolled **Population**: Children N = 6779 **Setting:** Community	**Drug Class:** Live vaccine, bacterial Shortage: Sanofi-Pasteur BCG strain Replacement: BCG-10 (derived from the Moreau strain)	Adverse events following immunization	BCG-10 had a similar safety profile to that reported for other BCG strains
Nzolo et al. (2018)[38] DRC	**Study design**: Retrospective cohort, uncontrolled **Population**: People receiving preventative fractional dose yellow fever vaccination during an outbreak N = 7466998 **Setting:** Community	**Drug Class:** Live vaccine, viral Shortage: 17DD yellow fever vaccine, full dose Replacement: 17DD yellow fever vaccine, fractional dose	Adverse events following immunization	Fractional dose vaccination had an acceptable safety profile
			Serious adverse events following immunization	Serious adverse events were reported by 5 individuals
Antimicrobials and Adjuncts				
Haiduc et al. (2021)[22] USA	**Study design**: Retrospective cohort **Population**: Adults in hospital with febrile neutropenia N = 150 **Setting:** Hospital	**Drug Class:** Cephalosporin Shortage: Cefepime Replacement: Cefepime (dose-sparing)	Hospital LOS	No difference
			Mortality, all-cause, infection-related	No difference

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
Patel et al. (2020)[31] USA	**Study design**: Retrospective cohort **Population**: Neonates N = 101 **Setting:** Neonatal ICU	**Drug Class:** Cephalosporin Shortage: Cefotaxime Replacement: Ceftazidime	Culture positive late-onset sepsis	Increased with the use of ceftazidime (NSS)
			Multidrug resistant organism infection	Increased with the use of ceftazidime (NSS)
			Stage II to III necrotizing enterocolitis	Increased with the use of ceftazidime
			Urinary tract infection	No difference
			Mortality	No difference
			Hospital LOS	No difference
			Adverse events	No occurrences in either group
Landry et al. (2019)[33] Canada	**Study design**: Retrospective cohort **Population**: Adults with uncomplicated cellulitis requiring IV therapy N = 203 **Setting:** ED	**Drug Class:** Uricosuric agent Shortage: Probenecid (in combination with IV cefazolin) Replacement: IV cefazolin only, continuous infusion	Recurrence (admission or ED visit for cellulitis within 30 days of treatment end)	No difference
			Adverse events: rash, nausea	No difference
COVID-19				
Swets et al. (2023)[39] The Netherlands	**Study design**: Retrospective cohort **Population**: Adults hospitalized for COVID-19 N = 5485 **Setting:** Hospital	**Drug Class:** Monoclonal antibody (interleukin-6 inhibitor) Shortage: Tocilizumab (IV) Replacement: Tocilizumab (fixed dose; low dose); Sarilumab	Mortality	Lower survival with fixed dose tocilizumab and sarilumab No difference in survival with low dose tocilizumab
			Hospital LOS	Shorter LOS with low dose tocilizumab and sarilumab No difference in LOS with fixed dose tocilizumab

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
			ICU admission or mortality	Higher ICU admissions or death with fixed dose tocilizumab, low dose tocilizumab, and sarilumab
Stukas et al. (2022)[20] Canada	**Study design**: Retrospective cohort **Population**: Adults with a diagnosis of pneumonia secondary to SARS-CoV-2 infection N = 153 **Setting:** ICU	**Drug Class:** Monoclonal antibody (interleukin-6 inhibitor) Shortage: Tocilizumab (IV), weight-based dose Replacement: Tocilizumab (IV), fixed dose	Duration of mechanical ventilation	No difference
			ICU LOS	No difference
			Hospital LOS	No difference
			Mortality	Higher mortality in the fixed dose group (NSS)
Lecronier et al. (2020)[27] France	**Study design**: Retrospective cohort **Population**: Patients with severe SARS-CoV-2 pneumonia N = 80 **Setting:** ICU	**Drug Class:** Protease inhibitor Shortage: Lopinavir/Ritonavir Replacement: Hydroxychloroquinine	Treatment escalation: intubation, ECMO, RRT	No difference
			Mortality	No difference
			Safety and tolerance outcomes: neutropenia, anemia, thrombocytopenia, increased ASP and ALT, acute renal failure, prolonged QT interval	No difference
Other				

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
Dannemiller et al. (2022)[16] USA	**Study design**: Retrospective cohort **Population**: Adults undergoing cardiac surgery N = 1544 **Setting:** Surgery	**Drug Class:** Antifibrinolytic agent Shortage: Epsilon-aminocaproic acid Replacement: Tranexamic acid	Safety events: mortality, cardiovascular, renal, seizure	No difference
Freeman et al. (2021)[21] USA	**Study design**: Retrospective cohort **Population**: Adults who qualified for general or continuous renal replacement therapy electrolyte replacement protocol N = 288 **Setting:** ICU	**Drug Class:** Electrolytes Shortage: IV electrolyte replacement products Replacement: Enteral electrolyte replacement	ICU LOS	No difference
			Mortality	No difference
			Duration of mechanical ventilation	Decreased in the shortage period group
Neto et al. (2021)[23] Brazil	**Study design**: Retrospective cohort, uncontrolled **Population**: Patients with atypical hemolytic uremic syndrome N = 24 **Setting:** Dialysis clinic	**Drug Class:** Monoclonal antibody Shortage: Eculizumab Replacement: None	Disease relapse	Increased after unplanned eculizumab interruption

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
McAlister and Youngson (2020)[30] Canada	**Study design**: Retrospective cohort, uncontrolled **Population**: Adults dispensed any of the recalled valsartan products N = 34726 **Setting:** Community	**Drug Class:** Angiotensin receptor blocker Shortage: Generic valsartan Replacement: Alternative angiotensin receptor blocker; brand name valsartan	Outpatient visits	Increased immediately after generic valsartan recall
			ED visits	Increased immediately after generic valsartan recall (older patients only)
			ED visits, hospitalizations for stroke or TIA	No difference
van Langenberg et al. (2020)[11] Australia	**Study design**: Prospective cohort **Population**: People with mild to moderate ulcerative colitis N = 31 **Setting:** Outpatient	**Drug Class:** 5-ASA Shortage: Balsalazide Replacement: alternative 5-ASA formulations (e.g., multi-matrix mesalazine)	Clinical activity	Higher than expected proportion of patients with worsening disease with alternative 5-ASA
			Adverse events	Higher than expected proportion of patients with significant side effects with alternative 5-ASA
			Remission	No difference
			Treatment escalation	No difference
			Mortality	No difference
			Flares requiring hospitalization	Increased with alternative 5-ASA
Yang et al. (2020)[32] USA	**Study design**: Retrospective cohort	**Drug Class:** Glucose-elevating agent	Symptomatic hypoglycemia	Lower incidence in the D10 group (NSS)

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
	Population: Adult patients with hyperkalemia receiving IV insulin N = 134 **Setting:** ED	Shortage: Dextrose 50% (D50) Replacement: Dextrose 10% (D10)	Adverse events, including extravasation	No occurrences in either group
Non-Drug				
Acadamia et al. (2022)[15] USA	**Study design**: Retrospective cohort **Population**: Adults N = 696 **Setting:** ED	**Drug Class:** Small-volume parenteral solutions Shortage: Intravenous piggy-back administration of penicillins and carbapenems Replacement: Intravenous push administration of penicillins and carbapenems	Drug-related adverse events	No difference
			Mortality	No difference
Tschumper et al. (2021)[24] USA	**Study design**: Retrospective cohort **Population**: Adults N = 90 **Setting:** Hospital	**Drug Class:** Small-volume parenteral solutions Shortage: Prolonged infusion (4-hour) of piperacillin/tazaobactam Replacement: continuous infusion of piperacillin/tazobactam	Hospital LOS	No difference
			Mortality	No difference
			Safety: thrombocytopenia	Higher incidence with continuous infusion (NSS)
			Safety: *Clostridioides difficile* infection, acute renal failure	No difference
			Safety: seizure	No occurrences in either group
			Readmission	Fewer readmissions with continuous infusion (NSS)

Study citation	Study characteristics	Drug characteristics	Relevant outcomes	Outcome results
Blair and Covington (2020)[25] USA	**Study design**: Retrospective cohort, uncontrolled **Population**: Adults N **=** 120 **Setting:** Hospital	**Drug Class:** Small-volume parenteral solutions Shortage: 4-hour extended infusion of piperacillin/tazobactam Replacement: continuous infusion of piperacillin/tazobactam	Acute kidney injury	Incidence with continuous infusion similar to previously reported results with extended infusion
Marsh et al. (2020)[29] USA	**Study design**: Retrospective cohort, uncontrolled **Population**: Adults N **=** 1000 **Setting:** Hospital	**Drug Class:** Small-volume parenteral solutions Shortage: Intravenous piggy-back administration of beta-lactam antibiotics Replacement: Intravenous push administration of beta-lactam antibiotics	Adverse events	Safety of intravenous push administration similar to previously reported results with intravenous piggy-back administration

5-ASA = 5-aminosalicylate; ADR = adverse drug reaction; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BCG = *bacille Calmete-Guerin*; ECMO = extracorporeal membrane oxygenation; ED = emergency department; GI = gastrointestinal; H1A = histamine-1 antagonist; H2A = histamine-2 antagonists; HDTMX = high-dose methotrexate; ICU = intensive care unit; IV = intravenous; LOS = length of stay; N2O = nitrous oxide; NSS = not statistically significant; NR = not reported; PACU = post-anesthetic care unit; RRT = renal replacement therapy; TIA = transient ischemic attack.

Conclusions

The development of a preventative approach could possibly help to mitigate the impacts of drug shortages. To achieve this, first, drugs that are potentially the highest impact need to be identified. Anticipating which drugs are likely to be most impactful during a shortage involves identifying those most at risk of supply chain disruptions and those most likely to cause patient harm. Ranking drugs based on their risk of shortage and their risk of harm during a shortage can help decision-makers put into place pre-emptive strategies. This report supports this objective by summarizing types of harm that may occur during drug shortages, and, although not the primary intent of this report, by identifying the types of drugs experiencing shortages studied in the literature. Most of the published trials examined the effectiveness and safety of alternative agents during drug shortages. Harms outcomes that were most frequently reported were adverse events or safety-related outcomes, health system usage, including length of stay, mortality, and disease progression. Similarly, a French registry study described the types of adverse drug reactions related to drug shortages as reported to a pharmacovigilance database.[7] The authors described harms from adverse drug reactions, serious adverse drug reactions, including hospitalization, life-threatening events, or death, and disease progression.[7] Primary studies that concluded that the examined drug shortage had negative consequences reported health system usage, adverse events, disease progression, and mortality as harms outcomes.[11,19,23,31,37,39]

This report summarizes the available evidence on the effect of drug shortages on patient outcomes and will be used in combination with other CADTH work to support future decision-making regarding drug shortages, including:

- An environmental scan of existing clinical tools or scoring systems available for drug shortage or supply chain disruptions
- Facilitation of a Delphi panel to support the identification of high-priority drugs based on their supply chain risk and clinical risk

References

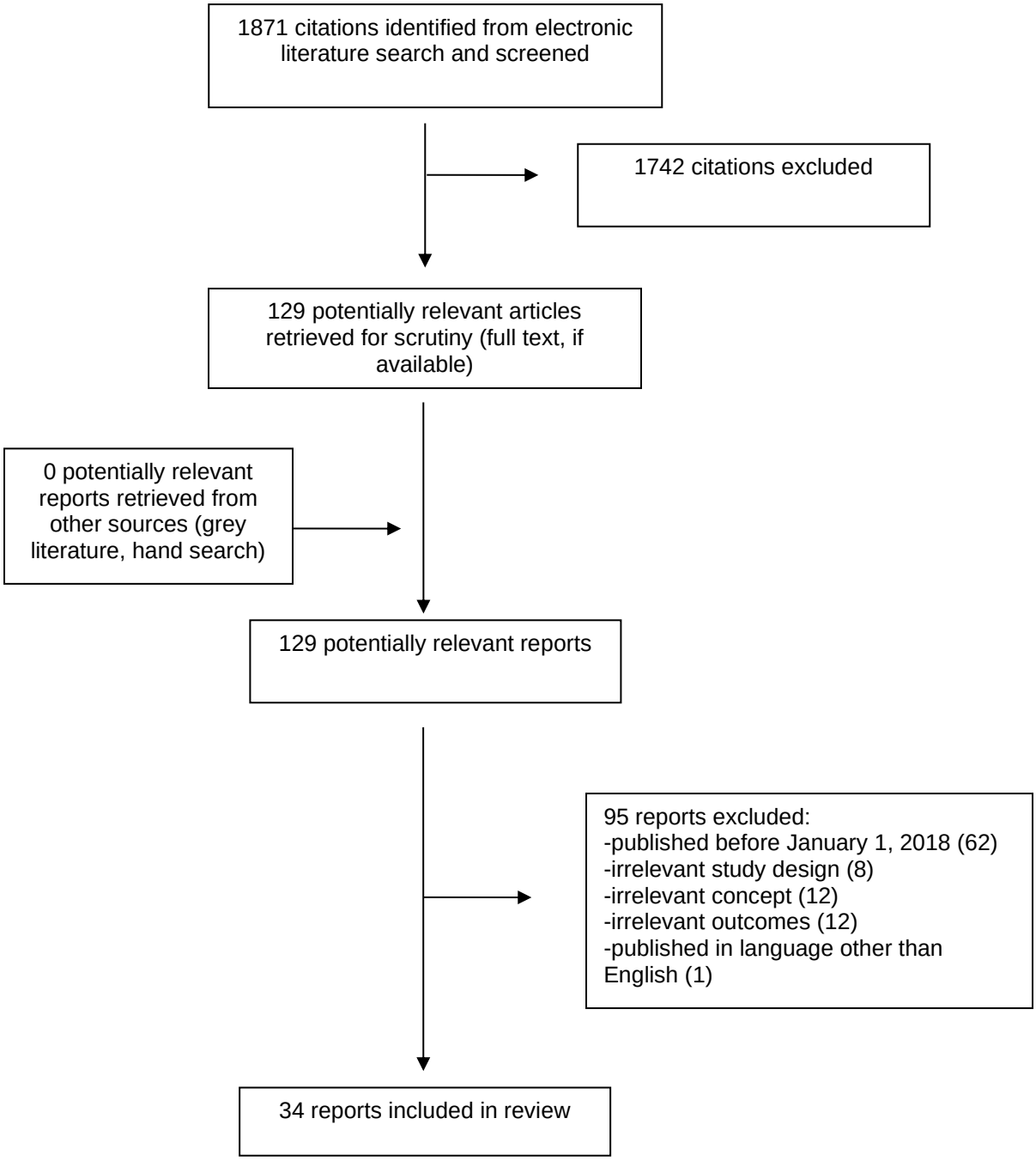
1. Drug Shortages in Canada. Ottawa (ON): Health Canada; 2023: https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/drug-products/drug-shortages/2022-2023-review/2022-2023-review-en.pdf. Accessed 2023 Nov 9.
2. Protocol for the Notification and Communication of Drug Shortages. Drug Shortages Canada; 2017: https://www.drugshortagescanada.ca/files/MSSC_Protocol_2017.pdf. Accessed 2023 Nov 9.
3. A Toolkit for Improved Understanding and Transparency of Drug Shortage Response in Canada. Drug Shortages Canada; 2017: https://www.drugshortagescanada.ca/files/MSSC_Toolkit_2017.pdf. Accessed 2023 Nov 9.
4. Aronson JK, Heneghan C, Ferner RE. Drug shortages. Part 1. Definitions and harms. *Br J Clin Pharmacol.* 2023;16:16.
5. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst.* 2021;10(1):89.
6. Phuong JM, Penm J, Chaar B, Oldfield LD, Moles R. The impacts of medication shortages on patient outcomes: A scoping review. *PLoS ONE.* 2019;14(5):e0215837.
7. Bourneau-Martin D, Babin M, Grandvuillemin A, et al. Adverse drug reaction related to drug shortage: A retrospective study on the French National Pharmacovigilance Database. *Br J Clin Pharmacol.* 2023;89(3):1080-1088.
8. Miyazato Y, Terada M, Ujiie M, et al. A nationwide prospective cohort study on safety of the 17D-204 yellow fever vaccine during a vaccine shortage in Japan. *J Travel Med.* 2023;30(2):05.
9. Rojas A, Hachey W, Kaur G, Korejwo J, Muhammad R. Enhanced safety surveillance of STAMARIL R yellow fever vaccine provided under the expanded access investigational new drug program in the United States. *J Travel Med.* 2023;31:31.
10. Cole JB, Stang JL, DeVries PA, Martel ML, Miner JR, Driver BE. A Prospective Study of Intramuscular Droperidol or Olanzapine for Acute Agitation in the Emergency Department: A Natural Experiment Owing to Drug Shortages. *Ann Emerg Med.* 2021;78(2):274-286.
11. van Langenberg DR, Cheng RK, Garg M. Outcomes of a drug shortage requiring switching in patients with ulcerative colitis. *World J Gastrointest Pathophysiol.* 2020;11(2):32-42.
12. Wong NX, Buttery J, McMinn A, Azhar Z, Crawford NW. Safety of the Polish BCG-10 Vaccine During a Period of BCG Vaccine Shortage: An Australian Experience. *Pediatr Infect Dis J.* 2020;39(6):e66-e68.
13. Lachance S, Bourguignon A, Boisjoly JA, et al. Impact of Implementing a Bendamustine-Based Conditioning Regimen on Outcomes of Autologous Stem Cell Transplantation in Lymphoma while Novel Cellular Therapies Emerge. *Transplant Cell Ther.* 2023;29(1):34.e31-34.e37.
14. Strobbe G, Gaboriau L, Abele M, et al. Impact of histamine-2 antagonist shortage on the incidence of hypersensitivity reactions to paclitaxel: a reconsideration of premedication protocols in France (PACLIREACT Study). *Eur J Clin Pharmacol.* 2023;79(9):1229-1238.
15. Academia EC, Jenrette JE, Mueller SW, McLaughlin JM. Evaluation of First-Dose, Intravenous Push Penicillins and Carbapenems in the Emergency Department. *J Pharm Pract.* 2022;35(3):369-376.
16. Dannemiller RE, Knowles DM, Cook BM, Goodberlet MZ, Kelly JM, Malloy R. Comparison of trauma-dosed tranexamic acid versus aminocaproic acid in cardiac surgery in the setting of drug shortage. *J Card Surg.* 2022;37(10):3243-3249.
17. John K, Cape K, Goodman L, Elefritz J. Impact of the Injectable Opioid Drug Shortage on Analgesia and Sedation Management in the Medical Intensive Care Unit: A Retrospective Cohort Study. *Hosp Pharm.* 2022;57(1):160-166.
18. Katsivalis KV, Kosacz J, Austin Szwak J. Opioid Use in Vaso-Occlusive Crisis During Intravenous Opioid Drug Shortage. *Hosp Pharm.* 2022;57(6):721-726.
19. Rodriguez-Monguio R, Lun Z, Bongiovanni T, Chen CL, Seoane-Vazquez E. Postoperative Respiratory Events in Surgical Patients Exposed to Opioid Analgesic Shortages Compared to Fully Matched Patients Non-exposed to Shortages. *Drug Saf.* 2022;45(4):359-367.
20. Stukas S, Goshua G, Kinkade A, et al. Reduced fixed dose tocilizumab 400 mg IV compared to weight-based dosing in critically ill patients with COVID-19: A before-after cohort study. *Lancet Reg Health Am.* 2022;11:100228.
21. Freeman L, Newsome AS, Huang E, Rowe E, Waller J, Forehand CC. Assessment of Electrolyte Replacement in Critically Ill Patients During a Drug Shortage. *Hosp Pharm.* 2021;56(4):296-301.
22. Haiduc M, Patel M, Walsh TL, Moffa MA, Bremmer DN. Impact of a cefepime shortage on dosing regimens and outcomes in hospitalized adults with febrile neutropenia. *J Oncol Pharm Pract.* 2021;27(2):297-304.
23. Neto ME, de Moraes Soler L, Vasconcelos HVG, et al. Eculizumab interruption in atypical hemolytic uremic syndrome due to shortage: analysis of a Brazilian cohort. *J Nephrol.* 2021;34(4):1373-1380.
24. Tschumper E, Dupuis K, McCrory K, Pitts W. Evaluation of Prolonged Versus Continuous Infusions of Piperacillin/Tazobactam During Shortages of Small Volume Parenteral Solutions. *J Pharm Technol.* 2021;37(6):271-277.

25. Blair K, Covington EW. Incidence and Risk Factors of Acute Kidney Injury in Patients Receiving Concomitant Vancomycin and Continuous-Infusion Piperacillin/Tazobactam: A Retrospective Cohort Study. *Ann Pharmacother.* 2020;54(11):1096-1101.
26. Farrell NM, Killius K, Kue R, Langlois BK, Nelson KP, Golenia P. A Comparison of Etomidate, Ketamine, and Methohexital in Emergency Department Rapid Sequence Intubation. *J Emerg Med.* 2020;59(4):508-514.
27. Lecronier M, Beurton A, Burrel S, et al. Comparison of hydroxychloroquine, lopinavir/ritonavir, and standard of care in critically ill patients with SARS-CoV-2 pneumonia: an opportunistic retrospective analysis. *Crit Care.* 2020;24(1):418.
28. Li H, Cimino SK. Clinical impact of the etoposide injection shortage. *J Oncol Pharm Pract.* 2020;26(1):187-192.
29. Marsh K, Ahmed N, Decano A, et al. Safety of intravenous push administration of beta-lactams within a healthcare system. *Am J Health-Syst Pharm.* 2020;77(9):701-708.
30. McAlister FA, Youngson E. Impact of the Generic Valsartan Recall in Alberta, Canada. *J Am Coll Cardiol.* 2020;75(15):1860-1862.
31. Patel PD, Bhagat P, Bartlett AH, Bondi DS. Comparison of Neonatal Outcomes With the Use Cefotaxime Versus Ceftazidime in a Neonatal Intensive Care Unit. *The Journal of Pediatric Pharmacology & Therapeutics.* 2020;25(2):117-123.
32. Yang I, Smalley S, Ahuja T, Merchan C, Smith SW, Papadopoulos J. Assessment of dextrose 50 bolus versus dextrose 10 infusion in the management of hyperkalemia in the ED. *Am J Emerg Med.* 2020;38(3):598-602.
33. Landry DL, Eltonsy S, Jalbert LP, Girouard G, Couture J, Belanger M. Continuous cefazolin infusion versus cefazolin plus probenecid for the ambulatory treatment of uncomplicated cellulitis: A retrospective cohort study. *J Assoc Med Microbiol Infect Dis Can.* 2019;4(2):108-112.
34. Nelson AC, Kehoe J, Sankoff J, Mintzer D, Taub J, Kaucher KA. Benzodiazepines vs barbiturates for alcohol withdrawal: Analysis of 3 different treatment protocols. *Am J Emerg Med.* 2019;37(4):733-736.
35. Roy AM, Lei M, Lou U. Safety and efficacy of a urine alkalinization protocol developed for high-dose methotrexate patients during intravenous bicarbonate shortage. *J Oncol Pharm Pract.* 2019;25(8):1860-1866.
36. Visage R, Kaiser N, Williams M, Kim A. Oral Methods of Urinary Alkalinization for High-dose Methotrexate Administration: Alternatives to Intravenous Sodium Bicarbonate During a Critical Drug Shortage. *J Pediatr Hematol Oncol.* 2019;41(5):371-375.
37. Neff MP, Wagner D, Phillips BJ, et al. Propofol Drug Shortage Associated With Worse Postoperative Nausea and Vomiting Outcomes Despite a Mitigation Strategy. *Aana J.* 2018;86(2):147-154.
38. Nzolo D, Engo Biongo A, Kuemmerle A, et al. Safety profile of fractional dosing of the 17DD Yellow Fever Vaccine among males and females: Experience of a community-based pharmacovigilance in Kinshasa, DR Congo. *Vaccine.* 2018;36(41):6170-6182.
39. Swets MC, Moss RJ, Kor F, et al. A comparison of the effectiveness of different doses of tocilizumab and sarilumab in the treatment of severe COVID-19: a natural experiment due to drug shortages. *Int J Infect Dis.* 2023;129:57-62.

Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies

Alt text: 1871 citations were identified, 1742 were excluded, while 129 electronic literature and 0 grey literature potentially relevant full text reports were retrieved for scrutiny. In total 34 reports are included in the review.



Appendix 2: References of Potential Interest

Scoping Reviews

Unclear Outcomes

Tucker EL, Cao Y, Fox ER, Sweet BV. The Drug Shortage Era: A Scoping Review of the Literature 2001-2019. *Clin Pharmacol Ther*. 2020;108(6):1150-1155.

Non-Randomized Studies

Not Direct Patient Harm Outcomes

Chun B, He M, Jones C, et al. Variation in Statewide Intravesical Treatment Rates for Non-Muscle Invasive Bladder Cancer During the Bacillus Calmette-Guerin Drug Shortage. *Urology*. 2023;177():74-80.

N'Kaoua E, Attarian S, Delmont E, et al. Immunoglobulin shortage: Practice modifications and clinical outcomes in a reference centre. *Rev Neurol (Paris)*. 2022;178(6):616-623.

Zhang B, Yeh DD, Ortiz-Reyes LA, Chang Y, Quraishi SA. Impact of nationwide essential trace element shortages: A before-after, single-center analysis of hospitalized adults receiving home parenteral nutrition therapy. *Nutr Clin Pract*. 2022;37(2):442-450.

Martei YM, Grover S, Bilker WB, et al. Impact of Essential Medicine Stock Outs on Cancer Therapy Delivery in a Resource-Limited Setting. *J Global Oncol*. 2019;5():1-11.

Hedlund NG, Isgor Z, Zwanziger J, et al. Drug Shortage Impacts Patient Receipt of Induction Treatment. *Health Serv Res*. 2018;53(6):5078-5105.

Additional References

Potentially relevant studies published prior to January 1, 2018

Alhogbani MM, Picard JA, Fassi-Fehri MH, Badet JL, Colombel CM. Prognostic impact of Bacillus Calmette-Guerin interruption at the time of induction and consolidation. *Urol Ann*. 2017;9(4):315-320.

Gross AE, Johannes RS, Gupta V, Tabak YP, Srinivasan A, Bleasdale SC. The Effect of a Piperacillin/Tazobactam Shortage on Antimicrobial Prescribing and Clostridium difficile Risk in 88 US Medical Centers. *Clin Infect Dis.* 2017;65(4):613-618.

Howard J, Wigley J, Rosen G, D'Mello J. Glycopyrrolate: It's time to review. *J Clin Anesth.* 2017;36():51-53.

Hsueh K, Reyes M, Krekel T, et al. Effective Antibiotic Conservation by Emergency Antimicrobial Stewardship During a Drug Shortage. *Infect Control Hosp Epidemiol.* 2017;38(3):356-359.

McLaughlin MM, Sutton SH, Jensen AO, Esterly JS. Use of High-Dose Oral Valacyclovir During an Intravenous Acyclovir Shortage: A Retrospective Analysis of Tolerability and Drug Shortage Management. *Infect.* 2017;6(2):259-264.

Vail E, Gershengorn HB, Hua M, Walkey AJ, Rubenfeld G, Wunsch H. Association Between US Norepinephrine Shortage and Mortality Among Patients With Septic Shock. *JAMA*. 2017;317(14):1433-1442.

VanderWeide LA, Abdel-Rasoul M, Gerlach AT. The Incidence of hypotension with continuous infusion atracurium compared to cisatracurium in the Intensive Care Unit. *Int J Crit Illn Inj Sci*. 2017;7(2):113-118.

Barber KE, Bell AM, Travis King S, Parham JJ, Stover KR. Impact of piperacillin-tazobactam shortage on meropenem use: implications for antimicrobial stewardship programs. *Braz J Infect Dis*. 2016;20(6):631-634.

Blaine KP, Press C, Lau K, Sliwa J, Rao VK, Hill C. Comparative effectiveness of epsilon-aminocaproic acid and tranexamic acid on postoperative bleeding following cardiac surgery during a national medication shortage. *J Clin Anesth*. 2016;35():516-523.

Cho S, Bales J, Tran TK, Korab G, Khandelwal N, Joffe AM. Effects of 14 Versus 21 Days of Nimodipine Therapy on Neurological Outcomes in Aneurysmal Subarachnoid Hemorrhage Patients. *Ann Pharmacother*. 2016;50(9):718-24.

Dotson B, Larabell P, Patel JU, et al. Calcium Administration Is Associated with Adverse Outcomes in Critically Ill Patients Receiving Parenteral Nutrition: Results from a Natural Experiment Created by a Calcium Gluconate Shortage. *Pharmacotherapy.* 2016;36(11):1185-1190.

Duan F, Wang EQ, Lam MG, et al. Superselective Chemoembolization of HCC: Comparison of Short-term Safety and Efficacy between Drug-eluting LC Beads, QuadraSpheres, and Conventional Ethiodized Oil Emulsion. *Radiology*. 2016;278(2):612-21.

Gawronski CA, Gawronski KM. Vitamin A Supplementation for Prevention of Bronchopulmonary Dysplasia: Cornerstone of Care or Futile Therapy?. *Ann Pharmacother*. 2016;50(8):680-4.

Kesteman T, Rafalimanantsoa SA, Razafimandimby H, et al. Multiple causes of an unexpected malaria outbreak in a high-transmission area in Madagascar. *Malar J.* 2016;15():57.

Malone C, Acheson JR, Hinds JD, McComiskey MH. Uterotonics for Non-emergent Caesarean Section: Protocol Change During UK-Licensed Drug Shortage. *Ulster Med J.* 2016;85(3):174-177.

Reed BN, Fox ER, Konig M, et al. The impact of drug shortages on patients with cardiovascular disease: causes, consequences, and a call to action. *Am Heart J*. 2016;175():130-41.

Storey MA, Weber RJ, Besco K, Beatty S, Aizawa K, Mirtallo JM. Evaluation of Parenteral Nutrition Errors in an Era of Drug Shortages. *Nutr Clin Pract.* 2016;31(2):211-7.

Chhim RF, Crill CM. Premixed Parenteral Nutrition Solution Use in Children. *Journal Pediatr Pharmacol Ther*. 2015;20(5):378-84.

Clothier HJ, Hosking L, Crawford NW, et al. Bacillus Calmette-Guerin (BCG) vaccine adverse events in Victoria, Australia: analysis of reports to an enhanced passive surveillance system. *Drug Saf*. 2015;38(1):79-86.

Hughes KM, Goswami ES, Morris JL. Impact of a Drug Shortage on Medication Errors and Clinical Outcomes in the Pediatric Intensive Care Unit. *Journal Pediatr Pharmacol Ther*. 2015;20(6):453-61.

Ladha KS, Nanji KC, Pierce E, Poon KT, Hyder JA. The Impact of a Shortage of Pharmacy-Prepared Ephedrine Syringes on Intraoperative Medication Use. *Anesth Analg.* 2015;121(2):404-9.

Romito B, Stone J, Ning N, et al. How Drug Shortages Affect Clinical Care: The Case of the Surgical Anesthetic Propofol. *Hosp Pharm.* 2015;50(9):798-805.

Shah S, Theodossiades J, Chapman K, Murdoch I. Impact of supply problems of preservative-free glaucoma medications on patients and hospital staff. *Ophthalmic Physiol Opt*. 2015;35(2):236-41.

Shahabi S, Fazlalizadeh H, Stedman J, Chuang L, Shariftabrizi A, Ram R. The impact of international economic sanctions on Iranian cancer healthcare. *Health Policy (New York).* 2015;119(10):1309-18.

Van Berkel MA, Fuller LA, Alexandrov AW, Jones GM. Methylene blue, midodrine, and pseudoephedrine: a review of alternative agents for refractory hypotension in the intensive care unit. *Crit Care Nurs Q*. 2015;38(4):345-58.

Anger KE, Belisle C, Colwell MB, et al. Safety of compounded calcium chloride admixtures for peripheral intravenous administration in the setting of a calcium gluconate shortage. *J Pharm Pract*. 2014;27(5):474-7.

Berger JL, Smith A, Zorn KK, et al. Outcomes analysis of an alternative formulation of PEGylated liposomal doxorubicin in recurrent epithelial ovarian carcinoma during the drug shortage era. *Onco Targets Ther*. 2014;7():1409-13.

Bible JR, Evans DC, Payne B, Mostafavifar L. Impact of drug shortages on patients receiving parenteral nutrition after laparotomy. *JPEN J Parenter Enteral Nutr*. 2014;38(2 Suppl):65S-71S.

Davis C, Javid PJ, Horslen S. Selenium deficiency in pediatric patients with intestinal failure as a consequence of drug shortage. *JPEN J Parenter Enteral Nutr*. 2014;38(1):115-8.

Dill S, Ahn J. Drug shortages in developed countries--reasons, therapeutic consequences, and handling. *Eur J Clin Pharmacol*. 2014;70(12):1405-12.

Dilworth TJ, Ibrahim OM, Mercier RC. Impact of an intravenous trimethoprim/sulfamethoxazole shortage on treatment outcomes among HIV-infected patients with Pneumocystis jirovecii pneumonia. *J Manag Care Spec Pharm*. 2014;20(12):1246-54.

Mazer-Amirshahi M, Pourmand A, Singer S, Pines JM, van den Anker J. Critical drug shortages: implications for emergency medicine. *Acad Emerg Med*. 2014;21(6):704-11.

Miller JL, Thomas AN, Johnson PN. Use of continuous-infusion loop diuretics in critically ill children. *Pharmacotherapy*. 2014;34(8):858-67.

Morgan KP, Snavely AC, Wind LS, et al. Rates of Renal Toxicity in Cancer Patients Receiving Cisplatin With and Without Mannitol. *Ann Pharmacother.* 2014;48(7):863-869.

Nickel RS, Keller F, Bergsagel J, et al. Mitoxantrone as a substitute for daunorubicin during induction in newly diagnosed lymphoblastic leukemia and lymphoma. *Pediatr Blood Cancer*. 2014;61(5):810-4.

Stollings JL, Diedrich DA, Oyen LJ, Brown DR. Rapid-sequence intubation: a review of the process and considerations when choosing medications. *Ann Pharmacother*. 2014;48(1):62-76.

Thoma BN, Li J, McDaniel CM, Wordell CJ, Cavarocchi N, Pizzi LT. Clinical and economic impact of substituting dexmedetomidine for propofol due to a US drug shortage: examination of coronary artery bypass graft patients at an urban medical centre. *Pharmacoeconomics*. 2014;32(2):149-57.

Tolia VN, Murthy K, McKinley PS, Bennett MM, Clark RH. The effect of the national shortage of vitamin A on death or chronic lung disease in extremely low-birth-weight infants. *JAMA, Pediatr*. 2014;168(11):1039-44.

Wiggins BS, Nappi J, Fortier CR, Taber DJ. Cardiovascular Drug Shortages: Predominant Etiologies, Clinical Implications, and Management Strategies. *Ann Pharmacother.* 2014;48(9):1177-1186.

Krisl JC, Fortier CR, Taber DJ. Disruptions in the supply of medications used in transplantation: implications and management strategies for the transplant clinician. *Am J Transplant*. 2013;13(1):20-30.

Nappi JM. A retrospective evaluation of the efficacy of intravenous bumetanide and comparison of potency with furosemide. *Pharm Pract.* 2013;11(1):44-50.

Neavyn MJ, Boyer EW, Bird SB, Babu KM. Sodium acetate as a replacement for sodium bicarbonate in medical toxicology: a review. *J Med Toxicol*. 2013;9(3):250-4.

Price B, Arthur AO, Brunko M, et al. Hemodynamic consequences of ketamine vs etomidate for endotracheal intubation in the air medical setting. *Am J Emerg Med*. 2013;31(7):1124-32.

Rider AE, Templet DJ, Daley MJ, Shuman C, Smith LV. Clinical dilemmas and a review of strategies to manage drug shortages. *J Pharm Pract*. 2013;26(3):183-91.

Trifilio S, Zhou Z, Mehta J, et al. Idarubicin appears equivalent to dose-intense daunorubicin for remission induction in patients with acute myeloid leukemia. *Leuk Res*. 2013;37(8):868-71.

Briere EC, Jackson M, Shah SG, et al. Haemophilus influenzae type b disease and vaccine booster dose deferral, United States, 1998-2009. *Pediatrics*. 2012;130(3):414-20.

Golembiewski J. Drug shortages in the perioperative setting: causes, impact, and strategies. *J Perianesth Nurs*. 2012;27(4):286-92.

Ipema HJ. Use of oral vitamin K for prevention of late vitamin k deficiency bleeding in neonates when injectable vitamin K is not available. *Ann Pharmacother*. 2012;46(6):879-83.

Kwak GY, Kwon HJ, Kim JH, et al. The immunogenicity and safety of DTaP interchangeable immunization among Korean children. *Vaccine*. 2012;30(31):4644-7.

Lowther SA, Shinoda N, Juni BA, et al. Haemophilus influenzae type b infection, vaccination, and H. influenzae carriage in children in Minnesota, 2008-2009. *Epidemiol Infect*. 2012;140(3):566-74.

Metzger ML, Billett A, Link MP. The impact of drug shortages on children with cancer--the example of mechlorethamine. *N Engl J Med*. 2012;367(26):2461-3.

Ralls MW, Blackwood RA, Arnold MA, Partipilo ML, Dimond J, Teitelbaum DH. Drug shortage-associated increase in catheter-related blood stream infection in children. *Pediatrics*. 2012;130(5):e1369-73.

Goldblatt J, Fletcher JM, McGill J, Szer J, Wilson M. Enzyme replacement therapy "drug holiday": results from an unexpected shortage of an orphan drug supply in Australia. *Blood Cells Mol Dis*. 2011;46(1):107-10.

Johnson PN, Miller J, Gormley AK. Continuous-infusion neuromuscular blocking agents in critically ill neonates and children. *Pharmacotherapy*. 2011;31(6):609-20.

Kranzer K, Ford N. Unstructured treatment interruption of antiretroviral therapy in clinical practice: a systematic review. *Trop Med Int Health*. 2011;16(10):1297-313.

Thomas JD, Jackson ML, Sharma D, et al. Haemophilus influenzae type b carriage among young children in metropolitan Atlanta in the context of vaccine shortage and booster dose deferral. *Clin Vaccine Immunol*. 2011;18(12):2178-80.

Jo YM, Song JY, Hwang IS, et al. Dose sparing strategy with intradermal influenza vaccination in patients with solid cancer. *J Med Virol*. 2009;81(4):722-7.

Anonymous. Continued shortage of Haemophilus influenzae Type b (Hib) conjugate vaccines and potential implications for Hib surveillance--United States, 2008. *MMWR Morb Mortal Wkly Rep*. 2008;57(46):1252-5.

Hrynash Y, Nadraga A, Dasho M. Effectiveness of a vaccination program against mumps in Ukraine. *Eur J Clin Microbiol Infect Dis.* 2008;27(12):1171-6.

Abuelreish M, Subedar A, Chiu T, Wludyka P, Rathore M. Increase in invasive pneumococcal disease in children associated with shortage of heptavalent pneumococcal conjugate vaccine. *Clin Pediatr (Phila).* 2007;46(1):45-52.

Sheth HS, Verrico MM, Skledar SJ, Towers AL. Promethazine adverse events after implementation of a medication shortage interchange. *Ann Pharmacother*. 2005;39(2):255-61.

Kiromat M, Vince JD, Oswyn G, Tefuarani N. The management of children with cancer in Papua New Guinea: a review of children with cancer at Port Moresby General Hospital. *P N G Med J.* 2004;47(3-4):138-45.