Prescription Drug Shortages:

Implications for Public Health and Potential Solutions

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Geneesmiddelentekorten:
Implicaties voor de gezondheidszorg en potentiële oplossingen

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1. Introduction

Chapter Summary:
Chapter 1 provides a description of the history of prescription drug shortages from the late 1990s to the present day landscape. This chapter also introduces the clinical and public health implications of drug shortages, as well as mitigation shortages that have been implemented to date. Finally, this chapter outlines the methods and goals of the research conducted within the context of this thesis.

2. Emergency Medicine/Acute Care

Mazer-Amirshahi M, Pourmand A, Singer S, Pines JM, van den Anker J. Critical drug shortages: implications for emergency medicine. Academic Emergency Medicine 2014;21: 704-11. PMID: 25951876.

Chapter Summary:
Chapter 2 discusses the clinical and public health implications of shortages as they apply to the practice of emergency medicine. Situations that may occur as a result of shortages, such as delayed or suboptimal therapy and medication errors are reviewed. Specific considerations to the specialty of emergency medicine are discussed and examples of how patient care is impacted are provided. For instance, we reviewed a case where a patient was given a fatal dose of methohexital when propofol was in short supply. We also explore how the healthcare system is impacted on a larger scale, such as increased cost and resource utilization, and increased pharmacy staff required to manage inventory during times of shortage. We discuss mitigation strategies to date at the governmental and non-governmental levels. We address challenges facing emergency medicine providers and offer strategies for bedside clinicians. Finally, future directions for mitigation and prevention are discussed. It should be noted that many of the situations and strategies presented are applicable to other specialties as well.

Hawley K, **Mazer-Amirshahi M**, Zocchi M, Fox E, Pines J. Longitudinal trends in U.S. drug shortages for medications used in emergency departments. Academic Emergency Medicine, 2016;23:63-9. PMID: 26715487.

Chapter Summary:
Chapter 3 is a retrospective study of the impact of shortages on drugs within the scope of adult emergency medicine from 2001-14. During the course of the study period, over a third of drugs impacted by shortages were within the scope of emergency medicine practice and there was an overall increase in shortages over time. Over 50% of the drugs on shortage were used for high-acuity or life-saving conditions and 10% of these high-acuity drugs had no substitute available. Generic injectable drugs were most commonly affected by shortages and infectious disease drugs were the most common type of drug impacted, followed by analgesics and toxicology drugs. The median duration of resolved shortages

was 9 months and the most common reason for shortage reported was manufacturing problems and delays. We discuss potential reasons for these findings and offer coping strategies for front line providers.

Mazer-Amirshahi M, Goyal M, Umar S, Fox E, Zocchi M, Hawley K, Pines JM. U.S. drug shortages for medications used in adult critical care, 2001-16. Journal of Critical Care 2017;41:283-8. PMID: 28622641.

Chapter Summary:
Chapter 4 is a study of drug shortages affecting medications used in adult intensive care units (ICUs) from 2001-2016. During the study period, there were nearly 2000 drug shortages and over 50% impacted medications used in the ICU. Nearly a quarter of medications on shortage were used for high-acuity or life-threatening conditions. Over 70% of shortages were for parenteral medications and nearly 40% were for single-source drugs. Generic drugs were also more commonly affected compared to their brand name counterparts. Therapeutic alternatives were available for the majority of the medications affected but nearly 25% of alternatives were also impacted during the study period. The median duration of resolved shortages was even longer than described for adult emergency medicine being13.6 months! The most commonly impacted medications, similar to prior studies were infectious disease drugs, which accounted for nearly 20% of ICU shortages. We discuss specific implications for the ICU, which is a particularly high-acuity environment and close by offering mitigation strategies for intensivists.

Mazer-Amirshahi M, Hawley K, Zocchi M, Fox E, Pines J, Nelson L. Drug shortages in the United States: implications for medical toxicology. Clinical Toxicology 2015;56:519-24. PMID: 25951876.

Chapter Summary:
Chapter 5 is a study of shortages for drugs used to treat poisoned patients from 2001-2013. We reviewed shortages of antidotes as well as medications used commonly in the management of poisoned patients. Toxicology shortages accounted for 8.1% of all shortages and shortages generally increased overtime, peaking in 2011. The median shortage duration was 5.5 months. Generic and injectable products were most commonly impacted and 41% of shortages involved single-source drugs. An alternative was available for 86% of drugs; however, 73% of alternatives were impacted at some point during the study period. The agent with the greatest number of shortages was naloxone. The most common class of toxicology drugs on shortage was sedative/hypnotics. Manufacturing problems was the most common reason for shortages. In the discussion, we draw attention to challenges faced by toxicologists and providers caring for poisoned patients, particularly with multiple naloxone shortages during the current opioid epidemic.

Mazer-Amirshahi M, Fox ER, Zocchi M, Pines JM, van den Anker J. Trends in U.S. sterile solutions shortages, 2001-2017. American Journal of Health Systems Pharmacy, 2018;75:1903-8. PMID: 30463866.

Chapter Summary:
Chapter 6 examines shortages of sterile medical solutions, including normal saline, dextrose, lactated ringers, and sterile water for injection over time. We found a substantial number of sterile solution shortages. The median shortage duration was 13.9 months but the longest shortage lasted over 10 years. The most common product type involved was saline solutions. The most commonly cited reason for shortage was manufacturing problems. While there here was an overall increase in the number of sterile solutions over time, there was a significant increase at the end of 2017, which correlated with Hurricane Maria, which precipitated a critical saline shortage. We discuss the potential clinical impact of these shortages and coping strategies for providers and health systems.

Mazer-Amirshahi M, Fox E. Saline shortages: many causes, no simple solution. New England Journal of Medicine, 2018. DOI:10.1056/NEJMp1800347. PMID: 29561694.

Chapter Summary:
Chapter 7 is a perspective piece from the New England Journal of Medicine that further examines the critical saline shortages precipitated by Hurricane Maria. We review the history of saline shortages and explore factors that contributed to the previously existing shortages, such as lack of manufacturing redundancy and transparency. These shortages were acutely worsened by the natural disaster. We review implications for patient care and discuss coping strategies for health systems and providers as well. Finally, we offer policy strategies to prevent future shortages.

3. Pediatrics

Donnelly K, Zocchi M, Katy T, Fox E, van den Anker J, **Mazer-Amirshahi M.** Prescription drug shortages: implications for pediatric ambulatory care. Journal of Pediatrics, 2018. DOI: 10.1016/j.jpeds.2018.4.0008. PMID: 29752177.

Chapter Summary:
Chapter 8 is a study of drug shortages that impact the practice of general ambulatory pediatrics from 2001 to 2015. There were over 300 ambulatory pediatric shortages over the study period, with a median duration of 7.6 months. Similar to prior studies, infectious disease drugs were the most commonly impacted class of medications. Nearly 20% of shortages were for pediatric friendly formulations. An alternative agent was available for the majority of medications impacted; however, nearly 30% of alternatives were affected by shortages. In the discussion, we explore issues unique to pediatric shortages, such as a lack of safety and efficacy data for drugs in this population as well as a need

for palatable formulations. We close by offering mitigation strategies for general pediatricians and suggesting policy solutions, in order to protect this particularly vulnerable population.

Donnelly K, Zocchi M, Katy T, Fox E, Pines J, van den Anker J, **Mazer-Amirshahi M.** Prescription drug shortages: implications for pediatric emergency and critical care. Pediatric Emergency Care 2019; DOI:10.1097/PEC.0000000000001773. PMID: 30829846.

Chapter Summary:
Chapter 9 examines shortages involving pediatric emergency medicine and critical care (ICU) drugs. During the study period from 2001 to 2015, there were nearly 800 shortages impacting pediatric emergency and critical care. There was an overall increase in shortages over time, peaking in 2011. The median shortage duration was 7.6 months and similar to prior trends, infectious disease drugs and sterile injectable products were the most commonly impacted. Over a quarter of shortages impacted drugs used for high-acuity or life-threatening conditions. While most drugs affected by shortages had an alternative, 43% of alternatives were impacted. Pediatric friendly formulations were impacted in 11% of shortages. In the discussion, we explore the safety issues unique to pediatric emergency and critical care, which is a particularly high-acuity environment and ways to mitigate the impact.

Ziesenitz V, Fox E, Zocchi, Samiee-Zafarghandy S, van den Anker J, **Mazer-Amirshahi M.** Prescription drug shortages: impact on neonatal intensive care. Neonatology, 2018;115:108-15. PMID: 30384374.

Chapter Summary:
Chapter 10 examines shortages that affected the top 100 drugs used in the neonatal intensive care unit (NICU). Nearly 75% of the 100 most commonly used NICU drugs were impacted by multiple shortages. The median shortage duration was 8.8 months. Generic injectable medications were the most commonly impacted. A significant number of medications used in extremely low birth weight infants also experienced shortages. We discuss the potential consequences of these shortages in this particularly fragile population in the setting of critical illness. This is further confounded by the fact that medications have the least safety and efficacy data in neonates and some excipients are contraindicated in this age group, leaving few alternatives. In addition, dosing must be very precise, and as such, adult formulations may not be a suitable alternative and dilution and compounding may lead to medication errors.

4. Infectious Diseases

Quadri F, **Mazer-Amirshahi M,** Fox E, Hawley K, Zocchi M, Pines J, May L. Antibacterial Drug Shortages from 2001 to 2013: Implications for Patient Safety

in Clinical Practice. Clinical Infectious Disease 2015;60;1737-42. PMID: 25908680.

Chapter Summary:
Chapter 11 focuses on shortages of the most commonly impacted drug class-antimicrobials. From 2001-2013, we found 148 antimicrobial shortages, with a median duration of 6 months. Over 20% of antimicrobials were impacted by multiple shortages. Shortages for broad-spectrum antibiotics were more common and nearly half of shortages involved medications used to treat high-risk pathogens such as methicillin-resistant *Staphylococcus aureus*. Cephalosporins and aminoglycosides were the most commonly impacted antimicrobial classes. We discuss mitigation strategies in the setting of increasing microbial resistance and a limited number of therapeutic options in the drug development pipeline.

Ziesenitz V, **Mazer-Amirshahi M,** Zocchi M, Fox E, May L. Trends in US vaccine and immunoglobulin shortages 2001-15. American Journal of Health-System Pharmacy, 2017; DOI: 10.2146/ajhp170066. PMID 28970246.

Chapter Summary:
Chapter 12 examines shortages for vaccines and immune globulins (agents used for passive immunity). There were 58 shortages noted, with a median duration of 16.8 months. Shortages for products that were for viral illnesses, such as hepatitis A, were more common. Thirty products on the pediatric schedule were on shortage and vaccine deferral was required for 21 shortages. Over half of the shortages were for single-source products. The most common reason for shortage was manufacturing problems. In the discussion, we focus on the public health implications in the setting vaccine deferrals for primary immunizations, as this may impact herd immunity, as well as coping strategies for clinicians.

5. Discussion and Summary

Prescription Drug Shortages: Implications for Public Health and Potential Solutions

Introduction

Prescription drug shortages have reached critical levels in the United States and represent a significant threat to healthcare quality and patient safety. A prescription drug shortage is defined by the U.S. Food and Drug Administration (FDA) as a scenario in which "the total supply of all clinically interchangeable versions of an FDA-regulated drug product is inadequate to meet the projected demand at the user level." Alternatively, the American Society of Health-System Pharmacists (ASHP) defines a shortage as "a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent."[1]

Although drug shortages have been in existence for decades, they have become much more severe in recent years.[2,3] In the late 1990s, there were a limited number of drug shortages. They were often not long-standing and rarely impacted patient care. However, in response to these shortages and concerns over the potential for disruption caused by the turn of the millennium (Y2K), the FDA developed the Drug Shortage Program (DSP) in 1999.[2] The DSP remained relatively inactive until the early 2000s when there was a significant increase in drug shortages.[2]

The increase in drug shortages that occurred was attributed to a variety of factors, although some underlying themes prevail. The most commonly occurring reason for shortage has been reported as quality problems at manufacturing facilities. Quality problems generally refer to particulate matter, microbial contamination, or formulation instability.[2] In addition, the FDA has issued citations to several manufacturers for violations of good manufacturing practices, which has delayed production and even closed facilities. It is costly and time consuming to bring facilities up to current standards, which can have a serious impact on the supply chain.[5]

In addition to quality problems, market factors have also contributed to the rise in drug shortages. Manufacturing sterile injectable products is costly and only a handful of companies make these products, due to limited profit margins, particularly for generic drugs.[6] In addition to a limited number of manufacturers, several companies have consolidated their resources into a small numbers of facilities because this is a more cost effective approach. This has produced a fragile manufacturing system with a lack of redundancy.[7] When there is a problem at one facility, there is often not enough capacity or redundancy in the system to avoid a shortage. This is also why generic injectable drugs are disproportionately impacted by shortages.[2, 7]

Additional reasons for shortages exist, such as increased demand or natural disasters. For example, in late 2017, a critical shortage of saline solution was precipitated when Hurricane Maria impacted Baxter International's Puerto Rico manufacturing facility. This facility made nearly 50% of small volume saline bags supplied to the United States. At the same time, a second saline manufacturer, B. Braun Medical Inc., was cited for quality problems at one of its facilities, leaving only one major saline manufacturer (ICU

Medical Inc.) at full capacity. In addition, the shortage was further exacerbated by a severe influenza season during which intravenous saline was in high demand.[8]

Drug shortages can have a profound impact on patient care and the healthcare system as a whole. This can take the form of delayed or suboptimal care when first line therapies are not available. One study revealed that 80% of hospitals reported a delay in treatment due to drug shortages.[9] In addition, medication errors can occur when providers must use alternative therapies they are less familiar with. In fact, one survey found that 89% of hospitals attributed a patient safety issue or medication error directly to drug shortages.[9] An associated press report attributed 15 deaths to medication shortages.[10] In addition to the human costs, there is also a significant financial burden placed on the healthcare system by shortages. It is estimated that hospitals spend an additional $230 million annually due to the higher costs of therapeutic substitutions.[9, 11] There is also the increased time and staff resources required to mitigate shortages. There are currently limited data regarding both the human and economic consequences of shortages.

There have been efforts to mitigate the impact of drug shortages; however, shortages remain a major public health problem. As mentioned previously, the FDA's DSP was established in 1999, however; it was not that active until there was an increase in the number of shortages reported, around 2005.[2] The FDA has worked in a variety of ways to prevent and mitigate shortages. The FDA has worked with manufacturers to bring facilities into compliance and assists by coordinating with other manufacturers of products impacted by shortages. The FDA maintains an active drug shortage website to disseminate information. Other actions the FDA may take is to allow for temporary importation of products, extension of expiration dates, and allowing for filtering of products with particulate matter. Despite these strategies, the number of shortages continued to increase. One criticism is that the FDA has limited regulatory and enforcement authority. FDA does not have the authority to require a manufacturer to produce a specific product or volume of product. There were limited reporting requirements on the part of manufacturers who anticipated shortages as well as limited enforcement authority on the part of the FDA for those who failed to comply with current regulations.[12]

In response to the rising number of drug shortages, the Food and Drug Administration Safety and Innovation Act (FDASIA) was passed in 2012.[13] FDASIA expanded the requirement that manufacturers report anticipated shortages or product discontinuation to the FDA. The FDA was also provided authority to expedite the review of drug applications and manufacturing facilities in cases where these actions would mitigate a shortage situation. FDASIA also provided for the establishment of a drug shortages task force, with the goals of both mitigating existing shortages and enacting long-term solutions to prevent new shortages.[13] At the same time, FDASIA had some significant shortcomings. The FDA still lacks enforcement authority to punish manufacturers who do not comply with notification requirements. In addition, FDA also does not have the authority to require a company to manufacturer to make a particular drug, no matter how great the need. There has been much debate over future directions, which could include additional legislation and incentives to manufacturers, to name a few.

Local government and non-governmental initiatives have also helped to mitigate current shortages. The ASHP provides valuable shortage information and guidance for providers and health systems on their drug shortages website.[14] On a local level, state and regional emergency medical services and some state boards of medicine have implemented protocols to mitigate shortages.

At the institutional and health systems level, providers have been managing shortages in an attempt to optimize patient care and prevent medication errors. This may be in the form of minimizing waste, designing substitution protocols, developing a framework for ethical distribution of limited resources, or staff education, to name a few examples.

Despite widespread knowledge of drug shortages and mitigation initiatives, drug shortages remain at critical levels. At the same time, it is less clear what the optimal strategies are to combat shortages. Until recently, it was unclear to what extent shortages impacted particular specialties and patient care settings. In addition, there are limited data as to how shortages directly impact patient safety, particularly because adverse drug events related to shortages are likely under reported. Finally, there are limited data as to how delays in therapy or suboptimal therapy due to shortages have impact patient outcomes.

Examples of Mitigations Strategies for Drug Shortages to Date

Governmental/Regulatory	Increased notification requirements Facilitation of inspections Coordination between manufacturers FDA drug shortages website Expedite new product approvals Temporary importation Extension of expiration dates Allowing for particulate matter Proposal of FDA Task Force
Industry	Development of business continuity plans Compliance with good manufacturing practice Providing advanced notification
Non-Governmental	ASHP drug shortages website Patient advocacy groups Specialty organization involvement (e.g. American College of Emergency Physicians)
State and Local Efforts	Texas Board of Medicine shortage website Texas EMS protocols during times of shortage
Health Systems and Providers	Promote awareness of current shortages Minimize waste of products in shortage Proactively develop protocols for

	substitution Staff education and engagement Report adverse events related to shortages Monitoring of inventory by pharmacy staff Ethical framework for rationing

This thesis is intended to explore the impacts of drug shortages across a wide range of specialties, care settings, and populations. This work will explore trends in drug shortages over time and the potential implications for patient care and public health. The goals of this thesis are to:

1. To review the history and current state of prescription drug shortages, using the specialty of emergency medicine as an example (Chapter 2).

2. To describe trends over time in drug shortages as well as clinical implications and potential solutions for acute care medicine. Chapter 3 will examine shortages related to adult emergency medicine and Chapter 4 will explore shortages affecting medications used in the adult intensive care unit. Chapter 5 will cover shortages impacting antidotes and drugs used in the treatment of poisoned patients. In Chapter 6, we evaluate shortages in sterile solutions and in Chapter 7 we further explore the critical saline shortages that occurred following Hurricane Maria.

3. To describe trends over time in drug shortages and clinical implications for the special population of pediatrics. This is of particular importance because of the limited therapeutic options with safety and efficacy data in the pediatric population. Chapter 8 describes and discusses the considerations unique to the practice of ambulatory pediatrics. Chapter 9 evaluates trends over time and implications in the setting of pediatric emergency and critical care. Chapter 10 examines one of the most fragile of populations and that with the fewest therapeutic options, the neonate. In this chapter we evaluate the impact of shortages impacting the most commonly used neonatal intensive care unit drugs, including those used in extremely low birth weight infants.

4. To describe trends over time and clinical implications for infectious disease drugs. We choose to explore this subspecialty in further detail because when examining shortages in the aforementioned specialties, infectious disease drugs were the most heavily impacted. In addition, there are increasing concerns regarding increasing resistance with few novel drugs in the development pipeline. Chapter 11 focuses specifically on antimicrobial shortages. Chapter 12 examines trends in vaccine shortages.

5. To discuss potential interventions and future areas of study. Chapter 13 will summarize key findings and offer additional mitigation and prevention strategies and explore areas of future study.

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Critical Drug Shortages: Implications for Emergency Medicine

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Abstract

Prescription drug shortages have become increasingly common and more severe over the past decade. In addition, reported shortages are longer in duration and have had a greater effect on patient care. Some of the causes of current drug shortages are multifactorial, including the consolidation of drug manufacturers, quality problems at production plants that restrict the supply of drugs, and a lack of financial incentives for manufacturers to produce certain products, particularly generic medications. Generic injectable medications are most commonly affected by shortages because the production process is complex and costly for these drugs, and profit margins are often smaller than for branded medications. Many commonly used emergency department (ED) generic injectables have been affected by shortages, including multiple resuscitation and critical care drugs. Several reports have shown that shortages can potentially have major effects on the quality of medical care, including medication errors, treatment delays, adverse outcomes, and increased health care costs. Currently, no published data exist outside of case reports that directly link ED-based drug shortages to overall patient safety events; however, there are several examples in the ED where first-line therapies for life-saving medications have been in short supply, and alternatives have higher rates of adverse events, narrower therapeutic indexes, or both. Aside from increasing notification about shortages, the U.S. Food and Drug Administration has little power to coerce manufacturers to produce medications during a shortage. Therefore, ED providers must learn to mitigate the effects of shortages locally, through active communication with pharmacy staff to identify safe and effective alternatives for commonly used medications when possible. Particularly given the effect on critical care medications, therapeutic alternatives should be clearly communicated to all staff so that providers have easy access to this information during resuscitations. This review focuses on the etiology of drug shortages, their effect on the ED, and potential solutions and mitigation strategies.

ACADEMIC EMERGENCY MEDICINE 2014;21:704–711

Prescription drug shortages have become increasingly common and more severe over the past decade, a trend that is projected to continue into the foreseeable future.[1–4] Although typically associated with oncology drugs, drug shortages can affect a wide variety of medications and can lead to delays in treatment, suboptimal treatment, or no treatment being available when indicated.[5,6] Drug shortages can also contribute to medication errors and increased health care costs.[7,8] Shortages have had a dramatic effect on the practice of emergency medicine, as many commonly used medications in the emergency department (ED) have been affected.[3,9] This review will focus on the etiology of drug shortages, their effect on the ED, the role of the U.S. Food and Drug Administration (FDA), and potential solutions and mitigation strategies.

THE DEFINITION AND SCOPE OF THE PROBLEM

According to the FDA, a drug shortage occurs when "the total supply of all clinically interchangeable versions of an FDA-regulated drug product is inadequate to meet the projected demand at the user level."[10] Drug shortages have existed for decades; however, historically they were more infrequent and relatively short-lived and were not broadly disruptive to patient care.[11,12] The primary reasons for the recent increase in drug shortages are a consolidation of manufacturing for

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generic injectables and greater scrutiny on the manufacturing process, which has identified quality problems that can be expensive to address. This has been superimposed on ephemeral economic issues with generic drugs, such as low profit margins and lack of penalties for running out of drug. As a result, over the past decade, drug shortages have increased considerably. In 2005, the FDA's Drug Shortage Program (DSP) reported limited supplies of 61 medications. By 2011, this number increased more than fourfold, to 251 medications, the vast majority being sterile injectable medications, many of which are used in EDs.[3,10] Existing shortages are severe and have reported effects on patient care. One recent survey found that 89% of hospitals implicated a drug shortage as a potential cause for a medical error or patient safety issue.[13] In 2012, an Associated Press article reported 15 deaths over the course of 15 months directly attributed to drug shortages.[14] While chemotherapeutic drugs have been most commonly involved in shortage-related deaths, several therapeutic classes used in the ED have also been implicated, including opioid analgesics, electrolyte solutions, antibiotics, and phytonadione.[13–15] In one survey, 80% of institutions reported that drug shortages were responsible for delays in or cancellations of treatment.[13] The vast majority of institutions also reported significant increases in operating costs as a result of drug shortages. Increased costs can result from buying more costly brand name and alternative medications, price increases due to limited supplies, compounding services, and administrative time to locate alternative supplies and effectively manage and distribute existing inventories.[7,13] It has been estimated that it costs $216 million annually for hospitals to manage drug shortages.[7] Finally, there is the ultimate cost to the patient, who may experience adverse effects as a result of a drug shortage.[2,5,16]

WHY DRUG SHORTAGES OCCUR

The etiology of drug shortages is multifactorial and varies depending upon the specific product involved. Yet, there are common themes that underlie the vast majority of shortages. The most frequent cause of drug shortages is identified broadly as "quality problems." This includes issues such as microbial contamination, particulate matter found in vials, or tablet disintegration.[1] There may be a shortage of raw materials to make the medication or problems with shipping.[4] Another major reason for drug shortages is increased demand; for example, oseltamivir demand has exceeded supplies during influenza season. Some older medications that were on the market prior to the implementation of current FDA safety and efficacy standards are in the processes of being reviewed to bring them into compliance. During this process, these medications may also experience interruptions in supply.[1]

One of the major factors that has contributed to the recent surge in drug shortages has been the changing landscape of pharmaceutical manufacturing, particularly as it pertains to generic injectable drugs. The manufacturing of sterile injectable products is often complex, costly, and specialized, and only small numbers of manufacturers make these products. Over the past decade, manufacturers have been consolidating production into fewer facilities in an effort to control costs.[4] This has important implications because problems at one manufacturing facility can have a profound effect on the supply chain. Because of the lack of redundancy in the supply chain, it is more difficult for a small number of facilities to make up for production problems at one specific manufacturing plant.[1,4]

Another related factor is that production facilities must meet manufacturing quality standards. Recently, the FDA has issued warnings to six of the top 10 manufacturers of sterile injectable products for severe violations of current good manufacturing practices.[17] This is particularly an issue for generic drugs, because manufacturers may be unwilling or unable to make capital investments to sufficiently upgrade infrastructure to address manufacturing problems. Generic manufacturers will not get the return on their investment because generic medications yield much smaller profit margins compared to their brand name counterparts. This is in part due to Medicare legislation that sets fixed prices for generic drugs.[18] In some cases, problems at production facilities have led to permanent shutdown of manufacturing plants. Manufacturers may also choose to discontinue the production of products that do not have large market shares or have limited target populations (such as orphan drugs), as they do not generate sufficient revenue to justify costs.[19,20] For those manufacturers who choose to upgrade their facilities to FDA standards, the process can be time-consuming and also slows production of medications in short supply. In addition, the process for new manufacturers to enter the marketplace is costly and also takes a significant amount of time.[18] Finally, in the current climate, pharmaceutical manufacturers are not held directly accountable for failing to meet market demand or product quality standards. These factors alone and in combination further contribute to the lack of redundancy in pharmaceutical manufacturing, which can potentiate drug shortages.[17]

THE EFFECT OF SHORTAGES IN THE ED

Common ED Medications Affected

There are several medications currently on the FDA drug shortage list that potentially affect ED care.[3] Many medications in short supply are routinely used for critical care patients, including drugs for rapid sequence intubation (RSI), seizures, antidotes, and resuscitation. Other commonly used medications also affected include analgesics, antiemetics, and anticoagulants[3] (Table 1). It is important to note that these shortages also have the potential to affect supplies to emergency medical services (EMS) in the prehospital setting.

Substitution Errors

Shortages of commonly used ED medications can have an effect on patient care and outcomes for many reasons. First, providers in the ED often memorize specific medications and dosages for high-acuity conditions, such as those requiring RSI or for status epilepticus. When alternative medications must be prescribed because of a shortage, the prescriber may be less

Table 1
Recently Reported Shortages for Common ED Therapeutic Categories

Therapeutic Category	Agents Involved	Reasons for Shortage	Potential Substitute
Analgesics	Fentanyl IV Hydromorphone IV Ketorolac IV Morphine IV	Good manufacturing practice Increased demand Manufacturing delay Other	Fentanyl transmucosal Hydromorphone oral Ketorolac oral Morphine oral Oxycodone oral
Antiemetics	Metoclopramide IV Ondansetron IV Prochlorperazine IV Promethazine IV	Good manufacturing practice Increased demand Manufacturing delay Product discontinuation Shipping delay Other	Metoclopramide oral Ondansetron oral Prochlorperazine oral, suppository Promethazine oral, suppository
Antimicrobials	Amikacin IV Doxycycline IV Oseltamivir liquid Sulfamethoxazole/ trimethoprim IV Tobramycin IV	Good manufacturing practice Increased demand Manufacturing delay Shipping delay Other	Gentamicin IV Doxycyline oral Oseltamivir capsules Sulfamethoxazole/TMP oral Gentamicin IV
Benzodiazepines	Diazepam IV Lorazepam IV Midazolam IV	Increased demand Manufacturing delay Product discontinuation	Diazepam oral, rectal Lorazepam oral Oxazepam, chlordiazepoxide, barbiturates for alcohol withdrawal
Electrolyte solutions	Calcium chloride IV Calcium gluconate IV Magnesium sulfate IV Potassium chloride IV Sodium bicarbonate IV	Increased demand Manufacturing delay Other	For electrolyte deficiency could use oral preparations, but in fatal electrolyte abnormality of cardiac dysrhythmia no substitute Potassium acetate IV Sodium acetate IV
Local anesthetics	Bupivacaine injection Lidocaine injection	Increased demand Manufacturer delay Product discontinuation	Benzocaine topical Lidocaine topical Procaine injection Tetracaine injection
Rapid sequence induction	Etomidate IV Propofol IV Succinylcholine IV	Increased demand Manufacturing delay Shipping delay Other	Ketamine IV Methohexital IV Rocuronium IV Vecuronium IV

familiar with available alternatives, specifically, proper dosing, administration procedures, and contraindications. When patients are in extremis, as commonly occurs in the ED, there is limited time to consult a drug reference, nor are medications commonly reviewed prior to administration unless there is a dedicated ED pharmacist available around the clock. These factors can contribute to medication errors.[8,21] Nursing administration errors also can be facilitated by drug shortages.[22] In one case, methohexital was being used as a substitute during a shortage of propofol. The methohexital, which is not commonly used, was improperly diluted and a patient received a fatal overdose.[14]

Use of Therapeutic Alternatives

Another potential consequence of ED drug shortages is that alternative agents may be less effective or have more adverse effects. For example, the FDA has listed succinylcholine in short supply for over a year.[3] This has resulted in the use of alternative paralytics for RSI, such as rocuronium. Alternative paralytics may be less effective than succinylcholine or have the unwanted effect of prolonged paralysis, leading to suboptimal intubating conditions and increasing the risk of complications.[23] As another example, several benzodiazepines that are considered first-line treatment for ethanol withdrawal (midazolam, lorazepam, and diazepam) have had reported shortages within the past year.[3,24] Barbiturates may be used as a substitute for benzodiazepines in a shortage situation. While barbiturates are effective to treat withdrawal, they have more adverse effects and a narrower margin of safety.[24,25]

Delayed or Inadequate Treatment

In some shortage scenarios, there may not be an alternative treatment, which can lead to delayed treatment or nontreatment. Some hospitals have the practice of relocating medications that are in short supply from the floors to the pharmacy to better manage use. This practice can be dangerous when the medication is needed during an emergency and can have potentially fatal consequences in the ED and critical care settings.[26] Shortages that have affected several opioid analgesics can also result in other consequences, such as inadequate pain control.[27] When a medication is completely unavailable, there may also be adverse outcomes. This has been described in the oncology literature; however, this may also affect the ED.[28–30] For example, during previous influenza seasons, there have been shortages of both oseltamivir and influenza vaccines. This can have a

major effect on the ED and may pose a public health hazard during an epidemic, when patients at high risk of complications go untreated and more patients present to the ED because of the lack of vaccination.[31]

Different Concentrations

Medication errors can also occur when there is a change in concentration or packaging due to a shortage. Under routine circumstances, drugs of the same concentration are often stocked in the ED. However, during a shortage, pharmacy purchasers may need to procure medications in nonroutine concentrations. In one reported case that happened in a gastroenterology suite, there was a shortage of the usual ketamine concentration (10 mg/mL). Instead the pharmacy was using the 50 mg/mL concentration because that was what was available. The provider did not properly dilute the medication and a patient was overdosed, experiencing confusion and delirium.[32] Such errors have also been reported with different concentrations of opioids and benzodiazepines.[14]

Compounding Errors

In an effort to ensure access to medications during shortages, some pharmacies are compounding these products themselves. Also, many products traditionally available in premixed packages now have to be admixed in pharmacies prior to dispensing. The process of compounding medication introduces another step that can potentially lead to errors. One case that was reported involved a pharmacy that compounded a small batch of bupivacaine and epinephrine; however, too much epinephrine was put into the admixture. The drug was administered to two patients who developed significant adverse effects.[14] In addition to calculation errors, there is also concern regarding microbial contamination of compounded products, particularly in light of the recent fungal meningitis outbreak.[33–35] Small-scale pharmacy compounding does not have to comply with the same quality control standards as large-scale manufacturing operations, increasing the potential for microbial contamination, improper labeling, and substandard product.[34,35]

Compromised Sterility and Infectious Complications

During shortages, efforts to preserve scarce resources can have unwanted consequences. It is not uncommon practice for sterile single-use vials of injectable products to be penetrated multiple times to conserve medication despite violating labeling recommendations. This practice can lead to compromised sterility and infectious complications. In addition, improper use can lead to disease transmission between patients, including hepatitis B and C and the human immunodeficiency virus. This was reported in Nevada when 50-mL vials of propofol were reused for multiple patients to conserve the medication. This practice resulted in the transmission of hepatitis C virus between patients.[36]

Increased Costs and Resource Utilization

Drug shortages can also increase health care costs. For drugs that have been affected by shortages, the price of the product often increases due to market forces. Although profit margins may increase, it is often not enough to overcome the underlying reasons shortages occur, particularly for generic drugs, as their prices are often fixed by Medicare legislation.[18] Because generic drugs are disproportionately affected by shortages, health care facilities may need to purchase higher cost brand name products or more expensive alternative medications. Patients in the ambulatory setting may also have to bear the burden of more costly alternative therapies when purchasing medications at the pharmacy. Drug shortages have also sparked the formation of a "gray market," where distributors buy up available supplies of medications on the shortage list. These distributors then can sell the medications at significantly higher prices. One study reported up to a 335% increase in drug prices on the gray market during a shortage.[13,37] In addition, the labor costs can also be higher to manage inventory and locate medications during times of shortage.[7,8]

MITIGATION STRATEGIES

The Role of the FDA and Governmental Interventions

In response to shortages in the late 1990s and concerns about potential disruptions from turn of the millennium (Y2K), the FDA established the DSP in 1999. The program was relatively small and less active until 2005, when drug shortages started to become more pronounced. At that time, the DSP had begun tracking drug shortage reports and became more active in resolving and mitigating the effects of shortages.[1] The DSP can serve various roles, depending on the characteristics of the particular shortage. In addition, the FDA has specialists with diverse knowledge to deal with different aspects of drug shortages. Once the DSP has been notified that the potential for a shortage exists, the program works with manufacturers to address the reasons for compromised supply to prevent or mitigate the shortage. The DSP will determine the necessity of the medication involved and focus efforts on medications deemed to have a greater necessity and those with limited therapeutic alternatives.[38] The reasons for the potential shortage are identified and addressed when possible. This might involve the DSP helping to identify different suppliers of raw materials or alternative manufacturers. In addition, the DSP can expedite FDA review of supplemental applications and facility inspections. The DSP can also provide guidance in bringing manufacturing facilities up to required standards.[1,38]

One of the most important ways in which drug shortages are mitigated is through the dissemination of information on the FDA's website. This is maintained and updated daily by the DSP.[3] Included is information on which drugs are experiencing shortages, specific products affected, the duration of the shortage, reasons for the shortage, availability, and anticipated release date if known. Timely knowledge of anticipated or actual shortages can allow health care providers and institutions to implement strategies to minimize the effects of the shortage.[1]

There are additional roles that the FDA can perform to mitigate drug shortages. The FDA has allowed for

temporary importation of medications affected by shortages that meet U.S. quality standards. The FDA has permitted the distribution of medications that have particulate matter found on inspection if a filter is used prior to administration to eliminate risk to the patient.[39] Another way the FDA has increased supplies of medications affected by shortage is to extend expiration dates on medication that is on the market and about to expire. An example of this practice involved coral snake antivenin, which was discontinued by the manufacturer and would otherwise be completely unavailable to treat potentially life-threatening envenomations.[40]

Although the FDA plays a critical role in the management of drug shortages, it has limited regulatory authority. Currently, the FDA cannot require a manufacturer to produce a specific product or regulate the volume of product produced. In addition, the FDA cannot determine how the product is distributed or to whom it is distributed. Pharmaceutical manufacturers are not required to specify production goals to the FDA, and the FDA does not have the ability to reprimand manufacturers who do not meet these goals or current quality standards.[20]

Prior to the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, manufacturers had to provide advanced notification of anticipated shortages only in selected circumstances. The passage of FDASIA helped to expand the authority of the FDA in managing drug shortages.[39] Specifically, it requires all manufacturers of medically important drugs to notify the FDA in advance if they anticipate production problems or plan to discontinue a product. These early notification clauses also include biologic products.[39] In late 2011, President Obama also issued an executive order to promote the voluntary reporting of potential shortages. This advanced notification may allow the FDA, other manufacturers, distributors, and health care facilities to mobilize resources to minimize the effects of anticipated shortages. The FDA was also provided authority to expedite the review of drug applications and manufacturing facilities in cases where these actions would mitigate a shortage situation. The FDASIA also allows health care facilities and third parties to report shortages and has loosened restrictions on hospitals that repackage medications that are in short supply. Finally, FDASIA provides for the establishment of an FDA task force to develop a strategic plan for the future management of drug shortages that was submitted to Congress in October 2013. The initial strategic plan focused on two main priorities: strengthening mitigation response and developing long-term prevention strategies (Table 2).[41] The FDA must provide Congress with an annual report regarding the state of drug shortages in the United States.[39]

One major shortcoming of FDASIA is that there are no provisions for penalties for manufacturers who do not comply with notification requirements. The FDA can issue publically available letters of noncompliance to manufacturers but cannot levy civil or monetary penalties. In addition, the FDA cannot force manufacturers to produce a particular medication, nor can they penalize manufacturers for the quality of products produced.[39] Although the initial response by manufacturers has been positive, it is unclear if this is adequate incentive to ensure compliance with FDASIA. One report found that there was a significant increase in the number of shortages that were both reported and prevented; however, there has not been a decline in the total number of drug shortages since the passage of FDASIA.[42]

Table 2
Key Elements of the FDA's Strategic Plan to Address Drug Shortages

Goal 1: Strengthen Mitigation Response
Develop and/or streamline internal FDA processes
Improve data and response tracking
Clarify manufacturer's roles and responsibilities
Enhance public communication about drug shortages
Goal 2: Develop Long-term Prevention Strategies
Develop methods to prioritize and incentivize manufacturing quality
Use regulatory science to identify early-warning signals of shortages
Increase knowledge to develop new strategies to address shortages

Because drug shortages continue to be a major problem after the passage of FDASIA, there has been much debate over what additional steps can be taken to further mitigate the situation. Many have proposed holding manufacturers responsible for failure to comply with FDASIA notification requirements by allowing civil and monetary penalties.[42] In 2011, there were bills introduced and supported primarily by Democrats into the Senate and House of Representatives, both called the Preserving Access to Life-Saving Medications Act. These bills would allow for such penalties and further expand the authority of the FDA. At this time, neither bill has been enacted into law.[43,44] There has been some opposition to these bills primarily by the Republican party, which has traditionally been a strong supporter of the pharmaceutical industry, a major opponent of such legislation.[45] Another option would be to provide incentives to manufacturers for keeping their facilities in good working order and for expanding their capacity to produce medications that may be affected by shortages. These incentives could take the form of tax credits, rebates, or temporary market exclusivity.[43] Such incentives would in part address some of the major underlying causes of drug shortages, in particular the profitability of generic injectable drugs. Another intervention that has been proposed by Republicans would be to remove price limitations on injectable generic drugs that are imposed by Medicare legislation, which would allow prices to increase based on market forces, increasing profitability for manufacturers.[46] At the same time, this would also increase drug costs for Medicare programs, health care facilities, and patients, which could have unintended consequences.[18]

Nongovernmental Efforts

There are a variety of strategies that can be employed to prevent or mitigate the consequences of drug shortages both in the ED and on a larger scale. In addition to the FDA's DSP, the American Society of Health Systems Pharmacists (ASHP) has become a valuable resource.[47]

The ASHP regularly maintains a website with detailed shortage information, focusing on clinical management and ensuring optimal drug therapy. The organization has drafted guidelines for the management of shortages and purchasing guidelines for pharmacies.[48,49] The ASHP website also provides therapeutic alternatives to drugs in current shortages when available.[47] In response to widespread drug shortages, many institutions have attempted to develop specific evidence-based protocols for substitutions when possible. One recent example included the use of sodium acetate as a replacement for sodium bicarbonate as an antidote for specific poisonings.[49] Information from these various sources can be used by hospital-based pharmacy staff, ED administration, and providers, to mitigate the effects of shortages.

At the state level, the Texas Medical Board has set an example by working to promote awareness and mitigate the effects of drug shortages. The board has taken the step of acknowledging that shortages can affect patient care, provides resources on its website, and has made it a point to take shortages into consideration when addressing complaints to the board.[50] In addition, the Texas Department of State Health Services has also issued guidance for EMS providers in managing shortages.[51] Hopefully these state and local initiatives will continue to develop and augment national-level efforts.

The Role of EDs and Hospitals

Although oncology drugs have been most commonly affected by shortages, there have been valuable lessons learned that can be translated into the ED. Oncology practitioners have become vigilant in identifying potential shortages and being proactive in inventory management. In efforts to expand existing supplies, different formulations (preservative containing vs. preservative free) have been substituted when possible. In addition, to minimize waste from partially used vials, multiple patients are scheduled for their chemotherapy on the same day to avoid wasting leftover medication. Finally, when medication supplies cannot provide treatment for all patients, an ethical framework has been designed for prioritizing patients who should receive existing drugs. Examples of patients who receive priority during times of shortage include those undergoing curative therapy, those on regimens with proven survival benefits, those with cancers without acceptable alternative regimens, pediatric patients, and those patients involved in clinical trials.[52] Such strategies have helped to mitigate the effects of shortages in the oncology population and some principles may be applied to managing shortages in the ED; however, drug shortages are becoming a mounting problem for a broader range of patients.

When it comes to managing ED drug shortages, we recommend a proactive approach. ED providers, pharmacists, and administrators should become familiar with current medication shortages that may affect their departments. Frequent communication with the pharmacy department and the hospital pharmacy and therapeutics ("P and T") committee can mitigate the effects of shortages. P and T committees can assist in prioritizing use of medications in short supply and designing protocols for substitution. Emergency physicians play an active role in P and T committees in many institutions. When an ED shortage occurs, it is important to identify available therapeutic alternatives. It is equally important to ensure that there are protocols in place for use of alternative medications and that staff is properly educated regarding use.[9] One strategy might be to spell out alternative drug names and doses in a large sign in critical care rooms to ensure that providers have a back-up when common RSI medications are in short supply. Alternatively, clinical decision support at the point of electronic order entry might even suggest appropriate alternatives for a medication in shortage. When no therapeutic alternative exists, there should be an organized and ethical approach for allocating existing supplies.[10] In these situations, patients with the greatest need for the medication should receive priority.[10] For example, when tetanus vaccine was in short supply, only patients with high-risk wounds were vaccinated.[9] When resources permit, ED-based pharmacists can play a critical role in managing drug shortages. In addition to managing shortages in the ED, EMS medical directors must also be aware of current shortage trends, identify therapeutic alternatives, and revise protocols as necessary to ensure that patients in the prehospital setting receive the best possible drug therapy.[53]

Because drug shortages might result in adverse medical outcomes, ED providers could potentially be held liable. At the same time, there is little legal precedent with regard to liability in such situations and the details of each individual case will often determine liability. Currently, pharmaceutical manufacturers are not liable for adverse outcomes that result from drug shortages.[1] Providers and health care facilities are not likely to be held liable simply because a medication was not available, but more likely because there were not proper policies in place to mitigate the effects of the shortage or because a medical error occurred in using an alternative medication.[45] Liability for adverse outcomes can be minimized in health care facilities by taking a proactive approach, primarily by being aware of and anticipating shortages, having appropriate protocols in place when a shortage occurs, educating providers, and performing continuous quality review.[45] Similarly, in the prehospital setting, knowledge of current shortages with proactive incorporation into protocols and education of providers is critical in avoiding liability.[54] In the ED, in addition to being aware of shortages and protocols, providers should document that the rationale for using alternative medications was related to a shortage of the preferred drug. In addition, if there is a delay in therapy or adverse drug event pursuant to a drug shortage, this should also be carefully documented and risk management involved.[9]

CONCLUSIONS

Drug shortages are caused by a variety of factors and most commonly involve generic parenteral medications. Many of these drugs are commonly used in the ED, particularly in the critical care setting, and may affect patient care and increase health care costs. Current policy initiatives have had a limited effect on addressing drug shortages. ED providers must be aware of short-

ages and take an active role in mitigating their effects on patient care. Ultimately, a multifaceted approach involving regulators, manufacturers, providers, and other stakeholders will be required to address this growing public health problem.

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Longitudinal Trends in U.S. Drug Shortages for Medications Used in Emergency Departments (2001–2014)

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Abstract

Objectives: This was a study of longitudinal trends in U.S. drug shortages within the scope of emergency medicine (EM) practice from 2001 to 2014.

Methods: Drug shortage data from the University of Utah Drug Information Service were analyzed from January 2001 to March 2014. Two board-certified emergency physicians classified drug shortages based on whether they were within the scope of EM practice, whether they are used for lifesaving interventions or high-acuity conditions, and whether a substitute for the drug exists for its routine use in emergency care. Trends in the length of shortages for drugs used in EM practice were described using standard descriptive statistics and regression analyses.

Results: Of the 1,798 drug shortages over the approximately 13-year period (159 months), 610 shortages (33.9%) were classified as within the scope of EM practice. Of those, 321 (52.6%) were for drugs used as lifesaving interventions or for high-acuity conditions, and of those, 32 (10.0%) were for drugs with no available substitute. The prevalence of EM drug shortages fell from 2002 to 2007; however, between January 2008 and March 2014, the number of EM drug shortages sharply increased by 435% from 23 to 123. From January 2008 to March 2014 shortages in drugs used as a direct lifesaving intervention or for high-acuity conditions increased 393% from 14 to 69, and shortages for drugs with no available substitute grew 125% from four to nine. Almost half (46.6%) of all EM drug shortages were caused by unknown reasons (the manufacturer did not cite a specific reason when contacted). Infectious disease drugs were the most common EM drugs on shortage, with 148 drug shortages totaling 2,213 months during the study period.

Conclusions: Drug shortages impacting emergency care have grown dramatically since 2008. The majority of shortages are for drugs used for lifesaving interventions or high-acuity conditions. For some, no substitute is available.

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Drug shortages are defined by the U.S. Food and Drug Administration (FDA) as "a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug."[1] A 2014 Government Accountability Office (GAO) report reviewed trends in drug shortages and reported that the number of active shortages each year almost tripled between 2007 and 2012, from 154 in 2007 to 456 in 2012.[2] Quality control problems, such as bacterial contamination or the presence of glass or metal

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particles in drug vials that resulted in supply disruptions, were the most frequently cited causes; however, the report also cited that half of studies reviewed by the GAO suggested that the immediate cause of drug shortages are driven by underlying economics of the drug market.[2]

A wide range of medications used both in the emergency department (ED) and in prehospital settings, such as antidotes, heparin, and nitroglycerin, have recently been affected by national drug shortages. Not having commonly used medications to treat high-acuity conditions such as respiratory distress, cardiac dysrhythmias, and overdoses can reduce the ability of ED providers to deliver quality care because in many cases substitutes are considerably less effective, and physicians are not as familiar with their use.[3] In addition, not having commonly used medications to treat everyday conditions, such as prochlorperazine for headache and nausea, can lead emergency physicians (EPs) to choose other less effective medications or use more expensive alternatives. In a proceedings report from the Health and Human Services' Emergency Care Coordination Center, it was estimated that 40% of drug shortages affect emergency care.[4] To the best of our knowledge no studies in peer-reviewed journals have directly analyzed data to estimate the actual proportion nor assessed what specific types of medications have been in shortage in emergency care for the longest periods of time.

We describe trends in U.S. drug shortages affecting emergency care from 2001 into 2014 and categorize the medications based on whether they are used for life-threatening illnesses or high-acuity conditions and whether a substitute exists. We also describe shortages affecting specific therapies.

METHODS

Study Design

This was a secondary data analysis. This study was determined to not be human subjects research by the institutional review board at the George Washington University.

Study Setting and Population

We used drug shortage data from the University of Utah Drug Information Service (UUDIS) from January 2001, when data collection started by this service, to March 2014. UUDIS receives reports of drug shortages submitted via the American Society of Health-System Pharmacists (ASHP) public website (www.ashp.org/shortage). Anyone can report a drug shortage on this website. Drug information specialists at UUDIS research these shortage reports by contacting product manufacturers to verify if a shortage exists and, if so, to determine the reason and an estimated resupply date. If the investigation shows a shortage exists, information is then transferred to ASHP and is posted at the ASHP public website. When possible, online postings on the ASHP website contain information about alternative medications as well as potential safety implications. UUDIS frequently updates the information based on the estimated resupply dates. UUDIS and ASHP define a drug shortage as "a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent."[5] For example, a shortage of prefilled syringes of a specific product may cause significant logistic and safety issues, even if the same product is available in vials. This clinician-focused definition results in a larger number of drug shortages tracked than by the FDA. UUDIS considers a shortage to be resolved when all National Drug Codes either are back in stock or have been discontinued. Data from UUDIS were used in this study for our analysis instead of taking data directly from the FDA because prior to the FDA Safety Innovation Act of 2012 (FDASIA) the FDA did not publish shortages in a publicly available database.

Study Protocol

To describe the extent of drug shortages in the field of emergency medicine (EM), two board-certified, practicing EPs (one is JMP) (one of whom also has a Doctor of Pharmacy degree and is a board-certified medical toxicologist [MMA]) independently reviewed data from the UUDIS on 1,798 pharmaceutical products. For each drug entry, the two physicians assessed: 1) whether or not the drug is used in the general scope of EM practice; 2) whether drugs within the scope of ED practice were used as a direct intervention for a lifesaving or high-acuity condition (i.e., medications used for resuscitation/intubation such as succinylcholine or vasopressors or medications used in Advanced Cardiovascular Life Support such as epinephrine or amiodarone); and 3) whether a substitute for the drug exists for the common ED practice indication (i.e., naloxone is the only reversal agent for opioid overdose). The kappa coefficient for inter-rater agreement for whether the drug was used in ED practice was 0.69 (95% confidence interval [CI] = 0.65 to 0.72), for whether it was used for a direct intervention for a high-acuity condition was 0.59 (95% CI = 0.52 to 0.66), and whether a substitute exists was 0.70 (95% CI = 0.58 to 0.81). Kappa coefficients in the range of 0.61 to 0.80 are considered to have substantial agreement while 0.41 to 0.60 are considered to have moderate agreement.[6] All discrepancies were discussed between the two physicians for a final categorization for each variable.

Additional data from UUDIS included were the year of the shortage and the length of the shortage; in addition, medications were classified by one EP (MMA) into the following categories based on the primary indication in EM: allergy/immunology, analgesia, cardiology, cardiovascular, critical care, endocrine, fluids/electrolytes, gastrointestinal, hematology, infectious disease, local anesthetics, miscellaneous, musculoskeletal, neurology, obstetrics/gynecology, ophthalmology, psychiatry, pulmonology, sedative-hypnotic, topical, and toxicology. The EP with the pharmacy degree determined these categories. This EP also conducted the review of pharmaceutical data from the UUDIS.

Data Analysis

Data were described using standard descriptive statistics. A Shapiro-Wilk test found that shortage time was not normally distributed. Therefore, we used the Wilcoxon rank-sum (Mann-Whitney) tests and

Kruskal-Wallis tests to assess differences in shortage time by reasons for shortage, acuity, substitute availability, and year. To calculate differences in shortage time with a 95% CI, we used Hodges-Lehmann median distances. Shortages for drugs that were discontinued were not used in analyses of shortage time (n = 23). The analyses used all available data in the UUDIS, and therefore no calculations to anticipate needed sample sizes for comparisons were performed.

Visual inspection of the drug shortages by month showed two distinct temporal trends—a downward (negative) trend from 2002 to the end of 2007 and an upward (positive) trend from the beginning of 2008 to 2014. A segmented regression analysis of drug shortages before and after January 2008 was performed to assess these trends. Time was coded as a continuous variable in 1-month intervals from 1 (January 2001) to 159 (March 2014). We excluded the first year of data collection (2001) from the regression equation to adjust for a time lag for drugs to first appear on the shortage list. For analytic purposes, drugs that were on shortage for more than one time period were counted as separate shortages. The total number of EM drugs on shortage was regressed on a constant, a linear trend term (x), a dummy variable equaling zero prior to January 2008 and one thereafter, and a post-January 2008 trend term (x–84) as described by Wagner et al.[7] A Durbin-Watson test indicated presence of serial autocorrelation and was corrected for by using the Cochrane-Orcutt transformation.[8] A Shapiro-Wilk test confirmed that the residuals were normally distributed. A Breusch-Pagan/Cook-Weisberg test indicated presence of heteroscedasticity, and therefore robust standard errors were used. No outliers were detected using standard box-plot analysis (interquartile method).[9] A p-value of <0.05 was considered statistically significant for comparisons. Data were collected in Microsoft Excel and analyses were conducted using Stata 13.1.

RESULTS

Descriptive Analysis of Data

There were 1,798 drug shortages from January 2001 to March 2014, of which 610 (33.9%) were classified within the scope of EM (Table 1). Of the drugs used in EM, 52.6% (321 shortages) were for drugs used as a direct intervention for life saving or high-acuity conditions. This accounted for 17.9% of all drug shortages overall during the study time frame (321 of 1,798). Of these 321 shortages, 10.0% (32 shortages) did not have substitutes (Data Supplement S1, available as supporting information in the online version of this paper).

The median shortage time for EM drugs was 9 months (interquartile range [IQR] = 4 to 20 months). No significant differences were found in shortage times for drugs used as a direct intervention for high-acuity conditions or for drugs with no available substitute. Median shortage time for drugs used as a direct intervention for high-acuity conditions was nine months (IQR = 4 to 23) compared to nine months (IQR = 3.5 to 17) for drugs not used for this reason, with a median difference of one month (95% CI = 0 to 2 months). Median shortage time for drugs with no available substitute was 10.5 months (IQR = 4 to 22.5 months) compared to

Table 1
Categories of Drugs on Shortage used in Emergency Medicine and High-acuity Versus Non–High-acuity Drugs (January 2001–March 2014

Drug Category	Number of Shortages, Total = 610	Acuity of Shortage		Drug Most Frequently on Shortage (Number of Times on Shortage)
		High-acuity, Total = 321	Non–High-acuity, Total = 289	
Infectious disease	148 (24.3)	66 (44.6)	82 (55.4)	Acyclovir injection (6)
Analgesia	57 (9.3)	3 (5.3)	54 (94.7)	Hydromorphone (8)
Toxicology	52 (8.5)	51 (98.1)	1 (1.9)	Antivenin polyvalent injection (5)
Critical care	50 (8.2)	49 (98.0)	1 (2.0)	Epinephrine 1 mg/mL injection (7)
Gastrointestinal	48 (7.9)	9 (18.8)	39 (81.2)	Pantoprazole (8)
Miscellaneous	48 (7.9)	20 (41.7)	28 (58.3)	Dexamethasone (6)
Cardiology	39 (6.4)	36 (92.3)	3 (7.7)	Nitroglycerin injection (8)
Fluids/electrolytes	26 (4.3)	23 (88.5)	3 (11.5)	Calcium chloride (5)
Sedative-hypnotic	22 (3.6)	13 (59.1)	9 (40.9)	Phenobarbital Elixir (6)
Local anesthetics	21 (3.4)	4 (19.0)	17 (81.0)	Lidocaine/epinephrine (9)
Hematology	18 (3.0)	14 (77.8)	4 (22.2)	Desmopressin (2)
Pulmonology	18 (3.0)	5 (27.8)	13 (72.2)	Guaifenesin extended-release tablets (multiple suppliers) (4)
Cardiovascular	12 (2.0)	9 (75.0)	3 (25.0)	Bumetanide injection (3)
Neurology	11 (1.8)	6 (54.5)	5 (45.5)	Phenytoin (5)
Allergy/immunology	9 (1.5)	3 (33.3)	6 (66.7)	Diphenhydramine (3)
Ophthalmology	9 (1.5)	0 (0.0)	9 (100.0)	Tetracaine 0.5% eye drops (2)
Endocrine	8 (1.3)	6 (75.0)	2 (25.0)	Levothyroxine injection (4)
OB/GYN	5 (0.8)	4 (80.0)	1 (20.0)	Methylergonovine (4)
Psychiatry	4 (0.7)	0 (0.0)	4 (100.0)	Benztropine injection (2)
Musculoskeletal	4 (0.7)	0 (0.0)	4 (100.0)	Methocarbamol 500 mg tablets (4)
Topical	1 (0.2)	0 (0.0)	1 (100.0)	Gelfoam (1)

Data are reported as n (%).
OB/GYN = obstetrics and gynecology

9 months (IQR = 4 to 19) for drugs with an available substitute, with a median difference of 1 month (95% CI = –2 to 4 months).

Most Common Drugs on Shortage

Drugs were categorized by pharmacologic class to understand the landscape of the shortages (Table 1). The most common categories of EM drugs found on shortage during the study period were infectious disease, analgesia, and toxicology. For these categories, the most common drugs on shortage were acyclovir injection (infectious diseases), hydromorphone (analgesia), and antivenin polyvalent injection (toxicology).

Reasons for Shortages

Common reasons for drug shortages are presented in Table 2. For the EM drug shortages with a known reason, 25.6% were due to manufacturing delays or problems, 14.9% were due to supply and demand issues, and 4.4% were due to issues with raw materials. In 46.6% of shortages, manufacturers did not give a reason. Other reasons for shortages included business decisions, discontinued products, and regulatory reasons. Median shortage time was longest for drugs on shortage due to raw materials (18 months; IQR = 7 to 34 months) and shortest for regulatory issues (3 months; IQR = 1 to 13 months).

Trends in Data by Shortage Month

The number of EM drug shortages for each month from 2001 to 2014 is shown in Figure 1. Two distinct trends can be seen between 2002 and the end of 2007 and from the beginning of 2008 to March 2014. These trends were examined using segmented regression analysis. From January 2002 to December 2007, the number of EM drugs on shortage decreased from 52 to 20 at a rate of β –0.60 drugs per months (95% CI = β –0.77 to β –0.43). From January 2008 to March 2014, the number of drugs on shortage increased from 23 to 123 at a rate of 1.49 drugs per month (95% CI = 1.33 to 1.66). A similar trend was found in both high- and non–high-acuity conditions (Table 3).

Table 2
Most Common Reasons Given for Drug Shortage, January 2001 –March 2014

Reason for Shortage*	Number of Shortages, *n* (%)	Shortage Months	Median (IQR)
Manufacturing delays/problems	156 (25.6)	2,901	13 (6–26)
Supply and demand	91 (14.9)	1,364	10 (4–19)
Raw materials	27 (4.4)	596	18 (7–34)
Discontinued	23 (3.8)	NA	NA
Regulatory	11 (1.8)	151	3 (1–13)
Business decision	13 (2.1)	145	6 (3–14)
Other†	5 (0.8)	25	3 (2–8)
Unknown	284 (46.6)	3,532	7 (3–15)
Total	610	8,714	9 (4–20)

IQR = interquartile range; NA = not applicable.
*Reasons for shortages were given by the drug's manufacturer.
†Other = short-dated product (*n* = 2), natural disaster (*n* = 2), temporary plant closure.

DISCUSSION

We found that drug shortages for medications impacting emergency care fell from 2002 to 2008, but since 2008 have risen dramatically by more than 400%. Nearly half of the drugs in shortage were drugs used for high-acuity or life-threatening conditions, and in a minority of cases (32 over 13 years), there was no substitute available (Data Supplement S1). We were not able to directly determine the cause for the fall and subsequent rise in shortages in recent years; however, several factors likely contribute. A recent 2014 GAO report found no clear consensus on the underlying cause of drug shortages, citing quality problems or changes in the way that FDA conducts inspections may be contributing factors.[2] The GAO report also noted other potential causes such as the role of group purchasing organizations, changes in Medicare Part B reimbursement policy, or low-profit margins that limited investments infrastructure and may have caused manufacturers to exit the market.[2]

Specifically with respect to FDA inspection and compliance activities, increased FDA oversight of the manufacturing process may have contributed to temporary and permanent plant closures, leading to supply disruptions.[2,10] The House Committee Report highlighted that between 2009 and 2010 the number of warning letters sent by the agency increased by 42%, and between 2010 and 2011 the number of warning letters increased by an additional 156%.[10] Of the 219 drugs listed on the ASHP shortage list as of February 21, 2012, at least 128 (58% of the drugs on the shortage list) were produced by at least one facility undergoing FDA remediation.[10]

In addition, along with these factors, the 2008–2009 economic downturn may have played a role, since 2008 is the first year of rising drug shortages. However, even with the recent economic recovery, drug shortages have continued to grow. Of all EM drug shortages (*n* = 610), one in four were due to manufacturing delays or problems and 15% were due to supply and demand issues (Table 2), which suggest that shortages may be continuing due to market failure.

The majority of drugs in shortage over the study period were generic sterile injectable drugs. A common reason that is often cited behind the cause of generic shortages is the low reimbursement rates from Medicare Part B, which was initiated in the Medicare Modernization Act of 2003.[11] This part of the law commonly referred to as "ASP (average sales price) plus 6%," caps Medicare reimbursement to hospital outpatient clinics and individual physicians at 6% over the average sales price of the drug. Generic sterile injectables are already priced very low, so the profit margin remains low. Because there is a 6-month lag between manufacturers' submission of ASP data and when changes in sales prices are reflected in reimbursement, it is difficult for manufacturers to raise their prices more than 6% in any 6-month period. Even though this reimbursement policy does not apply to inpatient settings, it still creates risks in markets like sterile injectables, where the

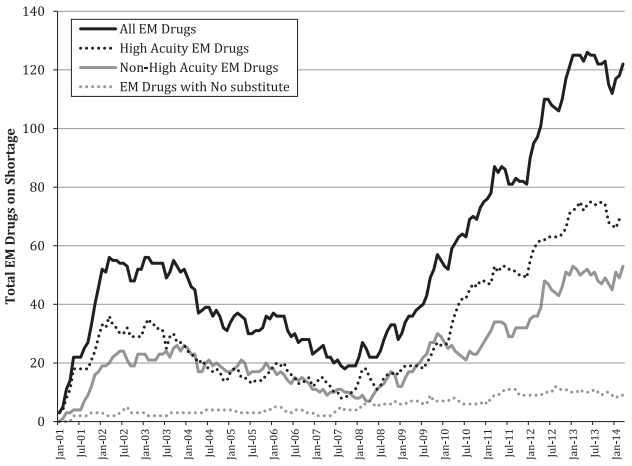

Figure 1. Shortages of emergency medicine drugs, January 2001 through March 2014. EM = emergency medicine.

manufacturing process is not trivial and the constant drive to lower costs can leave little room for investment in expansion or improvement of manufacturing facilities. Another frequently cited cause of the shortage in sterile injectables is that the number of manufacturers in the market is very small, and therefore there is a lack of "capacity," which means another line or facility would not be available to manufacture the same product if active lines or facilities were deemed inoperable.[11] While data show that the overall quantity and range of drugs produced by generic oncology manufactures has increased substantially, the capacity of these manufacturing facilities have remained stable.[12] Shortages are then concentrated in drugs where the volume of sales and drug prices were declining in years preceding the shortage, suggesting that manufacturers may be diverting resources to more profitable product lines.[12]

Drug shortages are of particular concern in emergency care settings where providers must rapidly treat ill and injured patients. In our study, some of the drugs that were most commonly on shortage included medications such as epinephrine and amiodarone, which are used in relatively rare emergency situations and also more commonly used medications that have a variety of indications, such as promethazine, lorazepam, and diphenhydramine. For most medications, substitutes exist but may not be as effective and may have more side effects or providers may not have as much experience using them. This could lead to increases in medication errors, such as issues with dosing or interactions.

In 32 drugs over the 14-year period, there was no substitute for a drug on shortage. These include antidotes that reverse the effects of drug overdose (therapeutic or recreational drugs) or are treatments for exposure to toxic substances. The longest affected medication in the infectious disease category was the rabies immune globulin. While relatively rare, this can put patients at serious risk if unavailable. Shortages of other injectables like naloxone are also problematic because there is no other substitute for opioid intoxication.[13]

Table 3
Segmented Regression Analysis of Monthly Drug Shortages: January 2002–March 2014

Shortages	β Coefficients	95% CI
All EM drugs		
Trend January 2002–December 2007	–0.60	–0.77 to –0.43
Trend January 2008–March 2014	1.49	1.33 to 1.66
Trend change	2.09	1.80 to 2.38
R^2	0.76	
Non–high-acuity drugs		
Trend January 2002–December 2007	–0.23	–0.31 to –0.16
Trend January 2008–March 2014	0.60	0.52 to 0.69
Trend change	0.83	0.70 to 0.97
R^2	0.66	
High-acuity drugs		
Trend January 2002–December 2007	–0.33	–0.56 to –0.10
Trend January 2008–March 2014	0.87	0.71 to 1.02
Trend change 2008–2014	1.20	0.87 to 1.52
R^2	0.54	
No substitute available		
Trend January 2002–December 2007	0.03	–0.00 to 0.06
Trend January 2008–March 2014	0.08	0.05 to 0.10
Trend change 2008–2014	0.05	0.00 to 0.09
R^2	0.49	

EM = emergency medicine.
*The estimates have been corrected for first-order autocorrelation by means of the Cochrane-Orcutt procedure.[8]

With increasing drug shortages in the United States, hospital systems and pharmacies need to inform front-line EM providers of these shortages and have hospital-wide protocols available for delivery of care when critical drugs are on shortage. While local and regional systems can collaborate to prepare for shortages and put protocols in place to protect patients to the best of their ability, the root cause of drug shortages should be aggressively explored at the national level by policymakers, manufacturers, physician-led organizations, and patient advocacy groups. Attempts should continue to be made by the FDA and other relevant organizations to provide high-quality, timely information about the availability of medically necessary drugs to hospital pharmacies.

LIMITATIONS

Data collected by UUDIS are limited because they depend on voluntary reports of shortages by clinicians; therefore, drug shortages may have existed that are not included in the UUDIS data set. We did not conduct an anticipated needed sample size analysis because we used all available data in the UUDIS. However, this is the most comprehensive available source of drug shortage information.

This study is also limited because we relied on two physician reviewers to categorize the UUDIS drug list. For example, the decision on whether or not a drug had a substitute was a subjective distinction made by two physician reviewers. The inter-rater agreement in these classifications was reasonably high and was resolved after discussion; however, had these classifications been performed by other physicians, results may have been different. We also only examined drug shortages in the hospital setting and did not describe shortages impacting prehospital care. We removed discontinued drugs because many did not have any shortage time calculated. This action may have caused an underestimate of total shortages and shortage time in cases where a drug was on shortage for a period of time and then later discontinued.

Another limitation is that the data includes active shortages. By definition, these shortages have not been resolved, and therefore we do not know their actual duration. For example, an active shortage that began in January 2014 will only appear to have a shortage time of 3 months (January 2014–March 2014). However, the actual time of this shortage may be longer. As a result, the shortage times reported may be underestimated.

CONCLUSIONS

Drug shortages affecting emergency care have grown dramatically since 2008. The majority of shortages are for drugs used for lifesaving interventions or high-acuity conditions. For a minority of drugs, no therapeutic alternative is available. Further work is needed to understand the impact of drug shortages on ED quality of care and outcomes. Drug shortages continue to be a national concern to public health and should be prevented by the continued efforts made by industry and government. Until the problem is resolved, attempts should continue to be made by the FDA and other relevant organizations to provide high-quality, timely information about the availability of medically necessary drugs to hospital pharmacies.

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Supporting Information

The following supporting information is available in the online version of this paper:

Data S1. Emergency Medicine Drug Shortages for Drugs with No Substitute, January 2001 – March 2014.

U.S. drug shortages for medications used in adult critical care (2001–2016)☆

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ABSTRACT

Purpose: We describe trends in U.S. shortages impacting critical care drugs from 2001 to 2016.
Materials and methods: Shortages within the scope of critical care were identified using data from the University of Utah Drug Information Services. Shortage characteristics were described using standard descriptive statistics and regression analysis.
Results: Of 1969 shortages reported, 1004 (51%) were for drugs used in critical care. New shortages fell from 2001 to 2004, then increased, peaking in 2011 (116). For critical care shortages, 247 (24.6%) involved drugs used for high acuity conditions. The majority of drugs on shortage were parenteral, (720; 71.7%) and 393 (39.1%) were single source drugs. Alternatives were available for 887 (88.3%) drugs, although 250 (24.9%) alternatives were impacted by shortages. Infectious disease drugs were the most common drugs on shortage, with 200 (19.9%) shortages, with a median duration of 7.7 months (IQR = 2.8–17.3). By the end of the study, 896 (89.2%) shortages were resolved and 108 (10.8%) remained active. The median duration for active shortages was 13.6 months (IQR = 5.8–58.4) while the duration for resolved shortages was 7.2 months (IQR = 2.8–17.3).
Conclusions: Although the number of new shortages peaked in 2011 and is now declining, there remain a substantial number of active shortages impacting critical care drugs.

1. Introduction

Prescription drug shortages are a major public health threat in the U.S [1]. The Food and Drug Administration (FDA) defines a drug shortage as "a period of time when the demand or projected demand for the drug within the U.S. exceeds the supply of the drug" [2]. Despite efforts to curb shortages, such as the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA), there was an increase in new drug shortages between 2013 and 2014. The American Society of Health-System Pharmacists (ASHP) reported there were more than triple the number of total new drug shortages in 2014 as there were in 2004 [3]. Many reported shortages have been attributed to business decisions and supply disruptions arising from quality control problems [4]. The most recent data from the Government Accountability Office (GAO) note many shortages are the result of a small number of manufacturers combined with quality problems at the facilities and low profit margins [5]. Survey data suggest that drug shortages can result in increased medication errors and adverse events translating into suboptimal care, higher institutional costs, and poorer patient experience [6,7]. Drug shortages have also been associated with delays in care [8].

The impact of shortages may be amplified in the critical care setting where providers deliver time-sensitive, life-saving, high intensity care. Shortages disproportionately impact sterile injectable medications, which are commonly used in critical care settings. Use of alternative medications, when available, may increase the likelihood of medication errors because of provider unfamiliarity, or increased toxicity, due to use of second-line medications that may have more adverse effects than first-line agents [9,10].

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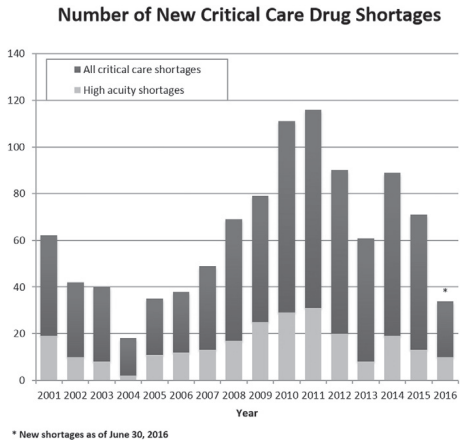

Fig. 1. Number of new critical care drug shortages.

While studies have examined overall and class-specific drug shortages, shortage trends pertaining specifically to critical care medicine are less well described [1,11-14]. The objective of this study was to describe trends in U.S. shortages impacting drugs used in critical care practice from 2001 to 16.

2. Materials and methods

2.1. Study design and setting

This was a retrospective study using shortage data from the University of Utah Drug Information Service (UUDIS) from January 2001 to June 2016. UUDIS receives reports of drug shortages submitted via the American Society of Health-System Pharmacists (ASHP) public website (www.ashp.org/shortage). Reported shortages are researched by Drug Information Specialists at UUDIS who contact product manufacturers to verify if a shortage exists. Once confirmed, they obtain the reason and an estimated resupply date. They transfer this information to the ASHP who posts it on the ASHP public website. UUDIS frequently updates the information based on the estimated resupply dates. UUDIS and ASHP define a drug shortage as "a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent." [12] For example, a shortage of a medication supplied in prefilled syringes may cause significant logistic and safety issues, even if the same medication is available in vials. This clinically focused definition results in more drug shortages tracked by the UUDIS than by the FDA, who defines a shortage as "a period of time when the demand or projected demand for the drug within the U.S. exceeds the supply of the drug" [2]. UUDIS considers a shortage to be resolved when all National Drug Code (NDC) line items are either back in stock or have been discontinued. Data pertaining to clinical outcomes regarding shortages are not collected by UUDIS. This study was determined to not be human subjects research by the Institutional Review Board at the MedStar Health Research Institute.

2.2. Data acquisition

To identify drug shortages in the field of critical care, a medical toxicologist/clinical pharmacologist/emergency physician, board certified critical care/emergency medicine physician, and a pulmonary medicine/critical care attending independently reviewed data from the UUDIS on 2161 pharmaceutical products. For each drug entry, we assessed: 1) whether or not the drug is used in the scope of adult critical care practice, 2) whether drugs within the scope of critical care practice were used as a direct intervention for a life-threatening or high acuity condition, and 3) whether a substitute for the drug existed for the critical care-related indication. Discrepancies were discussed between the three physicians for a final categorization of each variable.

We also investigated shortage trends based on length of shortage, whether the drug was a parenteral product, brand versus generic, or if the drug was a single source product (made by one manufacturer). In addition, medications were classified into the following categories based on the most common critical care-related indication for subgroup analysis: anesthesia/analgesia, allergy and immunology, cardiovascular, endocrine, gastroenterology, hematology, infectious diseases, fluids, electrolytes, and nutrition, neurology, pulmonology, psychiatry, renal,

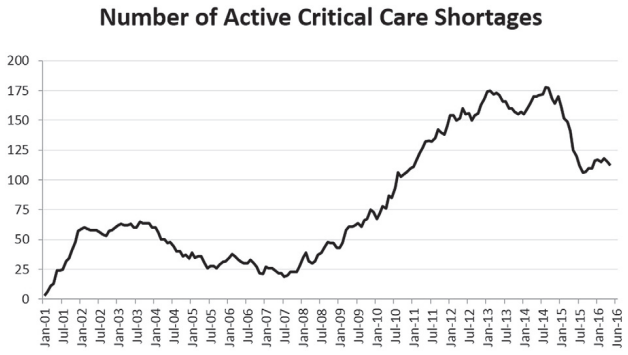

Fig. 2. Number of active critical care shortages.

Table 1
Drug shortages by therapeutic category.

Therapeutic category	Number of shortages n (%), total n = 1004	Median shortage months (IQR)	Most common drug on shortage (times on shortage, median shortage length)
Anesthesia, analgesia	147 (14.6)	10.2 (3.4–23.7)	Lidocaine (13×, 7.6 months)
Allergy and immunology	26 (2.6)	5.1 (3.0–18.6)	Diphenhydramine (4×, 10.8 months) Hydroxyzine (4×, 20.7 months)
Cardiovascular	154 (15.3)	8.1 (3.4–22.6)	Phentolamine (7×, 2.7 months)
Endocrine	26 (2.6)	9 (4.2–22.5)	Levothyroxine (6×, 9.6 months)
Gastroenterology	76 (7.6)	8.3 (2.9–18.9)	Pantoprazole (6×, 11.8 months) Prochlorperazine (6×, 10.1 months)
Hematology	45 (4.5)	6.6 (3.0–15)	Phytonadione (5×, 10.2 months)
Infectious diseases	200 (19.9)	7.7 (2.8–18.3)	Meropenem (9×, 7.9 months)
Fluids, electrolytes, nutrition	7 (0.7)	8.1 (6.0–13.9)	None with multiple shortages
Neurology	66 (6.6)	6.1 (2.8–16.2)	Edrophonium (7×, 7.4 months)
Pulmonology	52 (5.2)	5.2 (2.0–9.5)	Albuterol (6×, 1.1 months) Dexamethasone (6×, 7.7 months)
Psychiatry	12 (1.2)	8.2 (6.1–10.5)	Haloperidol (2×, 40.2 months) Zaleplon (2×, 5.5 months)
Renal	7 (0.7)	10.8 (1.8–41.9)	Acetazolamide (3×, 1.8 months)
Topical	34 (3.4)	5.9 (1.8–10.9)	Mupirocin (8 × 7.6 months)
Toxicology	48 (4.8)	6.7 (3.2–21.9)	Naloxone (5×, 4.6 months)

topical, and toxicology. When available, we examined the reason the shortage occurred; however, manufacturers were not required to release this information.

2.3. Data analysis

Data were described using standard descriptive statistics. A Shapiro-Wilk test demonstrated shortage duration was not normally distributed. Therefore, we describe average shortage durations using median and interquartile range (IQR). To calculate differences in shortage durations with a 95% confidence interval (CI), we used Hodges-Lehmann median distances. Drugs that were on shortage multiple times were counted as separate shortages. Discontinued drugs and drugs with a reported shortage length of less than one day were removed prior to analysis.

Visual inspection of critical care drug shortages reported by month indicated a non-linear (sigmoidal) trend with inflection points occurring in 2002, 2008, and 2013. A segmented linear regression approach was used to examine three linear trends from January 2002 to December 2007, January 2008 to December 2012, and January 2013 to June 2016. Time was coded in 1-month intervals from 1 (January 2001) to 186 (June 2016). A Durbin-Watson d-statistic found no presence of serial autocorrelation [15]. A Shapiro-Wilk test of the residuals found some evidence of non-normality and a Breusch-Pagan/Cook-Weisberg test indicated presence of heteroscedasticity; therefore, robust standard errors were used. No severe outliers were detected using standard box-plot analysis (interquartile method). A p-value of <0.05 was considered significant. Data were collected in Microsoft Excel (Microsoft, Seattle, WA) and analyses were conducted using Stata 14.2 (College Station, TX).

3. Results

3.1. Descriptive analysis of data

After removing discontinued drugs and drugs with a shortage length of less than one day (n = 192), a total of 1969 drug shortages were examined over the 15.5-year period. Of these, 1004 (51.0%) were classified as within the scope of critical care practice. A complete list of shortages and excluded drugs are included in Supplemental Appendixes 1 and 2. Fig. 1 shows the number of newly reported critical care shortages from 2001 to 2016. Although the number of new critical care drug shortages initially fell from 2001 to 2004, shortages increased significantly, peaking in 2011 with 116 new shortages. Fig. 2 shows the total number of critical care drugs on shortage, from 2001 to 2016. The data in this figure include any new shortages plus any shortages in previous months that had yet to be resolved. The total number of critical care drugs on shortage decreased at a rate of $\beta -0.7$ per month (95% CI = $\beta -0.7$ to $\beta -0.6$; $r^2 = 0.84$) from January 2002 to December 2007. From January 2008 to December 2012, the total number of critical care drugs on shortage increased at a rate of $\beta +2.5$ per month (95% CI = β 2.4 to $\beta -2.6$; $r^2 = 0.98$). From January 2013 to June 2016, the total number of critical care drugs on shortage decreased at a rate of $\beta -1.7$ per month (95% CI = $\beta -2.1$ to $\beta -1.4$; $r^2 = 0.70$). Similar trends can be seen in shortages of drugs used for high-acuity conditions.

Drugs were categorized by therapeutic category in order to understand the landscape of the shortages (Table 1). Infectious disease drugs were the most common critical care drugs on shortage, with 200 (19.9%) shortages with a median shortage duration of 7.7 months (IQR = 2.8–18.3), followed by cardiovascular drugs with 154 shortages (15.3%) with a median duration of 8.1 months (IQR = 3.4–22.6), and anesthesia/analgesia drugs with 147 (14.6%) shortages with a median duration of 10.2 months (IQR = 3.4–23.7).

Across all therapeutic categories, 247 (24.6%) shortages were for critical care drugs used for high acuity or life-threatening conditions (Table 2). The majority of critical care drug shortages (720; 71.7%) were parenteral. Three hundred and ninety-three (39.1%) were single source drugs. No alternative was available for 117 critical care drugs (11.7%). Alternatives were available for 887 (88.3%) critical care drugs on shortage, although 250 (24.9%) of those alternatives were also impacted by a shortage during the study period (Table 2).

By the end of the study period, 896 (89.2%) critical care shortages had been resolved and 108 (10.8%) drugs remained on active shortage. The median duration for active shortages was 13.6 months (IQR = 5.8–58.4)

Table 2
Characteristics of critical care shortages.

	Number of shortages n (%)	Median length of shortage in months (IQR)
Total ICU shortages	1004 (100)	7.4 (2.9–18.8)
Total active shortages	108 (10.8)	13.6 (5.8–58.4)
Total resolved shortages	896 (89.2)	7.2 (2.8–17.3)
Total generic drug shortages	725 (72.2)	8.6 (3.5–22.5)
Total single source shortages	393 (39.1)	5.2 (2.1–13.2)
Total parenteral shortages	720 (71.7)	8.6 (3.2–24.9)
Total high acuity shortages	247 (24.6)	9.9 (3.7–26.6)
Total shortages with no alternatives available	117 (11.7)	5.8 (2.5–20.1)
Total shortages with alternatives available	887 (88.3)	7.7 (3.1–18.8)
Total shortages with alternatives impacted (of drugs with substitute available)	250 (24.9)	12.5 (5.3–31.4)

Table 3
Examples of drug shortages for medications used in adult intensive care units (2001–2016).

Medication	Therapeutic category	Number of times short during study period	Potential impact
Amino acid solutions	Fluids, electrolytes, nutrition	Total = 8 1/30/09 to 02/13/09 03/19/09 to 11/11/09 8/05/10 to 07/20/11 03/31/10 to 06/08/10 02/01/12 to 06/13/13 08/06/13 to 04/14/14 03/04/15 to 04/29/16 06/29/16 to ongoing	Customized parenteral nutrition not possible during the shortage.
Amiodarone	Cardiovascular	Total = 3 03/27/02 to 11/28/06 01/10/08 to 11/05/13 03/12/14 to 10/02/14	May have limited stock for use during post-operative period and for use during Advanced Cardiac Life Saving (ACLS)
Calcium chloride	Fluids, electrolytes, nutrition	Total = 5 10/17/10 to 04/23/02 02/06/06 to 70/10/06 02/15/07 to 11/03/08 06/11/10 to 03/14/11 04/13/11 to ongoing	May have limited stock available for use during Advanced Cardiac Life Saving (ACLS) as well as unfamiliar presentations (vials vs. syringes)
Cisatracurium	Anesthesia, analgesia	Total = 4 11/19/01 to 12/03/03 08/14/09 to 07/01/10 08/12/11 to 10/05/11 01/15/14 to 05/19/15	Shortage occurred at the same time as alternative neuromuscular blocking agents
Dobutamine	Cardiovascular	Total = 2 04/30/01 to 07/07/04 12/02/11 to 10/09/14	Shortage occurred at the same time as other pressors
Dopamine	Cardiovascular	Total = 4 04/24/06 to 07/11/06 03/26/10 to 05/17/10 09/20/10 to 03/27/15 05/20/16 to ongoing	Shortages occurred at the same time as other pressors
Epinephrine injection	Cardiovascular	Total = 5 02/11/09 to 02/27/09 07/22/10 to 01/13/11 05/25/10 to 12/06/10 05/02/11 to 11/16/11 01/12/12 to ongoing	May have limited stock available for use during Advanced Cardiac Life Saving (ACLS) as well as unfamiliar presentations (vials vs. syringes)
Lorazepam	Anesthesia, analgesia	Total = 3 01/4/07 to 07/09/07 05/23/08 to 09/29/15 02/11/16 to current	
Nitroglycerin	Cardiovascular	Total = 4 03/16/17 to 07/30/07 08/28/09 to 05/28/10 08/09/10 to 10/28/11 06/27/12 to 06/30/15	First-line treatment for patients with acute MI. Required the use of nitroglycerin ointment as an alternative in some cases.
Norepinephrine	Cardiovascular	Total = 3 05/21/01 to 07/11/01 04/26/10 to 07/07/10 11/18/10 to 01/26/15	Use of alternatives may lead to greater mortality
Propofol	Anesthesia, analgesia	Total = 3 12/12/07 to 08/11/08 10/16/09 to 10/06/11 03/30/12 to 06/19/14	Other sedatives may have been required during this shortage.
Piperacillin/tazobactam	Infectious diseases	Total = 5 05/03/01 to 12/03/03 10/03/05 to 11/29/06 01/24/05 to 08/02/05 07/13/10 to 05/11/11 05/08/13 to current	Commonly used antibiotic – shortage occurred at the same time as many potential alternatives.
Vecuronium	Anesthesia, analgesia	Total = 3 09/04/02 to 12/03/03 11/30/07 to 03/25/08 09/16/08 to ongoing	Shortage occurred at the same time as alternative neuromuscular blocking agents

while the median duration for resolved shortages was 7.2 months (IQR = 2.8–17.3), with a median difference of 6.2 (95% CI = 3.1–12.4). Median shortage duration for drugs used for high acuity conditions was greater than that of drugs used for non-high-acuity conditions (9.9 months vs. 7.3 months), with a median difference of 1.9 months (95% CI = 0.7–3.4). Median shortage duration for drugs with no available alternative was not statistically different from drugs with an available alternative. A list of high-impact shortages is presented in Table 3.

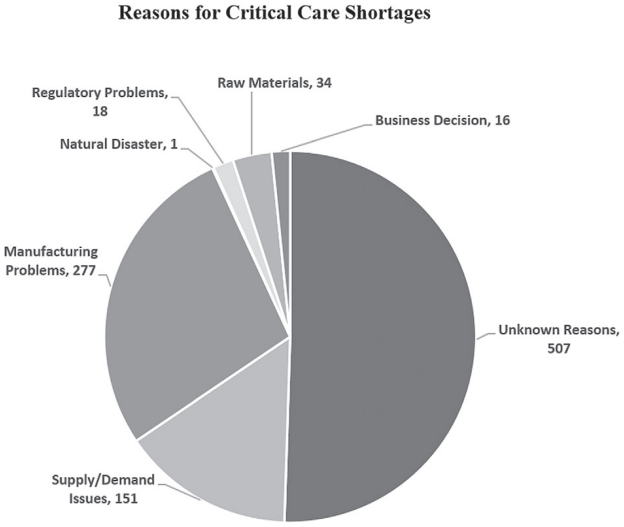

Fig. 3. Reasons for critical care shortages.

3.2. Reasons for shortages

Of the 1004 critical care drug shortages, 27.6% were due to manufacturing delays or problems, 15.0% were due to supply and demand issues, and 50.5% of drugs were on shortage for reasons not provided by the manufacturers (Fig. 3). The rest of the delays were due to raw material shortages, business decisions, regulatory issues, and natural disasters. Median shortage time was longest for drugs on shortage due to problems obtaining raw materials (14.7 months, IQR = 7.6–34.2) and shortest for delays due to regulatory issues (4.2 months, IQR = 1.4–12.5).

4. Discussion

We found a substantial number of critical care drug shortages during the study period. Trends in shortages fluctuated over time and the reasons for these fluctuations are likely to be multi-factorial [16]. The initial increase in shortages in 2005 has been in part attributed to increased FDA oversight and scrutiny at manufacturing sites [8,15,16]. There was a significant increase in the number of shortages that occurred starting in 2008, which coincided with the economic downturn in the U.S. Interestingly, shortages have declined but persisted despite economic recovery. Many of the critical care drugs impacted by shortages were generic injectable products. This may be due in part to low reimbursement rates and lower profit margins for these products from Medicare Part B, which was initiated as part of the Medicare Modernization Act of 2003 [17]. Low profit margins or declining sales may force manufacturers to concentrate their production efforts on more profitable products [18].

Another reason cited for the increase in shortages has been manufacturing problems, which we also found in our study. One area of concern has been increased FDA inspection and compliance activities, as well as FDA scrutiny of the manufacturing process. This has resulted in temporary cessation of manufacturing activities at many production sites, which can contribute to supply disruptions. One investigation showed that 58% of the drugs on the ASHP's shortage list were produced by at least one facility undergoing FDA remediation [19]. With low profit margins and high production and remediation costs, some manufacturers have chosen to close a number of plants, resulting in a lack of redundancy in the manufacturing system and further supply disruptions.

New critical care shortages began to level off in 2012 and declined from 2013 to 2016. Like the increases in shortages, the decline\ in shortages is also multi-factorial. There has been an economic recovery from the 2008 recession. In addition, there have been multiple initiatives to combat drug shortages, particularly the passage of the FDASIA in 2012, which expanded the FDA's authority to manage shortages [20]. The FDA also implemented a task force with a strategic plan to further develop mitigation and prevention strategies [21]. Associating the decline in shortages with the FDASIA would take a much more robust analysis, additional data, and could be an area for future research. Also, the FDA does not make the number of shortages reported to them publicly available. There is a GAO analysis from 2014 that showed that since the implementation of the 2012 FDASIA, the FDA has prevented more shortages [4].

The most commonly affected medication class was antimicrobials, representing nearly 20% of all shortages. Shortages of antimicrobials may lead to use of substitute drugs with more limited activity against pathogens. Piperacillin/tazobactam, which is recommended by the Infectious Disease Society of America to be administered within 3 h of diagnosis of certain infections causing septic shock, was on shortage for over five years during the study period [22]. Delays may have devastating effects in septic shock patients who are usually cared for in the ICU. Kumar and colleagues demonstrated a >7% increase in mortality per hour effective antimicrobials were not administered [23]. Cardiovascular drugs were the second most common class of medications impacted by shortages. Amiodarone, considered favorable in ICU patients because it is a multichannel blocker with less negative inotropic effects than other agents with the same indication, was the most common cardiovascular drug on shortage [24]. In addition, there were shortages of norepinephrine, considered by many the first-line vasopressor for septic shock. A recent study demonstrated that during times of

norepinephrine shortage, phenylephrine use increased, which was associated with an increase in mortality [25]. Almost 15% of all shortages were analgesics including fentanyl, an agent recommended by the Society of Critical Care Medicine to control pain in the ICU [26].

There are several ways to address drug shortages at the institutional and departmental levels. Intensivists must work proactively as part of an interdisciplinary team including pharmacy and nursing. Protocols should be established for the use of alternative therapies during times of shortage to prevent medication errors in combination with staff education. In addition, allocation schemes should be in place in the event of an ethically challenging case in which a drug needs to be rationed with preference given to one patient over another [27].

There were some limitations to this study that should be addressed. Data collected by UUDIS rely on clinicians to voluntarily report shortages; therefore, drug shortages never reported are not included in the UUDIS data set. However, this is one of the most comprehensive available sources of drug shortage information [5]. The major limitation of this study was that we could not assess the actual impact shortages had on individual institutions or on patient care, either in the form of delayed/suboptimal therapy, resultant medication errors, or adverse outcomes, as these data are not collected by UUDIS. We could not describe the severity of shortages affecting a particular product (e.g., whether the product was in limited supply or completely unavailable). Our methods would have underestimated the duration of shortages that were active at the end of the study period. Data were not collected pertaining to time and costs of mitigating shortages.

This study is also limited because we relied on three physician reviewers to categorize the UUDIS drug list. The inter-rater agreement for classification of ICU drugs was substantial with a kappa statistic of 0.63. Had these classifications been done by other physicians, included medications may have been somewhat different. We also only examined drug shortages in the adult critical care setting and did not describe shortages impacting pediatric critical care. We removed discontinued drugs because many did not have any shortage time calculated. This may have resulted in an underestimate of both shortage time and total number of shortages in cases where a drug was on shortage for a period of time and subsequently discontinued.

5. Conclusion

Drug shortages impacting critical care rose from 2001 to 2012 and declined from 2013 to 2016. However, even in 2016, shortages still impact a substantial number of medications used in critical care practice. Although mitigation strategies have reduced the number of new shortages reported, a large number of long standing shortages remain. Critical care providers must be cognizant of drug shortages and take a proactive role in mitigation in order to prevent adverse patient outcomes. The clinical impact of these shortages as well as optimal mitigation strategies remain areas of prospective study.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2017.06.005.

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Drug shortages: Implications for medical toxicology

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Context. Drug shortages have significantly increased over the past decade. There are limited data describing how shortages impact medical toxicology of drugs. *Objective*. To characterize drug shortages affecting the management of poisoned patients. *Materials and Methods*. Drug shortage data from January 2001 to December 2013 were obtained from the University of Utah Drug Information Service. Shortage data for agents used to treat poisonings were analyzed. Information on drug type, formulation, reason for shortage, shortage duration, marketing, and whether the drug was available from a single source was collected. The availability of a substitute therapy and whether substitutes were in shortage during the study period were also investigated. *Results*. Of 1,751 shortages, 141 (8.1%) impacted drugs used to treat poisoned patients, and as of December 2013, 21 (14.9%) remained unresolved. New toxicology shortages increased steadily from the mid-2000s, reaching a high of 26 in 2011. Median shortage duration was 164 days (interquartile range: 76–434). Generic drugs were involved in 85.1% of shortages and 41.1% were single-source products. Parenteral formulations were often involved in shortages (89.4%). The most common medications in shortage were sedative/hypnotics (15.6%). An alternative agent was available for 121 (85.8%) drugs; however, 88 (72.7%) alternatives were also affected by shortages at some point during the study period. When present, the most common reasons reported were manufacturing delays (22.0%) and supply/demand issues (17.0%). Shortage reason was not reported for 48.2% of drugs. *Discussion*. Toxicology drug shortages are becoming increasingly prevalent, which can result in both suboptimal treatment and medication errors from using less familiar alternatives. *Conclusion*. Drug shortages affected a substantial number of critical agents used in the management of poisoned patients. Shortages were often of long duration and for drugs without alternatives. Providers caring for poisoned patients should be aware of current shortages and implement mitigation strategies to safeguard patient care.

Keywords Drug shortages; Antidotes; Medical toxicology

Introduction

Over the past decade, prescription drug shortages have become increasingly common and more severe.[1–4] In 2005, the FDA's Drug Shortage Program (DSP) reported limited supplies of 61 medications. By 2011, this number increased more than fourfold, to 251 medications.[3] In addition to being more frequent, recent shortages have been of longer durations and are more likely to impact patient care.[5,6] Drug shortages can result in treatment delays or require suboptimal treatment with a less effective or more toxic alternative medication. If an alternative therapy is not available, patients may go without indicated treatment.[2,7,8] Drug shortages can also compromise patient safety because they may lead to medication errors or non-treatment due to the lack of availability of an effective treatment. One survey demonstrated 89% of hospitals reported that a patient safety issue was potentially caused by a drug shortage.[9] A recent Associated Press article drew attention to 15 deaths reported over 15 months attributed to drug shortages.[10]

Drug shortages most commonly occur with generic injectable products, and a great deal of attention has been focused on shortages affecting chemotherapeutic agents.[11–14] Shortages have also been reported of important critical care drugs and antidotes, such as sodium bicarbonate.[15,16] Drug shortages can have significant implications for the management of poisoned patients; however, there are limited data describing the extent to which shortages affect such medications. The objective of this study is to describe trends in drug shortages that can impact the management of poisoned patients.

Methods

The University of Utah Drug Information Service (UUDIS) began collecting national drug shortage data in January

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2001, and publishes critical drug shortage information on a public website (www.ashp.org/shortage) hosted by the American Society of Health-System Pharmacists (ASHP).[17,18] There is a legal agreement between UUDIS and ASHP for the provision of services and maintenance of the database. UUDIS defines a shortage as a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent.[17] This definition differs slightly from, but is more inclusive than, the FDA definition of a shortage. For example, a shortage of prefilled syringes of a specific product may cause significant logistic and safety issues, even if the same product is available in vials. UUDIS receives voluntary reports of drug shortages via the reporting feature on the ASHP website. Clinical pharmacists at UUDIS then research each shortage reported, to verify if a shortage actually exists. This research includes determining all potential manufacturers of a reported drug shortage and all relevant National Drug Codes (NDCs). Next, each manufacturer is contacted to determine which of their drugs, based on NDC codes, are in shortage at the national level. UUDIS collects the following drug shortage data: generic and product name, therapeutic category, date shortage began, resolved date, duration, reason for the shortage, controlled substance schedule (if applicable), and whether or not the drug is an injectable product. The manufacturers are also asked for a reason for the shortage as well as an estimated release date; however, they are not required to provide a reason. If most manufacturers are having a national shortage of the same drug, then UUDIS will post information at the ASHP drug shortage website noting which products are affected, which products are available, specific methods for accessing the product, reasons for the drug shortage, and estimated resupply dates. UUDIS considers a shortage to be resolved when all suppliers have all formulations of a product available or have discontinued their products. UUDIS also follows FDA's drug shortage website and will generally resolve shortages when FDA considers the shortages resolved. The Government Accountability Office (GAO) considers the UUDIS data to be the most comprehensive and reliable source of drug shortage information for several reasons. Although both FDA and UDDIS collect data on drug shortages, UDDIS data are more detailed, with a broader definition of shortages. Additionally, the ASHP website provides clinicians with recommendations for alternatives or management strategies, which the FDA does not do.[19,20]

The data set was restricted to shortages that occurred between January 1, 2001 and December 31, 2013. An a priori list of medications used to treat poisoned patients was developed prior to reviewing the list of pharmaceutical shortages. Two board-certified medical toxicologists independently and systematically reviewed all pharmaceutical products affected by shortages and identified agents that are used to treat poisonings (both antidotes and medications commonly used to treat toxicological conditions). All discrepancies were discussed between the two physicians until a consensus was reached. General supportive medications such as vasopressors and drugs used for rapid sequence intubation were not included. The list generated by systematic review was more comprehensive than the a priori list and was therefore used for the rest of the analysis. Shortage data were then further analyzed focusing on the type of drug involved, formulation, reason for shortage, shortage duration, marketing status (brand vs. generic), and if the drug was a single-source product (produced by one manufacturer). For some portions of the analysis, products were grouped together based on therapeutic category. The availability of a substitute therapy and whether the alternative was also affected by a shortage at any time during the study period as well as multiple shortages (those that were resolved but then had another shortage) of the same drug were also noted. Descriptive statistics were used to characterize trends in drug shortages over time. Univariate analysis found that drug shortage time (in months) was not normally distributed (right skewed). Therefore, we used the non-parametric two-sample Wilcoxon rank-sum (Mann–Whitney) test to compare shortage times and describe average shortage time using median and interquartile ranges (IQRs). Discontinued products were not included in analyses of shortage time. A p value of < 0.05 was considered significant. Data were collected in Microsoft Excel (Microsoft, Seattle, WA) and analyzed using Stata 13.1 (College Station, TX). The data do not meet the definition of human subjects' research, and therefore were exempt from Institutional Review Board or IRB review. A comprehensive list of products affected by

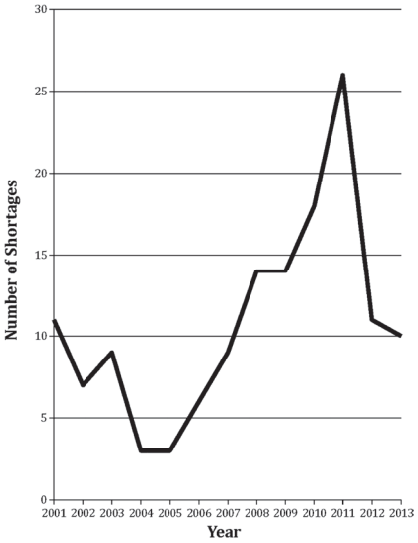

Fig. 1. Number of shortages of medical toxicology drugs reported annually.

Table 1. Medical toxicology agents without alternatives in short supply.

Agent	Number of shortages	Days in shortage	Percent of study period on shortage
Antivenin *Latrodectus mactans* (Black widow spider)	3	362 with ongoing shortages since 12/2010	31
Deferoxamine	1	1140	24
Digoxin antibody fragments	2	262	6
Lipid emulsion	1	Ongoing shortages since 11/2008	39
Mannitol	1	Ongoing shortages since 11/2011	16
Methylene blue	3	898 with ongoing shortages since 3/2013	25
Naloxone	6	1601	35
PEG 3350	1	121	3
Pralidoxime	3	1089	23
Protamine	4	1228	26

shortages is listed in a Supplementary Appendix (To be found online at http://informahealthcare.com/doi/abs/10.3109/15563650.2015.1043441).

Results

Number and duration of shortages

There were a total of 1,751 drug shortages reported to UUDIS from January 2001 to December 2013. Of these shortages, 141 (8.1%) affected products used to treat poisoned patients. The median number of shortages reported annually was 10 (range: 3–26). The total number of new shortages reported annually increased steadily from the mid-2000s, reaching a high of 26 in 2011, with a decline in recent years (Fig. 1). The year 2011 also experienced the longest median shortage duration (23 months). Of the 141 shortages, 21 (14.9%) remained active (had not been resolved) as of December 31, 2013. The median duration of resolved shortages was 164 days (range: 0–2193, IQR: 76–434). A total of 37 drugs experienced multiple shortages. The drugs with the greatest number of shortages were sodium bicarbonate and naloxone, each with 6 shortages each during the study period.

Types of drugs impacted

Generic drugs were involved in the vast majority of shortages (85.1%, $n = 120$), and 41.1% ($n = 58$) of shortages were single-source products. In addition, single-source products had a significantly longer median shortage duration (10 vs. 5 months, $p = 0.0011$). There was no difference in median shortage months when comparing brand to generic medications ($p = 0.34$). Parenteral drugs were more commonly affected by shortages (126, 89.4%) than were orally administered medications; however, the median shortage duration was not different between the two groups ($p = 0.89$). The most common type of medications involved was sedative/hypnotics (benzodiazepines/barbiturates). Antihypoglycemic agents had the longest median shortage duration (17.5 months, IQR: 7.5–28) (Table 1). An alternative agent was available for 121 (85.9%) drugs; however, 88 (72.7%) of these alternatives were affected by a shortage at some time during the study period. There was no difference in median shortage duration between drugs with therapeutic alternatives compared with those without therapeutic alternatives ($p = 0.62$). In addition, there were several agents without therapeutic alternatives that were impacted by multiple shortages (Table 2).

Table 2. Types of medical toxicology drugs affected by shortages.

Type of medication	Number of shortages ($n = 141$)*	Percent of drugs	Total shortage months**	Percent of study period on shortage***	Median shortage months (IQR)**
Anticholinergic antidotes	8	5.7	97	53	7 (4.5–13.5)
Antihypoglycemic antidotes	8	5.7	151	54	17.5 (7.5–28)
Antivenom/immune Fab	7	5.0	118	71	8 (4–37)
Chelators	6	4.3	86	44	15 (6–22)
Cholinergic antidotes	9	6.4	181	70	10 (4–31)
Cyanide antidotes	6	4.3	51	24	4.5 (2–5)
Decontamination products	2	1.4	27	17	27
Electrolytes	15	10.6	262	65	12 (5–31)
Hematologic	13	9.2	153	61	7 (3–23)
Other	24	17.0	396	81	12 (5–26)
Naloxone	6	4.3	37	24	5.5 (3–15.5)
Sedative/hypnotics	22	15.6	336	85	9 (4–22)
Vitamin/elements	15	10.6	78	44	3 (2–6)

*Includes both active and resolved shortages.
**Does not include products that were discontinued/withdrawn ($n = 9$).
***Refers to the percentage of time during the study period when at least 1 drug of that type was on shortage.

Table 3. Reported reasons for medical toxicology shortages.

Reason for shortage	Number of drugs (n=141)*	Percent of drugs	Total shortage months	Percent of study period on shortage**	Median shortage months (IQR)
Business decision	3	2.1	73	37	15 (1–57)
Discontinued/withdrawn product	9	6.4	NA		NA
Low inventory	1	0.7	4	3	
Manufacturing delays	31	22.0	569	76	16 (4–27)
Raw materials	5	3.6	127	44	25 (9–27)
Supply/demand	24	17.0	301	72	9 (4.5–17)
Not reported	68	48.2	899	98	5.5 (4–22.5)

*Includes both active and resolved shortages.
**Percent of study period refers to the percentage of time during the study period when at least 1 drug was on shortage for that reason.

Reasons for shortage

The reason for shortage was not reported for 48.2% of the drugs. When present, the most common reasons reported were manufacturing delays (22.0%), followed by supply/demand issues (17.0%). The median number of shortage months was the highest for drugs where a reason for shortage was raw materials (25 months, IQR: 9–27), followed by those with manufacturing delays (16 months, IQR: 4–27). A complete list of reasons for shortage is presented in Table 3.

Discussion

Our findings demonstrate an increase in the number of shortages for drugs used to treat poisoned patients over time. In addition, many drugs had multiple shortages with long cumulative durations. Several drugs in the same class experienced shortages, as did certain drugs without any alternative. These shortages have the potential to impact the care of poisoned patients, primarily due to the lack of treatment when indicated, or through the need for an alternative or suboptimal treatment. In addition, there is an increased risk for medication errors while using unfamiliar therapeutic alternatives.[15,18–20]

Lack of treatment when indicated, particularly for commonly used drugs and for those used to treat high acuity conditions, is a major concern. The most striking example in our study was the opioid receptor antagonist, naloxone. Naloxone is commonly used to treat opioid overdose, a potentially fatal condition, and there is currently no therapeutic equivalent available for use in the U.S. There were multiple naloxone shortages during the study period of considerable duration. Lack of access to naloxone can have public health implications in the setting of the current prescription drug abuse epidemic along with rising rates of heroin abuse.[21–24] Demand for naloxone has also increased secondary to public access programs designed to mitigate the morbidity and mortality associated with opioid overdose.[25] This mismatch in supply and demand for naloxone can have potentially fatal consequences for patients with opioid poisoning. This situation may be further complicated by recent rises in naloxone prices.[26]

Drug shortages may also force providers to use less effective or more toxic therapeutic alternatives, or less evidence-based therapies to treat poisoned patients. For example, there were multiple shortages of sodium bicarbonate, an antidote used to treat common poisonings including tricyclic antidepressant or salicylate overdose, during the study period. Sodium acetate has been proposed as a therapeutic alternative; however, there is less evidence regarding the efficacy of this drug for overdose compared with sodium bicarbonate. There are also potential toxicities, including hypotension, which require that lower infusion rates be utilized.[16] Another example encountered in our study pertains to benzodiazepines, which are the first-line agents for ethanol withdrawal, drug-induced seizures, and agitation.[27,28] Several benzodiazepines (midazolam, lorazepam, and diazepam) had shortages during the study period.[3] Barbiturates may be used as a substitute for benzodiazepines, but while effective for these indications, they have more adverse effects and a narrower margin of safety.[27,28] This situation was further complicated by the fact that certain barbiturates and propofol, another benzodiazepine alternative, were also impacted by shortages during the study period.

Therapeutic alternatives can also be more logistically difficult to use than standard therapies. For example, when there is a shortage of fomepizole, intravenous or oral ethanol can be used as an equally effective alternative. At the same time, there are several disadvantages to the use of ethanol. Intravenous ethanol may necessitate the placement of a central venous catheter for higher concentrations due to venous irritation. Additionally, intensive care unit admission may be required for close observation as patients may be clinically intoxicated and for frequent dose titration and laboratory monitoring; however, this practice may vary based on individual institutional policies. Furthermore, some hospitals may not stock or permit the use of intravenous, or even oral, ethanol.

Medication errors can occur as a result of drug shortages, particularly when providers are forced to use a therapeutic alternative with which they are less familiar. For example, shortages of calcium chloride and calcium gluconate were quite frequent and the dosing between the two products is not interchangeable. Errors can also occur when different concentrations, than are usually stocked, are used during a shortage situation or when products are extemporaneously compounded.[15,29,30]

Several attempts have been made to mitigate the impact of drug shortages on the national level with a focus on policy reform.[31–33] On a local level, medical toxicologists and other

providers who care for poisoned patients can take a proactive approach by designing protocols for the allocation of existing supplies, substitution protocols, and staff education.[15,34,35] Participation in institutional Pharmacy and Therapeutics or Drug Shortage committees and frequent communication with the pharmacy department are also potential roles served by medical toxicologists. It is also important for individual providers to be cognizant of shortages as to avoid poor patient outcomes and potential liability.[15,16]

The practice of stock-piling antidotes or other medications in anticipation of a shortage is currently not recommended.[18,36] Antidote par levels (the minimum quantity of a stocked item which is automatically reordered when stock falls below a preset level) are important tools for institutions to ensure an adequate treatment course is available. Expert consensus guidelines are available outlining suggested par levels and most poison centers offer suggested par levels for their local area.[37] Routine checks of par levels are also important as antidotes may be infrequently used. While par levels are an important tool to ensure antidote availability, par levels are a poor tool to prevent drug shortages. Shortages of antidotes are frequently long in duration. A par level of one month would be insufficient to last through a shortage. It is also difficult to predict which antidotes may be in short supply and impractical to store large quantities of all potential antidotes. Additionally, many antidotes are manufactured by just a single source. If all products are compromised due to a recall for poor quality, having a large par level will make no difference to the organization.[18] Many antidotes are also used for other therapeutic uses (methylene blue and sodium bicarbonate) and if only small amounts of product remain, Pharmacy and Therapeutics Committees or Ethics Committees may elect to reserve some products for antidote use.[9,18]

Because of the way we identified agents used to treat poisoned patients, some medications may not have been included. Additionally, because we did not include medications that were used for more general supportive measures and less specifically for poisoned patients, (such as vasopressors and rapid-sequence intubation drugs), the true impact of drug shortages in this patient population may have been underestimated. The major limitation of this study was that we could not assess the actual impact shortages had on individual institutions or on patient care, either in the form of suboptimal therapy or in terms of resultant medication errors. We could also not describe the severity of shortages affecting a particular product (e.g., whether the product was in limited supply or completely unavailable). There were limited data pertaining to the comparative efficacy of some therapeutic alternatives. Finally, we could not account for the time and resources used by institutions to mitigate shortages. These are areas for additional prospective study.

Conclusions

There was a significant increase in shortages affecting drugs used in the treatment of poisoned patients. The impact of these shortages at the patient level is unclear. Future research should evaluate patient harm derived from shortages. Medical toxicologists and other providers who care for these patients should be cognizant of current shortages that may impact their practice and implement mitigation strategies proactively to prevent adverse outcomes for poisoned patients.

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Supplementary material available online

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Longitudinal trends in U.S. shortages of sterile solutions, 2001–17

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Purpose. Trends in the shortages of sterile solutions in the United States were evaluated.

Methods. A retrospective review of shortage data from the University of Utah Drug Information Service (UUDIS) was performed. Shortages of sterile solutions, including saline, dextrose, lactated Ringer's, and sterile water for injection, were identified. We extracted the product name, reason for the shortage, shortage duration, and primary use of the solution, examining trends in shortages over time.

Results. There were 37 sterile solution shortages in the UUDIS data set, 22 of which had been resolved. The mean ± S.D. duration of a resolved shortage was 13.9 ± 9.6 months. The most common category of solution shortage was for saline products (n = 11). Manufacturing delay was the most common reason given for shortages (n = 19). In 2017, 12 new shortages were reported, and 15 solutions remained in shortage by year's end. This was the highest number of shortages at any time during the study period. The longest active shortage was for 5% dextrose/0.45% sodium chloride, which began in October 2007 and has yet to be resolved.

Conclusion. There were 37 shortages of sterile solutions from 2001 through 2017. Shortages became more severe after Hurricane Maria damaged manufacturing facilities in Puerto Rico, with 12 new shortages reported in 2017.

Keywords: drug shortages, sterile solutions

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Prescription drug shortages have become commonplace in recent years.[1,2] Long-standing shortages of medications used across a broad range of specialties, such as cancer chemotherapy and antimicrobials, are increasing and pose a threat to patient safety.[1-4] The main reasons for these shortages include quality-related manufacturing problems and insufficient capacity and redundancy to maintain production continuity during manufacturing problems.[2] Drug shortages have not only affected therapeutics, but also basic medical supplies such as saline solutions.[5-7] For example, Hurricane Maria, which made landfall on Puerto Rico on September 20, 2017, affected Baxter International's manufacturing facility there and caused a preexisting shortage of saline solutions to reach critical levels.[5-8] The lack of redundancy and manufacturing capacity prolonged the recovery of recent fluid shortages.

Sterile solutions (e.g., 0.9% sodium chloride injection, 5% dextrose injection, lactated Ringer's injection, sterile water for injection) are used for a wide variety of indications. Larger-volume products can be used for fluid resuscitation or as maintenance or irrigation fluids. Smaller-volume products are used to reconstitute products for injection or dilute medications for administration via infusion.[9] Shortages of such products may impact patient care, as has been demonstrated

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in the current shortage of saline solutions.[4] However, limited data exist to describe the extent of shortages of sterile solutions. The purpose of this article is to describe trends in sterile solution shortages from 2001 through 2017.

Methods

Data on solution shortages were collected from the University of Utah Drug Information Service (UUDIS), which has been collecting national drug shortage data since January 2001 and provides all drug shortage content for the ASHP Drug Shortage Resource Center. The Government Accountability Office considers the data from UUDIS to be the most comprehensive and reliable source of drug shortage information available.[10] Detailed methods on how UUDIS collects and verifies drug shortage data are described elsewhere.[1] Briefly, UUDIS receives voluntary reports from clinicians and works to verify if a national shortage exists by directly contacting manufacturers to determine which products at the specific National Drug Code (NDC) level are affected. Each product is assigned a specific NDC. For example, 0.9% sodium chloride injection would have a different NDC code for each manufacturer and volume. UUDIS follows shortages until manufacturers verify that all drug presentation NDCs are either discontinued or available. This study was not human subjects' research and did not require review by the institutional review board.

We used the UUDIS's (and ASHP's) definition of a shortage: "a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent." This is a broader definition than that used by the Food and Drug Administration (FDA), which defines a shortage as "a period of time when the demand or projected demand for a medically necessary drug in the United States exceeds its supply."[2]

We examined all drug shortages reported in the UUDIS between the dates of January 1, 2001, and December 31, 2017, to identify shortages of sterile solutions. We included shortages involving sodium chloride, dextrose, lactated Ringer's, and sterile water as well as combinations of these products, such as dextrose plus sodium chloride. We included products used parenterally, such as fluids used for resuscitation, for maintenance hydration, and for reconstitution or dilution of other medications. We also included solutions used for irrigation. We excluded discontinued products and solutions used for other indications, such as 50% dextrose injection.

We extracted the product name, reason given for the shortage, date the shortage began, and date the shortage was resolved. UUDIS defines the start of a shortage as the date the drug was verified to be in short supply by the manufacturer. UUDIS considers a shortage to be resolved when all suppliers have all formulations available or have discontinued their products. UUDIS also follows FDA's drug shortage website and will generally list shortages as resolved when FDA considers the shortages resolved.

We calculated shortage duration as the length of time, in months, between the shortage start and shortage resolved dates to examine trends over time. We grouped shortages together for the 4 common types of fluids involved: dextrose solution, lactated Ringer's solution, sodium chloride, and sterile water. Solutions were also classified by their primary use in patient care (e.g., diluent vial, small volume, large-volume maintenance, large-volume resuscitation). Solutions were considered small volume if they were 250 mL or less and large volume if they were 500 mL or greater.

We calculated the mean shortage duration, in months, for shortages that had resolved by the end of the study period. We also counted the number of new shortages reported in each year as well as the number of products that remained on shortage at year's end. Data were managed in Microsoft Excel (Redmond, WA), and analyses were done with Stata version 14 (College Station, TX).

KEY POINTS

- The frequency of shortages of sterile solutions has increased in recent years, particularly after Hurricane Maria damaged manufacturing facilities in Puerto Rico in 2017.
- Shortages of solutions may compromise patient safety and require increased pharmacy resources.
- A multifaceted approach will be required to mitigate current shortages and prevent new shortages from occurring.

Results

There were 37 sterile solution shortages in the UUDIS data set, 22 of which had been resolved and 15 of which were active at the end of 2017 (Table 1). The mean ± S.D. duration of resolved shortages was 13.9 ± 9.6 months. The most common category of solution shortage was for those containing sodium chloride (n = 11). The most common solution types in shortages were large-volume maintenance solutions and small-volume products (n = 10 each). Manufacturing delays were the most common reason given for shortages (n = 19).

Table 2 displays the number of new shortages reported each year and the number of solutions that remained on shortage at year's end. In 2017, 12 new shortages were reported, and 15 solutions remained in shortage by year's end. This was the highest number of shortages at any time during the study period. Before 2017, the most solution shortages reported in any calendar year was 7, occurring in both 2013 and 2014. No shortages of solutions were reported from 2001 through 2006.

The product name and length of each resolved and active shortage are listed in the appendix. The longest resolved shortages were for sterile water injections (250 and >250 mL), which began in March 2013 and resolved in September 2015 (30 months). The longest active shortage was for 5% dextrose/0.45% sodium chloride, which began in October 2007 and had yet to be resolved.

Discussion

While the total number of sterile solution shortages was relatively small, even a single fluid shortage can have a tremendous impact on health systems, clinicians, and patients. This has been demonstrated by the recent shortage of saline, which has been worse since Hurricane Maria. In particular, small-volume saline bags were in severe shortage because Baxter International supplied nearly 50% of U.S. hospitals with this product.[5-8]

The work involved to minimize the impact of these shortages on patients cannot be underestimated. For example, making a switch to dilute a product in 5% dextrose injection or changing an i.v. infusion to i.v. push can result in hundreds of hours of work to make changes to electronic health record (EHR) systems, automated dispensing cabinets, smart pumps, and other technology. Imported products may not have bar codes, or those bar codes may not be compatible with scanners. However, for most fluid shortages, patients are not affected and are able to receive necessary treatments. Instead, the burden of these shortages is shouldered by the healthcare team (e.g., surgical technicians who must use smaller bags of i.v. fluids during large-volume irrigation shortages, informatics pharmacists who must make changes to order sets in EHR systems, pharmacy technicians who must make changes to automated dispensing cabinets). Even small changes might require pharmacists to reenter orders for every patient receiving the product during a shortage. This not only takes time but may cause medication errors during order entry.

Table 1. Characteristics of Shortages of Sterile Solutions, 2001–17

Characteristic	No. Shortages			Mean ± S.D. Shortage Duration, months
	Total	Active	Resolved	
All solution shortages	37	15	22	13.9 ± 9.6
Solution content				
5% Dextrose	7	4	3	21.3 ± 7.6
Lactated Ringer's	5	1	4	13.7 ± 12.0
Sodium chloride[a]	11	4	7	9.7 ± 7.6
Sterile water	8	3	5	19.6 ± 10.2
Other[b]	6	3	3	7.2 ± 3.9
Solution use				
Diluent vial	6	2	4	8.1 ± 6.2
Irrigation	5	1	4	13.0 ± 2.0
Large-volume diluent[c]	2	1	1	30.0[d]
Large-volume maintenance[e]	10	5	5	14.8 ± 11.0
Large-volume resuscitation[f]	4	2	2	15.0 ± 20.4
Small volume	10	4	6	14.5 ± 9.9
Shortage reason				
Manufacturing delays	19	7	12	14.5 ± 9.3
Natural disaster	1	1	0	Not applicable
Supply–demand mismatch	8	5	3	13.3 ± 1.4
Unknown	9	2	7	13.0 ± 12.7

[a]Includes solutions containing sodium chloride, including 0.9% and 0.45% sodium chloride, without other constituents.
[b]Includes electrolyte solutions, 10% dextrose solutions, and combined dextrose–sodium chloride solutions.
[c]Sterile water labeled for reconstitution of medications.
[d]Standard deviation not calculated.
[e]Solutions typically used to provide continuous hydration, such as solutions containing both dextrose and sodium chloride, or electrolyte solutions.
[f]Solutions typically used in large quantities during resuscitation efforts such as lactated Ringer's injection and 0.9% sodium chloride injection.

Many pharmaceutical products require di-2-ethylhexyl phthalate (DEHP)-free bags to prevent patient exposure to potentially toxic concentrations of DEHP. However, manufacturers may minimize the production of these bags during shortages, requiring workarounds such as draining 1-L bags to make 200-mL doses during severe shortages. When small-volume products are affected, medications administered via short infusions may have to be administered by i.v. push, which can increase nursing time and the risk of adverse drug events or medication errors. Medications may also need to be switched to oral formulations when possible, which also consumes pharmacy staff resources. These additional activities can affect patient care. Longer preparation times may delay patient doses. Frequent switching of concentrations and infusion times can lead to administration errors.

Shortages of the most basic necessities for hospitals represent a market failure. A small number of

Table 2. Numbers of New Solution Shortages, 2001–17

Year	New Shortages Reported	Active Shortages at Year's End
2001	0	0
2002	0	0
2003	0	0
2004	0	0
2005	0	0
2006	0	0
2007	4	4
2008	0	1
2009	0	1
2010	0	1
2011	1	2
2012	4	4
2013	7	6
2014	7	12
2015	0	5
2016	2	4
2017	12	15

manufacturers provide these items to hospitals on a just-in-time basis. There is little resiliency or additional capacity in the current system. Some manufacturers are unwilling to invest in new factories or new capacity in the United States, largely due to economic factors. Instead, they look to FDA to approve products manufactured abroad on a temporary basis to ameliorate shortages. FDA has taken action to improve the situation, such as approving new suppliers and allowing imported products. However, some of these interventions are only temporizing measures and do not fix the underlying problems that cause shortages. For example, no government agency can force manufacturers to add capacity or improve substandard facilities.

A recent roundtable discussion on shortages with clinician groups and representatives from FDA and the Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response provided 11 recommendations for improvement.[11] One recommendation was for FDA to implement manufacturing quality ratings, similar to star ratings for hospitals. This would require suppliers to disclose the true manufacturer of products. Hospital purchasers could make quality-based purchasing decisions with these changes. Another improvement would be for the government to include medication supplies as part of national security evaluations. Experience gained from the aftermath of Hurricane Maria demonstrates that the current system is unable to adequately withstand a natural disaster, as manufacturers are not required to have redundancy or business continuity plans for life-saving drugs.

On a smaller scale, health systems, institutions, and individual practitioners should be aware of current shortages and how they may impact patient care and implement mitigation strategies proactively. A variety of mitigation strategies and workarounds may be needed to minimize waste and conserve existing supplies, while ensuring patient safety and ethically rationing limited supplies when necessary.

There were several limitations to our study. Data collected by UUDIS rely on clinicians to voluntarily report shortages; therefore, shortages may have existed that are not included in the UUDIS data set. The major limitation of this study was that we could not assess the actual effect that solution shortages had on individual institutions or on patient care. The duration of shortages that were active at the end of the study period would also have been underestimated. Data pertaining to the time and cost of mitigating shortages were not collected.

Conclusion

There were 37 shortages of sterile solutions from 2001 through 2017. Shortages became more severe after Hurricane Maria damaged manufacturing facilities in Puerto Rico, with 12 new shortages reported in 2017.

Disclosures

Dr. Fox is affiliated with the University of Utah Drug Information Service, which receives financial support from Vizient to provide drug shortage information to both Vizient and ASHP; no funds from Vizient are provided directly to Dr. Fox. She has received complimentary registration without honoraria for the ASHP Midyear Clinical Meeting for participating in continuing-education sessions on drug shortages and has also received travel support without honoraria from the Idaho Society of Health-System Pharmacists for participating in continuing-education sessions on drug shortages. Dr. Fox is also a member of the *AJHP* Editorial Advisory Board. The other authors have declared no potential conflicts of interest.

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Appendix—Active and resolved solution shortages

Shortage Type and Solution	Date Notified	Date Resolved	Duration (months)
Resolved			
Sterile water for injection, 250 mL	3/22/13	9/22/15	30.0
Sterile water for injection, >250 mL	3/22/13	9/22/15	30.0
Lactated Ringer's injection, 1 L	2/11/14	7/26/16	29.4
5% Dextrose injection, >250 mL	2/18/14	7/26/16	29.2
0.45% Sodium chloride injection, 1 L	2/20/14	1/27/16	23.2
5% Dextrose injection, ≤250 mL	11/6/13	7/23/15	20.5
Sterile water for injection, vials	3/22/13	8/14/14	16.8
Lactated Ringer's irrigation	8/12/14	10/27/15	14.5
0.9% Sodium chloride injection, ≤250 mL	5/24/07	7/25/08	14.1
5% Dextrose injection, ≤250 mL	5/24/07	7/25/08	14.1
Sterile water for irrigation	8/12/14	10/13/15	14.0
0.9% Sodium chloride irrigation	8/12/14	9/24/15	13.4
10% Dextrose injection	8/1/14	7/22/15	11.7
Lactated Ringer's irrigation	11/9/16	9/14/17	10.2
Bacteriostatic water injection	8/1/12	3/1/13	7.0
Bacteriostatic sodium chloride injection, 0.9%, vials	8/27/12	3/11/13	6.4
Sodium chloride injection, 0.9%, vials	9/28/12	4/4/13	6.2
Dextrose 10% and electrolyte no. 48 injection	12/13/07	5/20/08	5.2
Multiple electrolytes injection type 1	6/25/13	11/12/13	4.6
Bacteriostatic sodium chloride injection, 0.9%, vials	9/28/12	12/12/12	2.5
Bacteriostatic sodium chloride injection, 0.9%, vials	12/20/11	2/23/12	2.1
Lactated Ringer's injection, 1 L	9/9/13	9/26/13	0.6
Active[a]			
5% Dextrose/0.45% sodium chloride injection	10/4/07	. . .[b]	122.9
0.9% Sodium chloride injection, 1 L	1/28/13	. . .	59.1
0.9% Sodium chloride irrigation	11/9/16	. . .	13.7
5% Dextrose injection, 250 mL	2/22/17	. . .	10.3
5% Dextrose injection, 500 mL	2/22/17	. . .	10.3
5% Dextrose injection, 1 L	2/22/17	. . .	10.3
5% Dextrose/0.9% sodium chloride injection	2/22/17	. . .	10.3

Continued on next page

Continued from previous page

Shortage Type and Solution	Date Notified	Date Resolved	Duration (months)
10% Dextrose injection, 250 mL	2/22/17	· · ·	10.3
5% Dextrose injection in DEHP-free bags[c]	5/4/17	· · ·	8.0
Sodium chloride injection, 0.9%, preservative-free vials	6/12/17	· · ·	6.7
Sterile water for injection, small volume (<100 mL)	8/4/17	· · ·	4.9
0.9% Sodium chloride injection, small volume (<150 mL)	8/25/17	· · ·	4.2
Lactated Ringer's injection	10/4/17	· · ·	2.9
Sterile water for injection, large volume (>150 mL)	12/20/17	· · ·	0.4
Sterile water for injection, vials	12/28/17	· · ·	0.1

[a]Length for active shortages calculated as of January 1, 2018.
[b]Not resolved.
[c]DEHP = di-2-ethylhexyl phthalate.

Saline Shortages — Many Causes, No Simple Solution

Maryann Mazer-Amirshahi, Pharm.D., M.D., M.P.H., and Erin R. Fox, Pharm.D.

Severe and long-standing prescription-drug shortages have become a major threat to public health and patient safety.[1] Despite increased awareness and mitigation strategies, the United States has experienced shortages of many lifesaving drugs and other supplies essential to patient care. There was already a shortage of saline solution, for example, when Hurricane Maria devastated Puerto Rico, home to a key saline manufacturer, causing the problem to reach critical levels.[2]

Saline is an inexpensive product — it's simply salt water — but proper manufacturing practices are required to keep it sterile, pyrogen-free, and free from particulate matter. Production demands are challenging, since very large quantities are needed: more than 40 million bags per month. Saline is required for virtually all hospitalized patients, whether as a component of a medication infusion or as a hydration, resuscitation, or irrigation fluid.[2] Unfortunately, shortages of saline have become commonplace in recent years (see table).

Most drug shortages occur with older, generic, injectable medications that are produced by a small number of suppliers — typically three or fewer. The United States gets its saline from just three companies: Baxter International, B. Braun Medical, and ICU Medical. Most shortages are caused by a quality or production problem at the manufacturing facility — causes that apply to the current saline shortage as well.[2,3] In addition, when one supplier experiences a shortage, other suppliers often have insufficient manufacturing capacity to make up the difference. Drug manufacturers are not required to have redundancy in their facilities or even a business contingency plan in case of a disaster, no matter how essential or lifesaving the medication they are producing.[1]

The shortage of small-volume saline bags (250 ml or less) became dire almost immediately after Baxter's Puerto Rico manufacturing plant was hit by Hurricane Maria.[2] Baxter supplies approximately 50% of U.S. hospitals with this product, which is used as a diluent to deliver a variety of parenteral medications. Despite this tremendous need, Baxter has no redundancy in manufacturing capacity for small-volume saline bags. The other two saline suppliers have not been able to increase their production enough to make up for the shortage.[2,3] In fact, saline produced by B. Braun was already in short supply before the hurricane, as the company

History of Saline Shortages in the United States.*

Product	Date Shortage Began	Date Shortage Resolved	Reason for Shortage
0.9% Sodium chloride, small-volume bags	5/24/2007	7/25/2008	Supply unable to meet demand
0.9% Sodium chloride, large-volume bags	1/28/2013	Not yet resolved	Manufacturing delays
0.9% Sodium chloride for irrigation	8/12/2014	9/25/2015	Manufacturing problems
0.9% Sodium chloride for irrigation	11/9/2016	Not yet resolved	Manufacturing delays
0.9% Sodium chloride, small-volume bags	8/25/2017	Not yet resolved	Manufacturing delays due to Hurricane Maria

* The reasons for shortages are as determined by the University of Utah Drug Information Service. Drug-shortage information is available at www.ashp.org/shortages.

worked to correct manufacturing-quality problems.[3]

The saline shortage had actually begun in 2014, affecting large- as well as small-volume products.[4] Large-volume saline products (>500 ml) are typically used as maintenance or resuscitation fluids or for irrigation. Although some shortages of large-volume saline solutions are attributable to problems at manufacturing facilities, increased demand for intravenous fluids due to a severe influenza season has also contributed to the current short supply.[2]

Saline shortages can affect patient care in various ways. Medication errors and adverse drug events can result when medications that are typically administered as short infusions are given by intravenous push or when providers choose less familiar but more readily available products as substitutes. Increased ad hoc compounding of drugs may result in dilution errors or microbial contamination.[3,4]

Fixing the problem is difficult and requires a multifaceted approach entailing both focusing on current shortages and working to prevent future ones. Neither Congress nor the Food and Drug Administration (FDA) can force any manufacturer to produce a medication, no matter how lifesaving the product or how critical the need. Incentives such as accelerated approval for another product or tax relief for funding facility repairs may help reduce shortages, yet these incentives may have the unintended consequence of precipitating more shortages if companies value the incentives more than current profits. Alternatively, moving forward, the Department of Homeland Security could mandate that saline be considered part of the essential infrastructure, which would require the relevant companies to develop business continuity plans, although implementing manufacturing redundancies would be costly and require significant time.

The FDA's Good Manufacturing Practice rules require a minimum level of quality, yet shortages continue to occur because of poor conditions at manufacturing facilities. It is costly and time consuming to bring facilities up to standard, and the process of doing so can interrupt the supply chain. Since drug companies are not required to disclose the identity or location of the manufacturer that produces a drug,[1] a complete list of medications affected by Hurricane Maria is available only to the FDA and not to clinicians who need to plan for patient care. Woodcock and Wosinska have argued that poor quality is due to a lack of transparency regarding which company actually makes a product, because without such transparency clinicians cannot purchase drugs and supplies on the basis of quality.[1]

Changing the transparency requirements and mandating manufacturing redundancies may not change the course of the current saline shortage, but they are important actions for preventing future shortages. In response to the current shortage, the FDA has recently approved saline products from two additional manufacturers; however, there is a lag time between approval and the arrival of these products on the market. The newly approved products may also cost more than the currently available ones, since most organizations purchase their saline in a bundle that also includes tubing, pumps, and other accessories.

Importation of products can help in some cases. In response to the current saline shortage, the FDA has permitted manufacturers to import saline from their facilities in other countries, such as Brazil.[2] Importation is usually a temporary measure, because the FDA generally cannot find a company with sufficient foreign supplies to share with the U.S. market without creating a shortage in the country providing the import. When it comes to saline, logistics make it impractical to

import products for long periods: saline is heavy and bulky, making air transport costly and shipment periods lengthy. The FDA has also permitted extension of product expiration dates when that can be done safely. And Baxter's facility in Puerto Rico is expected to be functioning again in the near future, which will help to ameliorate the current shortage.[2]

In the meantime, the saline shortage has required clinicians to use a number of work-arounds that consume valuable resources and increase health care costs.[3,4] Supplies may need to be reserved for the sickest patients, and providers require an ethical framework for rationing products,[4] while pharmacy staff closely monitor inventory. Some medications now have to be administered as direct injections over several minutes, which increases the time nurses must spend with each patient. Some institutions have switched to syringe pumps or use Buretrol (Baxter) infusion devices (which hold small quantities of fluids) to deliver medications. Hospitals are also using more expensive premixed products and are changing the concentration of some medications so they can be mixed in larger volumes, when small-volume bags are unavailable. Making such changes requires substantial informatics resources, because the ordering platform in the electronic health record must be altered.[4,5] To conserve large-volume saline bags, oral hydration is recommended when possible. For patients who cannot take oral fluids or who require aggressive resuscitation, alternative crystalloid solutions may be considered. During shortages of large-volume saline irrigation solution, sterile water or even tap water may be substituted when appropriate.[4]

The current shortage of saline solutions demonstrates the profound effects that drug shortages can have on patient care. It is anticipated that the situation will improve in the United States in the coming weeks to months, although hospitals will continue to face shortages of other basic products. In the meantime, a multifaceted approach will be needed to ensure that patients safely get the medications they need.

Disclosure forms provided by the authors are available at NEJM.org.

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Prescription Drug Shortages: Implications for Ambulatory Pediatrics

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Objective To describe contemporary drug shortages affecting general ambulatory pediatrics.

Study design Data from January 2001 to December 2015 were obtained from the University of Utah Drug Information Service. Two pediatricians reviewed drug shortages and identified agents used in ambulatory pediatrics. Shortage data were analyzed by the type of drug, formulation, reason for shortage, duration, marketing status, if a pediatric friendly-formulation was available, or if it was a single-source product. The availability of an alternative, and whether that alternative was affected by a shortage, also was noted.

Results Of 1883 products in shortage during the study period, 314 were determined to be used in ambulatory pediatrics. The annual number of new pediatric shortages decreased initially but then increased to a high of 38 in 2011. Of the 314 pediatric shortages, 3.8% were unresolved at the end of the study. The median duration of resolved shortages was 7.6 months. The longest shortage was for ciprofloxacin 500-mg tablets. The most common class involved was infectious disease drugs. Pediatric-friendly dosage forms were affected in 19.1% of shortages. An alternative agent was available for 86% drugs; however, 29% of these also were affected. The most common reason for shortage was manufacturing problems.

Conclusions Drug shortages affected a substantial number of agents used in general ambulatory pediatrics. Shortages for single-source products are a concern if a suitable alternative is unavailable. Providers working in the ambulatory setting must be aware of current shortages and implement mitigation strategies to optimize patient care. *(J Pediatr 2018;■■:■■-■■).*

Drug shortages are a significant issue facing pediatric health professionals. A drug shortage is defined as a time when the projected demand for a drug is expected to overwhelm the supply of the drug.[1] These shortages remain a consistent threat to optimal patient care and safety.[2] The driving forces behind these shortages include supply issues, quality concerns, and economic forces.[3] Despite recent interventions from the federal government and the Food and Drug Administration (FDA), drug shortages remain a critical issue that can negatively affect patient care.[4]

Drug shortages disproportionately affect pediatric patients.[5] The recent shortages of clindamycin suspension and intramuscular penicillin are just a few examples of medications used in the pediatric ambulatory setting that are affected by shortages. These shortages force healthcare providers to use medications that may be less familiar, less efficacious, less evidenced-based, or with more adverse effects. Even seemingly unrelated shortages can have devastating consequences for pediatric patients, such as when a shortage of sodium bicarbonate lead to an incorrect compounding of baclofen suspension.[6] This led to an invasive workup and intensive care unit admission for the patient. Fifty-six percent of children in the US use at least 1 prescription or over-the-counter medication at home per week, yet there are limited data describing shortages of medications used in the pediatric ambulatory setting.[7] Therefore, we describe trends in drug shortages for medications commonly used in ambulatory pediatrics.

Methods

Drug shortage data from January 2001 to December 2015 were obtained from the University of Utah Drug Information Services (UUDIS). UUDIS has clinical pharmacists who receive voluntary reports on drug shortages from clinicians and hospitals, confirm the shortage with the manufacturer, and compile data on the specific formulations of drug on shortage. They rely on the manufacturer to determine the reason for the shortage. They also confirm the end of a shortage with the manufacturer and the FDA. This drug-shortage information is published online on the

ASHP	American Society of Health-Systems Pharmacists
FDA	Food and Drug Administration
UUDIS	University of Utah Drug Information Service

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Web site of the American Society of Health-Systems Pharmacists (ASHP). UUDIS started this data compilation in January 2001.

A pediatrician practicing in emergency medicine and a specialist in pediatric emergency medicine reviewed pharmaceutical products affected by shortages in the UUDIS database and identified agents that are used in ambulatory pediatrics (n = 314). Identification was based on the practitioners' clinical experience in their respective fields. Pharmaceuticals primarily prescribed by subspecialties were excluded. An additional member of the study team, an emergency medicine physician who is also a registered pharmacist and board-certified clinical pharmacologist and practices at a pediatric hospital, reviewed discrepancies until a consensus was reached.

Shortage data were analyzed with a focus on the type of drug involved (eg, infectious disease, pulmonary), formulation, reason for shortage, shortage duration, marketing status (brand vs generic), and whether the drug was a pediatric-friendly formulation (liquid/chewable dosing form or having a pediatric concentration) or a single-source product (produced by one manufacturer). Drugs may have multiple uses, but they were included with the most common ambulatory care use, as determined by the authors. The availability of a substitute therapy and whether the alternative also was affected by a shortage at any time during the study period also was noted. Discontinued products were excluded. This study was not evaluated by an institutional review board because it does not involve human subjects.

The final dataset was analyzed for annual trends, shortage duration, and the reasons given for the shortages. To examine annual trends, counts of new shortages were aggregated by month and by year and were examined graphically. We then compared the number of shortages reported per month in the first half of the study period (2001-2008) with the last half of the study period (2009-2015) using the Wilcoxon rank-sum (Mann–Whitney) test. Shortage duration was defined as the number of days between the date of notification to the date of shortage resolution as reported by the UUDIS. Product discontinuations (shortages that lasted zero days) were excluded. A standard conversion factor of 30.4375 days = 1 month was used to convert shortage days to shortage months for ease of interpretation. Shortage duration was not normally distributed (long right tail) as evidenced by a histogram and confirmed by a Shapiro–Wilk W test for normal data. Therefore, shortage duration is presented as medians and IQRs. The nonparametric 2-sample Wilcoxon rank-sum (Mann–Whitney) test and the Kruskal–Wallis equality-of-populations rank tests were used to compare shortage durations.

To determine whether shortage length was changing over time, we used ordinary least-squares linear with month fixed-effects to estimate the annual (yearly) trend in shortage duration. We used the log of shortage duration as our outcome, so the coefficient of year can be approximately interpreted as the percent change in the dependent variable (shortage duration) per year. For all hypothesis tests, a P value of <.05 was considered statistically significant. For shortages still active as of December 31, 2015, data from the first quarter of 2016 were examined to determine whether the shortage had been resolved. If the shortage was still active as of March 31, 2016, shortage duration was calculated as the number of months between the shortage notification and March 31, 2016. Data were collected in Microsoft Excel (Microsoft, Seattle, Washington) and analyzed with Stata 14.1 (StataCorp LLC, College Station, Texas).

Results

After we excluded discontinued products (n = 221), a final dataset of 1883 drug shortages reported between January 2001 to December 2015 was examined. Of these, 314 (17%) were identified as being used in ambulatory pediatrics, 60 of which were identified as having a pediatric-friendly form (19.1%). Annual shortage totals by year are displayed graphically in **Figure 1**. There was a median of 22 ambulatory pediatric shortages reported each year from 2001 through 2015 (IQR = 11-28). Shortages became more frequent in the last half of the study period, where the median number of annual shortages increased to 28 between 2009 and 2015 (P = .003). For shortages of pediatric-specific drug forms, there was a median of 4.5 shortages per year (IQR = 1-7). Shortages of pediatric-specific forms became more frequent in the last half of the study period, averaging 7 new shortages per year (IQR = 4-8, P = .026).

Table I presents median duration of ambulatory pediatric drug shortages. Of the 314 shortages, 302 were resolved by the end of the study period (96.2%). The median duration of a resolved shortage was 7.6 months (IQR = 3.0-15.2). The 12 unresolved drug shortages had a median duration of 11.1 months (IQR = 5.1-41.9). Shortage duration experienced a continuous linear decline over the study period (2001-2015, P = .004), at a rate of approximately −4.8% per year (95% CI −7.9% to −1.5%). One in four drug shortages was administered parenterally, and the majority of these were vaccines. Parenterally administered drugs were on shortage longer than orally administered drugs (16.2 vs 6.2 months, P < .001). Drugs with no alternative available were on shortage longer compared with drugs with an alternative available (16.7 vs 6.8 months, P = .002), as were drugs produced by more than one manufacturer compared with single-sourced drugs (9.4 vs 6.0 months, P = .035).

A reason for the shortage was not reported for 159 of the pediatric ambulatory care drug shortages (50.6%). When a reason was reported, the most commonly cited was manufacturing problems (25.8%), followed by supply/demand issues (13.7%), raw material shortages (4.8%), regulatory issues (2.9%), and business decisions (1.6%). Shortage duration did not differ significantly based on the reason given for the shortage (P = .082).

Therapeutic classifications of the drug shortages are presented in **Table II**. The most common type of shortage for ambulatory pediatric drugs were used to treat infectious diseases (n = 60), with a median shortage of 8.9 months (IQR = 4.0-17.9). Vaccine shortages (n = 36) had a median length of 18.5

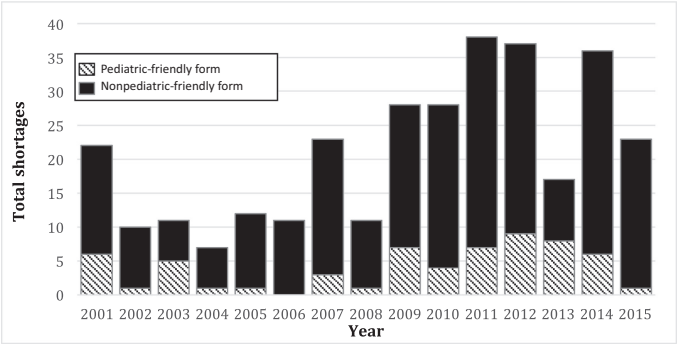

Figure 1. Annual number of pediatric ambulatory care drug shortages, 2001-2015.

months (IQR = 5.4-30.9) and were on shortage significantly longer than all other drug classifications ($P < .001$).

Figure 2 presents the 20 longest shortages during the study period. The longest shortage was for ciprofloxacin 500-mg tablets, which was on shortage from October 14, 2009 to August 25, 2015 (70 months). The longest active shortage (as of March 31, 2016) was for methylphenidate chewable tablets, which started February 8, 2011 (62 months).

Discussion

We found a substantial number of drug shortages that affect the practice of ambulatory pediatrics during our study period. Many drugs had prolonged shortages, some of which were not resolved at the end of this study period. Shortages overall increased over the course of the study, although the numbers of shortages appear to have reached a peak in 2011. This may be an effect of the FDA Safety and Innovation Act, passed in 2012. One section of this Act requires manufacturers to notify FDA of a shortage. Advanced notification allows FDA to ask other suppliers to increase production, expedite reviews, or take other actions to prevent shortages.[8]

Our study found that overall length of shortage was prolonged, at a median of 7.6 months but that median length of shortage had a slight decrease (4.8% per year). It may be that the FDA's efforts regarding early notification about shortages may be improving time to resolution. In the past years,

Table I. Ambulatory pediatric drug shortages, 2001-2015

Categories of drugs	Total shortages	%	Median duration, mo	IQR	*P* value
Active shortages*	12	3.8	11.1	5.1-41.9	.082†
Resolved shortages	302	96.2	7.6	3.0-15.2	
Generic	194.0	61.8	9.4	3.7-15.6	.133
Nongeneric	120.0	38.2	5.9	2.3-16.7	
Pediatric-specific form	60	19.1	9.7	4.2-17.6	.223
Not pediatric-specific form	254	80.9	7.1	3.1-14.5	
Single source	111	35.4	6.0	2.3-12.6	.035
Multiple sources	203	64.6	9.4	3.7-16.3	
Alternative available	270	86.0	6.8	3.1-13.8	.002
No alternative available	44	14.0	16.7	5.4-30.9	
Alternatives also impacted	91	29.0	10.1	3.4-15.6	.572
Parenteral	76	24.2	16.2	5.4-27.4	<.001
Not parenteral	238	75.8	6.2	2.8-12.8	
Reason for shortage					
Business decision	5	1.6	7.6	3.7-10.2	.082
Manufacturing problems	81	25.8	9.3	4.1-23.0	
Natural disaster/weather	2	0.6	2.3	2.3-2.3	
Raw materials	15	4.8	14.7	7.6-44.8	
Regulatory issues	9	2.9	5.3	1.4-11.8	
Supply/demand	43	13.7	6.5	3.0-16.1	
Unknown	159	50.6	6.6	3.1-13.0	

*Active shortage defined as still on shortage as of March 30, 2016.
†*P* values for shortage durations are from the Kruskal–Wallis equality-of-populations rank test.

Table II. Therapeutic classes of ambulatory pediatric drug shortages, 2001-2015

Categories of drugs	Total shortages	Percent	Median duration, mo*	IQR
Infectious diseases	60	19.1	8.9	4.0-17.9
Anesthesia, analgesia	37	11.8	9.6	3.1-19.5
Vaccine	36	11.5	18.5	5.4-30.9
Topical	35	11.1	5.7	3.3-13.4
Allergy and immunology	32	10.2	10.3	2.7-14.0
Gastroenterology	33	10.5	11.1	5.0-17.9
Pulmonary	25	8.0	4.2	0.9-6.1
Psychiatry	18	5.7	10.3	4.4-16.3
Gynecology	15	4.8	6.4	1.3-13.8
Fluids, electrolytes, nutrition	10	3.2	5.6	1.3-17.7
Ophthalmology	9	2.9	5.5	2.4-9.3
Ear, nose, and throat	3	1.0	2.4	1.3-5.2
Endocrine	1	0.3	24.0	24.0-24.0

*Kruskal–Wallis equality-of-populations rank test $\chi^2 = 34.9$ probability = .0005.

the pharmaceutical industry had been impacted severely by concerns about quality control. Seven of the major sterile injectable drug manufacturers were cited by the FDA during our study period, leading directly to shortages.[9] The rate of these citations to all drug manufacturers also increased from 2007 through 2013.[9] To improve quality concerns, manufacturers must slow or stop production to address the issue, leading to shortages. Sometimes a manufacturer can spend millions of dollars trying to fix a manufacturing concern and end up in bankruptcy themselves, continuing a shortage crisis.[10] Because our data count a resolution of shortage as either supply improving or the manufacturer discontinuing the medication, it is possible that the decrease in duration is due to companies discontinuing a struggling drug rather than continue to work on quality issues.

Drugs without an alternative were on shortage for significantly longer than those with a substitute. A critical medication on prolonged shortage could be devastating for certain pediatric patients. For example, oseltamivir is the only approved neuraminidase inhibitor for the treatment and prevention of influenza in children younger than the age of 7 years. It may reduce the duration of symptoms and, in addition, may decrease otitis media as a complication.[11] Oseltamivir was on shortage for multiple periods in the 15-year time span studied. This leaves one of our most vulnerable populations without a medication against an infection that has killed almost 1500 children since the 2004-2005 season.[12] In addition, the oseltamivir shortages of 2009, 2013, and 2014 affected the suspension of the drug, requiring compounding. The need for compounding has led to medical errors and contamination of sterile products in the past.[13]

Shortages of pediatric-friendly formulations can be particularly challenging for outpatient providers, as there is often

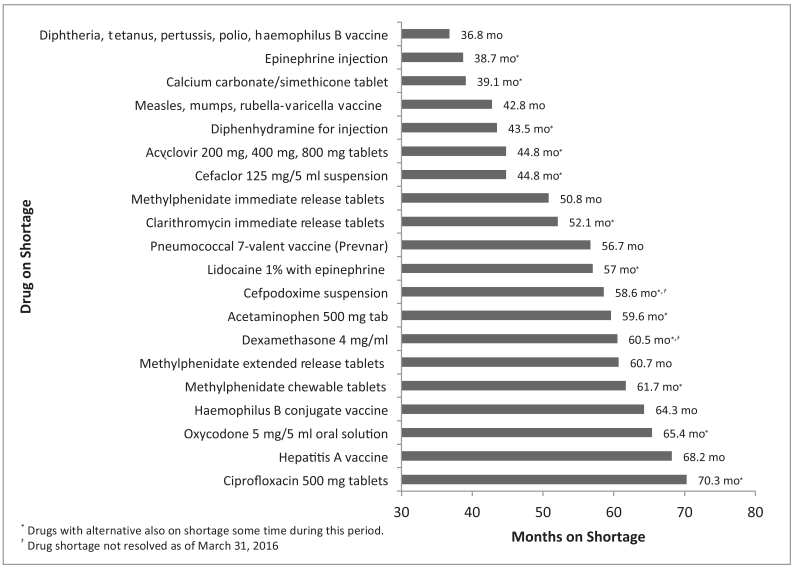

Figure 2. Twenty longest pediatric ambulatory care drug shortages.

not a therapeutic alternative that is palatable or available in a strength that is appropriate for pediatric use. Although there is some evidence suggesting that children as young as 4 years can be taught to swallow smaller pills,[14,15] children of any age may struggle with swallowing large tablets. Also, although adults will put aside palatability to take a prescribed medicine, a noxious taste can cause refusal in a young child.[16] If pediatric-friendly formulations are limited or not available, providers may need to rely on adult formulations that may not be well tolerated by children, ultimately resulting in reduced adherence. Also, compliance with a medication regimen can be challenging for any patient, but especially so for pediatric patients. Patient compliance with medication improves as the number of doses per day decreases.[17] One clear example of a medication shortage leading to more complex dosing is the recent shortage of intramuscular penicillin. When intramuscular penicillin went on shortage, providers had to use oral penicillin or amoxicillin for a 10-day course. This increase in dosing frequency may have contributed to reduced compliance with medication.

The drastic reduction in vaccine-preventable diseases is one of the great achievements in public health.[18] Although overall rates of vaccination coverage remain high, pockets of vaccine refusal and low vaccination acceptance have led to outbreaks of several vaccine preventable diseases.[19,20] Vaccine shortages made up 11.5% of the total number of drug shortages seen in the study period. Only endocrinology drugs had a longer median length of shortage than vaccines, likely falsely elevated by the small number of endocrinology specific drugs on shortage. Of the 20 pharmaceuticals on shortage for the longest period of time, vaccines accounted for one quarter of those affected. These shortages place children at an unacceptable risk of a developing a preventable disease.

Given these concerns about shortages, providers, pharmacists, and healthcare systems must be prepared for shortages. For pediatric ambulatory providers, often without a pharmacy department, the first challenge will be staying aware of the current shortages. Both the FDA and the ASHP maintain lists of the current drug shortages.[21,22] The ASHP drug shortage Web site content is supplied by UUDIS and provides evidence-based recommendations for managing the safety and clinical problems shortages can create. The ASHP site also will provide recommendations for alternatives. Once a shortage is identified, selecting an alternative medication and communicating that choice to potentially involved healthcare providers in a practice is the next step. For certain medications, the group will need to determine the patient populations that should receive priority, like the pneumococcal vaccine for patients with sickle cell anemia.

Ambulatory pediatric healthcare providers must be advocates for their patients. The American Academy of Pediatrics recommends additional measures to protect children from drug shortages, including creating a list of critical pediatric drugs, creating bidirectional information systems concerning drug shortages, and ensuring fair distribution of drugs during a time of shortage.[23] These healthcare providers can also contact their representatives to encourage supporting laws aimed at improving research on pediatric drugs and also their proper labeling.

Our study should be interpreted in light of several limitations. UUDIS data depend on voluntary reports from clinicians and hospitals about drug shortages. It is possible that our data underrepresent the true number of pediatric ambulatory care drug shortages experienced during this time period. The UUDIS also does not include information on medication harms or complications that result from drug shortages. Because reporting is voluntary, the reason for shortage may be omitted or obscured. More than one-half of the drugs on shortage lacked a reason for the shortage, because manufacturers were not required to report this information. Another limitation is that the data include active shortages. Because these shortages have not been resolved, we do not know their actual duration. A shortage that started 3 months before the end of our data collection may have gone on for much longer than currently documented. As a result, the shortage times reported may be underestimated.

We relied on 3 physician reviewers to determine whether a drug on shortage was used in general ambulatory pediatrics. This decision was a subjective distinction. Had others performed these classifications, different drugs might have been included or excluded. We also removed discontinued drugs because many did not have any shortage time calculated. This may have caused an underestimate of total shortages and shortage time in cases where a drug was on shortage for a period of time and then later discontinued.

The UUDIS data only document if an alternative to a drug on shortage was also on shortage at any time during our study. Given this limitation of the data, it is difficult to say how many options providers had at any single time during a shortage. Also, drugs may have many different indications, so a medication documented as an "alternative" may not have been appropriate in certain clinical scenarios. These factors may have caused an overstatement of the impact of having an alternative medication on shortage.

Drug shortages have been and will continue to be an issue for general ambulatory pediatrics. The impact of drug shortages on ambulatory pediatrics needs to be further studied. Pediatric-specific data need to be included in reports on drug shortages. To meet these drug shortage challenges, multiple stakeholders, including healthcare providers and systems, industry, and regulatory agencies, will need to collaborate. ■

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Prescription Drug Shortages
Pediatric Emergency and Critical Care Medications

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Objectives: Drug shortages have been increasing over the past 2 decades. There are limited data on drug shortages and their effect on pediatric emergency and critical care. Our objective was to describe pediatric emergency and critical care drug shortages.

Methods: Drug shortage data from January 2001 to December 2015 were obtained from the University of Utah Drug Information Services. Shortages were reviewed, identifying agents used in pediatric emergency and critical care. Shortage data were analyzed for the type of drug, formulation, shortage reason, duration, marketing status (generic vs brand name), or if it was a pediatric-friendly formulation, used for a high-acuity condition, or a single-source product. The availability of a substitute was also described.

Results: Of 1883 products on shortage, 779 were used in pediatric emergency or critical care. The annual number of shortages decreased from 2001 to 2004, but then increased, reaching a high in 2011. The median duration for resolved shortages was 7.6 months (interquartile range, 3.0–17.6 months). The most common category affected was infectious disease drugs. High-acuity agents were involved in 27% of shortages and in 11% of pediatric-friendly formulations. An alternative agent was available for 95% of drugs, yet 43% of alternatives were also affected at some time during the study period. The most common reported reason for a shortage was manufacturing problems.

Conclusions: From 2001 to 2015, drug shortages affected a substantial number of agents used in pediatric emergency and critical care. This has had implications to the medications available for use and may impact patient outcomes. Providers must be aware of current shortages and implement mitigation strategies to optimize patient care.

Key Words: pharmacology, drug shortages, critical care

(*Pediatr Emer Care* 2019;00: 00–00)

According to the Food and Drug Administration (FDA), drug shortages are "a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug."[1] Shortages are commonly caused by issues with the quality of the drug itself or quality issues within production facilities; however, lack of sufficient demand and other economic concerns have also been cited as causes.[2] Since the mid-2000s, drug shortages have increased in the United States and have been shown to negatively impact patient care.[3–6] Shortages have also lengthened in recent years, becoming increasingly likely to affect patients.[7,8]

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Care for children may be impacted by drug shortages. Many drugs lack pediatric indications, which in a shortage can lead to fewer options for treatment.[9] In particular, shortages of drugs used in pediatric emergency and critical care settings have the increased risk of harm given the immediate life-threatening nature of the conditions treated in those settings. Representatives of the American Academy of Pediatrics testified before the US Congress in 2012 to the harmful effects of drug shortages on children.[10] However, there has been limited research on drug shortages in these settings. In this study, we explore shortages of drugs used in pediatric emergency medicine and critical care from 2001 through 2015 and discuss the potential implications of these shortages on patient care.

METHODS

Drug shortage data from January 2001 to December 2015 were obtained from the University of Utah Drug Information Services (UUDIS). The UUDIS began collecting drug shortage information in January 2001 and publishes data on critical shortages online on the website for the American Society of Health-System Pharmacists. Clinical pharmacists at UUDIS confirm the shortage with the manufacturer and gather data. They also use information from both the manufacturers and the FDA to determine the end of the shortage. The UUDIS tracks the time a shortage begins as the date when the confirmed shortage is first reported. Shortages may have occurred in some organizations before this start date, whereas other organizations may not be impacted until a later date. The resolved date reflects the date when the drug is either confirmed to be available or discontinued by the manufacturers. The UUDIS data are considered to be the most comprehensive source of information about drug shortages by the US Government Accountability Office.[11]

Two study team members, one a pediatrician practicing in emergency medicine (T.K.) and one a specialist in pediatric emergency medicine (K.D.), reviewed pharmaceutical products affected by shortages in the UUDIS database and identified agents commonly or specifically used in pediatric emergency departments and critical care units. Identification was based on the practitioners' clinical experience in their respective fields. An additional member of the study team, an emergency medicine physician, who is also a registered pharmacist and board-certified clinical pharmacologist and practices at a pediatric hospital (M.A.), reviewed discrepancies until a consensus was obtained.

Shortage data were then analyzed focusing on the type of drug involved, formulation, reason for shortage, shortage duration, marketing status (brand vs generic), and if the drug was pediatric-friendly (liquid/chewable dosing form or pediatric concentration) or a single-source product (produced by one manufacturer). We also assessed the availability of a substitute therapy and whether the alternative was also affected by a shortage at any time during the study period. Substitutes are determined by UUDIS and can include medications in the same class as the drug on

shortage or drugs with the same indication. Drugs were also subjectively classified as a high- or low-acuity drug. High-acuity drugs were those commonly used to treat a life-threatening condition, such as cardiac arrest or sepsis. Discontinued products were excluded.

The final data set was analyzed for longitudinal trends, reasons for shortages, and shortage duration. Shortage duration was determined as the number of days between the date of shortage notification and date of resolution as reported by the UUDIS. Shortage duration was not normally distributed (long right tail), which was confirmed by a Shapiro-Wilk *W* test for normal data. Therefore, average shortage duration was described with medians and interquartile ranges (IQRs). The nonparametric 2-sample Wilcoxon rank sum (Mann-Whitney) test and the Kruskal-Wallis equality-of-populations rank tests with Bonferroni corrections were used to compare shortage durations. For shortages still active as of December 31, 2015, data from the first quarter of 2016 were examined to determine if the shortage had been resolved. If the shortage was still active as of March 31, 2016, shortage duration was calculated as the number of months between the shortage notification and March 31, 2016. Data were collected in Microsoft Excel (Microsoft, Seattle, Wash) and analyzed using Stata 14 (College Station, Tex). The study did not meet the definition of human subjects' research and therefore were exempt from institutional review board review.

RESULTS

After excluding discontinued products (n = 190), a final data set of 1935 drug shortages was examined. Of these, 779 (40%) were identified as being used in pediatric emergency or critical care, 84 of which were identified as available in a pediatric-friendly form (11%). Initial reviewers agreed on 435 drugs of a total of 842 potential identified pediatric critical care drugs. The 3 total reviewers then discussed shortages that were discordant until consensus was reached. The total number of new shortages by quarter is displayed graphically in Figure 1. On average, there were 11 new pediatric emergency and critical care shortages reported quarterly (IQR, 7.75–16.5). Beginning in the first quarter of 2005, shortages steadily increased, reaching a high of 32 in the first quarter of 2011 and then plateauing. The median number of new shortages in each 5-year range became more frequent in the last 5 years of the study period (Fig. 2).

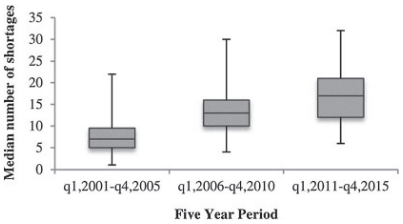

FIGURE 2. Box-and-whisker plot of median number of pediatric emergency care drug shortages reported per quarter, 2001 to 2015.

The median number of new shortages showed an increase during each period from 7 per quarter (IQR, 5–9.5) in 2001 to 2005, to 13 per quarter (IQR, 10–16) in 2006 to 2010, to 17 per quarter (IQR, 12–21) in 2011 to 2015 (P = 0.0001). For pediatric-friendly forms, the median number of new drug shortages by quarter rose from 0.5 per quarter (IQR, 0–1.5) in 2001 to 2005, to 1.0 per quarter (IQR, 0–2) in 2006 to 2010, to 2.0 per quarter (IQR, 1–2.5) in 2011 to 2015 (P = 0.048).

Table 1 presents median duration of pediatric emergency and critical care drug shortages. Of the 779 shortages, 706 were resolved by the end of the study period (91%). The median duration of a resolved shortage was 7.6 months (IQR, 3.0–17.6 months). A reason for the shortage was not reported for 375 of the pediatric emergency and critical care drug shortages (48%). When a reason was reported, the most commonly cited was for manufacturing problems (28%), followed by supply/demand issues (15%), raw material shortages (4%), business decisions (2%), and regulatory issues (2%). Median shortage duration was highest for drugs on shortage due to lack of sufficient raw materials (18.6 months; IQR, 4.3–35.2 months), followed by manufacturing problems (12.5 months; IQR, 5.1–31.3 months).

Therapeutic classifications are presented in Table 2. The most common types of shortage for pediatric emergency and critical care drugs were for those used to treat infectious diseases (eg,

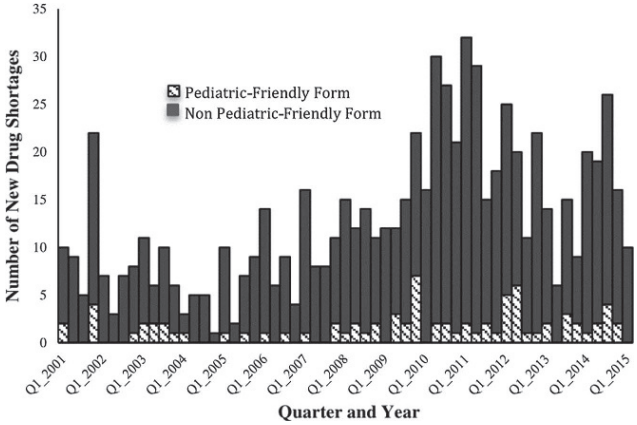

FIGURE 1. Total number of new pediatric emergency and critical care drug shortages, by quarter, 2001 to 2015.

TABLE 1. Pediatric Emergency and Critical Care Drug Shortages, 2001 to 2015

	Total Shortages	%	Median Duration, mo	IQR		*P*
Category of drug						
Active shortages*	73	9.4	25.6	7.8	59.6	<0.001†
Resolved shortages	706	90.9	7.6	3.0	17.6	
Generic	591	76.1	9.3	3.7	22.5	<0.001†
Nongeneric	188	24.2	5.0	2.3	14.8	
Pediatric-friendly	84	10.8	7.5	3.0	12.9	0.024
Not pediatric-friendly	695	89.4	8.4	3.4	22.3	
Single source	261	33.6	5.5	2.5	12.7	<0.001†
Not single source	518	66.7	9.9	4.1	23.5	
High acuity	208	26.8	8.7	3.7	29.7	0.027
Low acuity	571	73.5	8.2	3.2	18.1	
Alternative available	738	95.0	8.2	3.4	19.6	0.822
No alternative available	41	5.3	9.4	2.8	22.9	
Parenteral	460	59.2	8.4	3.5	19.9	0.884
Not parenteral	318	40.9	8.1	3.2	20.4	
Reason for shortage						
Business decision	13	1.7	10.3	3.7	13.8	<0.001†
Manufacturing problems	220	28.3	12.5	5.1	31.3	
Natural disaster/weather	2	0.3	3.4	0.7	6.2	
Raw materials	34	4.4	18.6	4.3	35.2	
Regulatory issues	12	1.5	5.2	2.7	14.5	
Supply/demand	120	15.4	7.3	3.0	15.7	
Other‡	3	0.4	3.2	2.9	9.9	
Unknown	375	48.3	6.2	2.7	14.7	

*Active as of March 30, 2016.

†Low inventory (x1), NDC transition (x1), short-dated product (x1), temporary plant closure (x1).

‡Statistically significant after Bonferroni correction for multiple comparisons.

acyclovir and vancomycin; n = 170), which were on shortage for an average of 9.1 months (IQR, 3.7–21.3 months). Drugs for pulmonary diseases (eg, albuterol and budesonide; 3.4 months; IQR, 1.3–5.5 months) were found to have significantly shorter duration of shortage as compared with drugs in other therapeutic classes after Bonferroni correction.

Figure 3 presents the 20 longest shortages during the study period. The longest shortage was for rabies immune globulin (Bay Rab), which had been on shortage for 165.3 months as of March 31, 2016. The longest resolved shortage was for heparin sodium injection (97.4 months, resolved March 2016). Several other long shortages still remained active as of March 31, 2016.

DISCUSSION

We found a substantial number of shortages of pediatric emergency and critical care medications from 2001 to 2015. In addition, many medications have had prolonged shortages, some of which were unresolved at the end of this study period. Although many drugs on shortage had alternatives, a large number of alternatives were also on shortage at some time during the study.

Drug shortages increased through 2011 and then leveled off. This may be due to the FDA Safety and Innovation Act of 2012. This act strengthened the ability of the FDA to manage and report on drug shortages. It requires drug manufacturers to notify the FDA if they anticipate a shortage or plan to discontinue a drug.[12] The FDA already had the power to expedite drug approval if it would alleviate a shortage, but this new advance notification may have helped the FDA, hospitals, and manufacturers avoid or mitigate shortages.

Our study found that overall length of shortage was prolonged, at an average of 8.6 months. We suspect that this was due to ongoing manufacturing and quality concerns with the products. Seven of the major sterile injectable drug manufacturers were cited for quality concerns by the FDA during our study period, leading directly to shortages.[13] The rate of these citations to all drug manufacturers also increased from 2007 through 2013.[13] Typically, to improve a quality concern, manufacturers must slow or stop production to address the issue, leading to shortages. One of the larger producers of pharmaceutical drugs, Ben Venue of Bedford, Ohio, spent an estimated 350 million dollars to improve manufacturing quality but eventually closed the site because of financial losses.[14] The FDA does not currently have the power to force a company to manufacture a drug or continue bolstering a struggling factory. Even when the FDA focuses intently on one area of shortage, delays can be significant. This was demonstrated by the severe shortage of normal saline caused by Hurricane Maria's devastating toll on Puerto Rico.[15]

The number of drug shortages seen in our study raises concerns about potential medication errors resulting from these shortages. The Institute for Safe Medicine Practices has recommended that the harms from drug shortages can be classified into 4 categories.[16] One, an alternative therapy is provided but leads to inadequate treatment. This harm was seen with the sterile ethanol shortage of 2011. Sterile ethanol has been shown to prevent central line infections in parental nutrition dependent intestinal failure patients. Providers trialed a less than once daily dosing regimen to maintain patients on ethanol locks during the shortage, which lead to increases in central line infections.[17] Two, an error is made with

TABLE 2. Therapeutic Classes of Pediatric Emergency and Critical Care Drug Shortages, 2001 to 2015

Class of Drug	Total Shortages	%	Median Duration, mo	IQR		*P**
Anesthesia, analgesia	104	13.4	10.6	4.1	25.4	0.055
Allergy and immunology	48	6.2	9.8	3.4	21.8	0.397
Cardiovascular	60	7.7	6.8	2.8	35.9	0.460
Endocrine	12	1.5	9.6	3.7	20.5	0.999
Ear, nose, and throat	3	0.4	4.1	2.4	5.2	0.201
Fluids, electrolytes, nutrition	103	13.3	8.2	3.7	23.2	0.627
Gastroenterology	68	8.8	11.3	4.1	22.7	0.454
Gynecology	3	0.4	11.9	1.3	29.1	0.969
Hematology	19	2.4	8.5	3.2	15.1	0.713
Infectious diseases	170	21.9	9.1	3.7	21.3	0.471
Neurology	35	4.5	7.8	4.0	18.9	0.854
Ophthalmology	15	1.9	6.3	2.4	9.5	0.200
Pulmonology	33	4.2	3.1	1.3	5.5	<0.001†
Psychiatry	4	0.5	8.3	7.1	38.7	0.486
Renal	3	0.4	23.5	7.8	41.9	0.186
Topical	41	5.3	6.0	2.6	10.9	0.017
Toxicology	48	6.2	6.0	3.0	18.7	0.297
Vaccines	10	1.3	18.6	4.1	36.8	0.131

*Each therapeutic class is compared with median duration of drug shortage not in the same class.

†Statistically significant after Bonferroni correction for multiple comparisons.

the alternative drug or the dose of a different form of the drug on shortage. There have been multiple reports of dosing errors when substituting hydromorphone for morphine, which could result in respiratory depression or death.[18] Three, the medication is omitted, leading to nontreatment for the patient. This has be seen in pediatric oncology, where there is no alternative regimen for a chemotherapeutic drug on shortage.[19] Four, an error when the hospital pharmacy attempts to compound a product or drug strength is no longer available.[16] In one case, a shortage of sodium bicarbonate injectable solution led to a solution of omeprazole being compounded with baclofen powder instead.[20] This error resulted in a pediatric intensive care unit (PICU) admission and extensive testing, including lumbar puncture and mechanical ventilation for the patient.

Most emergency department encounters for children occur at nonpediatric hospitals.[21] Only approximately one quarter

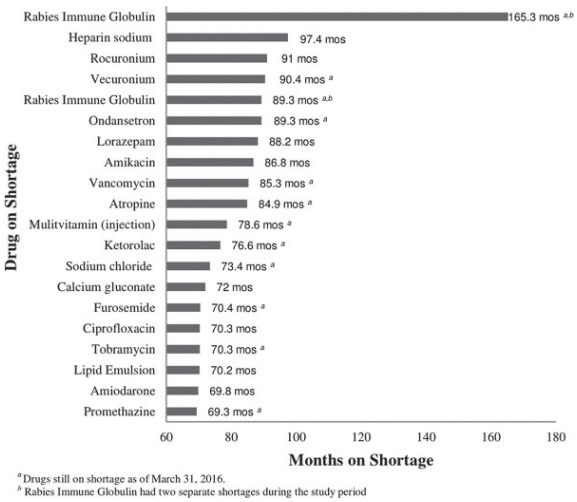

FIGURE 3. Twenty longest drug shortages.

of emergency department visits for children are at a children's hospital with an affiliated PICU.[22] A drug shortage could force providers with less pediatric experience to use unfamiliar medications. This could potentially lead to medical error. For example, the drug cefotaxime is commonly used for the empiric coverage of a neonate with fever. When on cefotaxime is on shortage, the American Academy of Pediatrics recommends substituting with ceftazidime.[23] Ceftriaxone, a very commonly used cephalosporin in pediatrics, is to be used with caution in infants and contraindicated in those neonates with hyperbilirubinemia or who are less than 41 weeks' gestational age. Although no documented cases have been reported, it is possible that during a shortage, providers looking for an alternative to cefotaxime would choose ceftriaxone instead given their familiarity with the drug. It is also possible, however, that these providers would be more comfortable using drugs not typically used in pediatrics and maybe be more equipped to handle a shortage.

Managing drug shortages is also extremely costly. Organizations must purchase more expensive alternatives and use additional staff time to manage the shortage. One study from 2011 estimated an annual cost of more than $200 million just in personnel costs to manage shortages.[24] Drug shortages also lead to higher costs for purchasing for group purchasing organizations, both through off-contract purchasing of the drug on shortage and through purchasing more expensive alternatives.[25]

Since 2013, the FDA has made an annual report to Congress on the state of drug shortages in the United States.[26] These reports are mandated by FDA Safety and Innovation Act and serve to summarize the shortages encountered and the FDA's response to these shortages. None of these reports directly address pediatric drug shortages or their impact on pediatric populations. In one national survey, pediatric patients made up 20% of those injured or affected by medication shortages.[16] With the prevalence of drug shortages seen in our study, information on pediatric specific drug shortages should be included in the annual report.

Given these concerns, there are steps that providers and hospitals can take to prepare for shortages. Providers should be familiar with the current shortages and how they may affect patient care. Collaboration with pharmacy administration and engagement in the hospital's pharmacy and therapeutics committee is key to plan how to use limited drug supplies and determine safe alternatives. This strategy has shown to be effective in protecting PICU patients from medication harms during a shortage of fentanyl and benzodiazepines. Pharmacists and providers outlined options for sedation and analgesia once aware of the shortage to prevent medication errors.[27]

Drug shortages also create an opportunity to institute evidence-based medicine in hospital guidelines. Using the right drug at the right time for the right patient may reduce the impact of shortages. For example, in a survey of NICU antibiotic prescribing, 28% of antibiotic courses were found to not be in compliance with Centers for Disease Control and Prevention recommendations for appropriate antibiotic use. An additional 24% of antibiotic days were found inappropriate, when the antibiotic administered could have been switched to one targeting an identified organism.[28] More judicious use of antibiotics could be used as a strategy to mitigate shortages. There is the possibility that reliance on evidence-based pathways could leave providers unprepared in the event of a shortage of a critical drug. Hospital and division leadership must be aware of this potential and plan accordingly.

The UUDIS data depend on voluntary reports from clinicians about drug shortages, which may have limited our study. It is possible that our data underrepresent the true number of pediatric emergency care drug shortages experienced during this period. We did not conduct an anticipated needed sample size analysis because we used all available data in the UUDIS. The UUDIS also does not include information on medications harms or complications that result from drug shortages. Also, drug shortages shorts may affect different hospital or regions at different times and with variable severity, which was not be included in our data. Nevertheless, this is the most comprehensive available source of drug shortage information.

This study is also limited because we relied on 2 physician reviewers to categorize the UUDIS drug list. The decision on whether or not a drug was used in pediatric emergency or critical care was a subjective distinction made by the 2 physician reviewers. Had these classifications been performed by others, results may have been different. We removed discontinued drugs because many did not have any shortage time calculated. This may have caused an underestimate of total shortages and shortage time in cases where a drug was on shortage for a period and then later discontinued.

Another limitation is that the data include active shortages. By definition, these shortages have not been resolved, and therefore, we do not know their actual duration. For example, an active shortage that began in October 2015 will only appear to have a shortage of 3 months (October 2015–December 2015). However, the actual time of this shortage may be longer. As a result, the shortage times reported may be underestimated.

Pediatric emergency and critical care shortages continue to impact many medications used in these settings and have accelerated in recent years. Further work is needed to understand the impact of drug shortages on pediatric emergency and critical care and patient outcomes. Pediatric-specific considerations, such as vital pediatric emergency drugs and specific pediatric formulations on shortage, need to be included in reports on drug shortages. Multiple stakeholders, including providers, health care systems, industry, and regulatory agencies, need to incorporate pediatric concerns in their plans for managing drug shortages.

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Prescription Drug Shortages: Impact on Neonatal Intensive Care

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Drug treatment · Neonatal intensive care · Neonatal intensive care unit · Neonate · Preterm and term infant · Extremely low birth weight infants · Drug shortage

Abstract
Background: Prescription drug shortages have increased significantly during the past two decades and also impact drugs used in critical care and pediatrics. ***Objectives:*** To analyze drug shortages affecting medications used in neonatal intensive care units (NICUs). ***Methods:*** Drug shortage data for the top 100 NICU drugs were retrieved from the University of Utah Drug Information Service from 2001 to 2016. Data were analyzed focusing on drug class, formulation, reason for shortage, and shortage duration. ***Results:*** Seventy-four of the top 100 NICU drugs were impacted by 227 shortages (10.3% of total shortages). Twenty-eight (12.3%) shortages were unresolved as of December 2016. Resolved shortages had a median duration of 8.8 months (interquartile range 3.6–21.3), and generic drugs were involved in 175 (87.9%). An alternative agent was available for 171 (85.8%) drugs but 120 (70.2%) of alternatives were also affected by shortages. Parenteral drugs were involved in 172 (86.4%) shortages, with longer durations than nonparenteral drugs (9.9 vs. 6.4 months, $p = 0.022$). The most common shortage reason was manufacturing problems (32.2%). ***Conclusions:*** Drug shortages affected many agents used in NICUs, which can have quality and safety implications for patient care, especially in extremely low birth weight infants. Neonatologists must be aware of current shortages and implement mitigation strategies to optimize patient care.

Introduction

The number of new prescription drug shortages has increased significantly during the past two decades. Prescription drug shortages have also impacted drugs used in the pediatric population [1]. With the passage of the US Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, reductions in the total number of new national drug shortages were observed but shortages

were not eliminated. On the contrary, significant shortages of medications used in acute care settings such as emergency or critical care in adults still exist and have a substantial impact on intensive care medicine [2–4]. The impact of drug shortages on pediatric care has been described for pediatric oncology and preventive medicine [5–8].

How national drug shortages impact medications used in neonatal intensive care units (NICUs) is an important issue as it will guide the mitigation strategies in the acute care setting for neonates. The objective of this study was to evaluate the impact of drug shortages on drugs used in the NICU based on the most frequently used NICU medications [9].

Methods

We used drug shortage data from the University of Utah Drug Information Service (UUDIS), which monitors prescription drug shortages in the USA. Methods for this work have been previously described [10]. In brief, UUDIS receives voluntary reports of drug shortages by health professionals. Each reported shortage is verified with the suppliers. UUDIS also attempts to verify the reason for the shortage and an estimated resupply date. If there is a critical national drug shortage, e.g. if a certain drug is on shortage by the majority of suppliers, then UUDIS will post this information on the website hosted by the American Society of Health-System Pharmacists (ASHP, www.ashp.org/shortage). A shortage is declared resolved by UUDIS when all suppliers have all presentations available, when impacted products have been discontinued, or when the FDA considers the shortage resolved.

UUDIS collects the following drug shortage data: generic product name, therapeutic category, date shortage began (date UUDIS was notified), resolved date, duration, reason for the shortage, controlled substance schedule (if applicable), whether the drug is an injectable product, and whether a product was discontinued. The data set of this analysis was restricted to shortages that occurred between January 1, 2001, and December 31, 2016.

The list of commonly used drugs for this study was derived from Hsieh et al. [9], who reported the most commonly used 100 NICU drugs and the top 20 agents used in extremely low birth weight infants (ELBW, birth weight <1,000 g) between 2005 and 2010 in a study within the Pediatric Trials Network. This study represented a sample size of 450,386 infants (including 29,336 ELBW infants, 3.6%) with a median gestational age of 35 (range 33–38) weeks, a median birth weight of 2,490 g and a median length of hospitalization of 10 (range 5–21) days receiving a total of 1,655,397 medication courses for 229 medications in 305 US NICUs.

Data Analysis

We characterized drug shortages based on the type of medication involved, length of shortage, route of administration (parenteral vs. nonparenteral), whether the medication was used for a life-threatening or high acuity condition, generic availability, and whether the drug was a single-source product (made by one facility). We also investigated whether impacted products had an available substitute for the most common NICU indication, and for those with alternatives if the substitute was also affected by a shortage at any point during the study period. We also included reasons for shortages when available.

Trend Analysis

We evaluated the number of new shortages by month and determined two distinct trends: an increasing trend from 2001 to the middle of 2010 and a declining trend from the middle of 2010 to 2016. To determine whether the two trends were significant, we included a dummy variable equal to 0 for months before July 2010, and equal to 1 for after July 2010. We used Poisson regression models allowing for autocorrelation to test for significance at a p value of less than 0.05. We first fit a standard Poisson model, adjusted by the time trend and the dummy variable. We checked for autocorrelation using a correlogram plot of the residuals and found third-order autocorrelation. We then fitted a Poisson regression model allowing for third-order autocorrelation using the Stata command "arpois." For shortages that resolved by the end of the study period (n = 199), we used the Kruskal-Wallis equality of proportions rank test and the 2-sample Wilcoxon rank sum (Mann-Whitney) test to compare shortage durations because shortage length was not normally distributed.

Results

Number of Shortages

From 2001 to 2016, a total number of 2,229 drug shortages were examined. Of those, 234 shortages were identified as belonging to the top 100 NICU drugs. After removing 7 discontinued drugs, 227 shortages (10.3% of total shortages) were included in the analysis. These 227 shortages were related to 74 of the top 100 NICU drugs.

Trends of Shortages over Time

Between 2001 and 2010, the number of new NICU drug shortages reported annually increased from 11 in 2001 to 36 by 2010 (p = 0.023 for trend, Fig. 1). By 2016, the number of new shortages decreased to 16. This trend was also found to be significant among parenteral drugs, which increased from 11 to 34 between 2001 and 2010 and declined to 14 by 2016 (p = 0.050). The majority of shortages (199, 87.7%) had been resolved by the end of the study period. The number of unresolved shortages of NICU drugs at the end of 2016 was 28 (12.3%).

Characteristics of Drugs on Shortage

The analysis of resolved NICU drug shortages according to clinical and product characteristics showed (Table 1) that a large number of the resolved NICU shortages involved generic formulations (n = 175, 87.9%), drugs which had a substitute available (n = 171, 85.8%), and parenteral

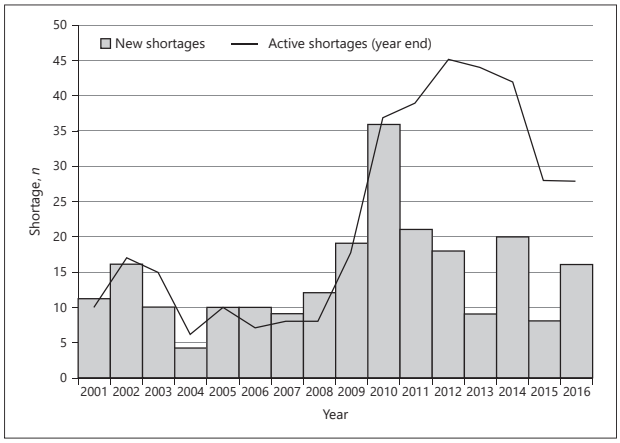

Fig. 1. Number of new and active shortages of drugs used in the NICU 2001–2016.

products (n = 172, 86.4%). Of the 171 shortages with a substitute available, 120 (70.2%) of the substitutes were also affected by a shortage during the study period.

Duration of Shortages

The median duration of a resolved shortage was 8.8 months (interquartile range, IQR, 3.6–21.3). The unresolved drug shortages were of a considerably longer duration (median) of about 28.5 months (p = 0.0021). The shortage duration for parenteral drugs was significantly longer than that of nonparenterally administered drugs (9.9 vs. 6.4 months, p = 0.022). We did not find any significant differences in shortage durations for the other characteristics examined (Table 1).

The median duration of a resolved shortage for drugs used in ELBW infants was 11.9 months (IQR 3.0–30.1) compared to 8.7 months for agents not used in ELBW infants (IQR 3.8–18.2, ns). For high acuity agents, the median duration of a resolved shortage was 8.6 months (IQR 3.0–25.8), compared to 9.3 months for not high acuity agents (IQR 4.4–18.2). However, if all therapeutic classes were compared (Table 2), the longest single shortage was for lorazepam injections (88.2 months).

The results for high acuity agents and drugs used in ELBW infants are shown in Tables 3 and 4, respectively.

Therapeutic Classes of Drugs on Shortage

The most frequent therapeutic class on shortage was antimicrobial agents (n = 91, 40.1%), followed by cardiovascular (n = 48, 21.1%), and anesthetic/analgesic (n = 27, 11.9%, Table 2). Shortage duration differed significantly between therapeutic classes as determined by a Kruskal-Wallis equality-of-populations rank test (χ^2 [9 df] = 17.259, p = 0.045). The longest shortage duration was found for drugs classified as fluids, electrolytes, and nutrition (22.3 months, IQR 1.6–43), and the shortest duration was found among pulmonary drugs (3.6 months, IQR 0.8–5.9). Across all therapeutic classes, the most frequent NICU drug on shortage was meropenem (9 times).

Reasons for Shortages

Of known reasons, manufacturing problems were most commonly cited (n = 73, 32.2%) followed by supply and demand issues (n = 39, 17.2%). A Kruskal-Wallis equality-of-populations rank test showed that there was not a statistically significant difference in shortage duration by reason for shortage (i.e., unknown reasons excluded, χ^2 [5 df] = 10.437, p = 0.064).

Discussion

The majority of the top 100 NICU drugs were impacted by drug shortages indicating a serious concern in neonatal care, especially for critically ill premature or ELBW infants. There are only a few therapeutic options based on lack of safety and efficacy data in this vulnerable population, since only 35% of the most commonly prescribed

Table 1. Characteristics of NICU drug shortages and analysis of resolved shortages according to clinical and product characteristics

	Shortages, *n* (%) (*n* of resolved shortages = 199)	Median length of shortage, months (IQR)	Two-sample Wilcoxon rank-sum (Mann-Whitney) test (median length of shortage)	
			z-score	*p* value
Shortage status as of December 31, 2016				
Active[1] (% of *n* = 227)	28 (12.3)	28.5 (6.6–63.9)	3.075	0.0021
Resolved (% of *n* = 227)	199 (87.7)	8.8 (3.6–21.3)		
Parenteral administration	172 (86.4)	9.9 (3.8–26.5)	2.293	0.0218
Other route of administration	27 (13.6)	6.4 (2.4–11.9)		
Drugs for ELBW infants (top 20)	46 (23.1)	11.9 (3–30.1)	0.943	0.3456
Not among the top 20 for ELBW infants	153 (76.9)	8.7 (3.8–18.2)		
High acuity medications	94 (47.2)	8.6 (3.0–25.8)	–0.108	0.914
Non-high-acuity medications	105 (52.8)	9.3 (4.4–18.2)		
Generics	175 (87.9)	9.3 (3.8–20.2)	1.136	0.256
Nongeneric drugs	24 (12.1)	6.9 (1.7–24.6)		
Single sourced products	66 (33.2)	8.7 (3.6–18.9)	–0.384	0.7007
Multiple sourced products	133 (66.8)	9.2 (3.7–21.3)		
Substitute available	171 (85.9)	9.4 (3.8–22.1)	1.025	0.3054
No substitute available	28 (14.1)	6.8 (2.9–17.4)		
Substitute also affected	120 (60.3)	9.9 (3.8–23.9)	0.791	0.4288
Substitute not affected	79 (39.7)	7.8 (2.9–20.2)		

[1] Durations for active shortages calculated as of December 31, 2016.

Table 2. Therapeutic categories of shortages involving drugs used in neonatal intensive care

Therapeutic category	Shortages, *n* (%) (total *n* = 227)	Median months on shortage (IQR)	Most common drug on shortage (total times on shortage)	Longest single shortage (total months)
Anesthesia/analgesia	27 (11.9)	17.7 (6.1–35.2)	morphine carpujects (4)	lorazepam injection (88.2)
Cardiovascular	48 (21.1)	9.2 (4.9–32.9)	dopamine injection (5)	alprostadil injection (84.5)
Endocrinology	18 (7.9)	10.6 (6–15.8)	dexamethasone injection (6) and levothyroxine injection (6)	levothyroxine injection (41.1)
Fluids, electrolytes, nutrition	4 (1.8)	22.3 (1.6–43)	vitamin A injection (3)	vitamin A injection (44.6)
Gastroenterology	11 (4.8)	18 (11.9–22.1)	metoclopramide injection (4×)	metoclopramide injection (40.0)
Infectious diseases	91 (40.1)	9.1 (3.7–17.4)	meropenem injection (9×)	fluconazole injection (59.2)
Neurology	10 (4.4)	4 (1.7–15.1)	phenobarbital injection (4×) and fosphenytoin injection (4×)	fosphenytoin injection (60.9)
Pulmonary	12 (5.3)	3.6 (0.8–5.9)	albuterol inhalation solution (3×) and budesonide inhalation 0.5 mg/2 mL (3×)	aminophylline injection (48.1)
Topical	1 (0.4)	9.3 (9.3–9.3)	erythromycin ophthalmic ointment (1×)	erythromycin ophthalmic ointment (9.3)
Toxicology	5 (2.2)	4.6 (2.8–7.1)	naloxone injection (5×)	naloxone injection (22.9)

Kruskal-Wallis equality-of-populations rank test: χ^2 with 9 df =17.259; probability = 0.0448.

Table 3. Shortages of high acuity drugs used in the neonatal intensive care unit

Therapeutic category	High acuity shortages, *n* (%) (resolved *n* = 94)	Median months on shortage (IQR)	Most common drug on shortage (total times on shortage)	Longest single shortage (total months)
Anesthesia/analgesia	8 (8.4)	23.6 (12.5–59.5)	diazepam (2) indomethacin (2) lorazepam (2) midazolam (2)	lorazepam (88.2)
Cardiovascular	23 (24.2)	8.7 (2.6–38.2)	dopamine (4) phenylephrine (4)	alprostadil (84.5)
Infectious diseases	44 (46.3)	9.9 (3.4–16.6)	meropenem (9)	fluconazole (59.2)
Neurology	9 (9.5)	4.0 (1.7–15.1)	fosphenytoin(4)	fosphenytoin (60.9)
Pulmonary	5 (5.3)	5.2 (0.9–5.7)	albuterol (3)	aminophylline (48.1)
Toxicology	5 (5.3)	4.6 (2.8–7.1)	naloxone (5)	naloxone (22.9)

Kruskal-Wallis equality-of-populations rank test: χ^2 with 5 df = 8.084; probability = 0.1517.

Table 4. Shortages of drugs used in ELBW infants in the neonatal intensive care unit

Therapeutic category	ELBW shortages, *n* (%) (resolved *n* = 46)	Median months on shortage (IQR)	Most common drug on shortage (total times on shortage)	Longest single shortage (total months)
Anesthesia/analgesia	7 (15.2)	21.5 (7.7–59)	morphine carpujects (3)	midazolam (60)
Cardiovascular	7 (15.2)	13.2 (2–54.2)	dopamine (4)	furosemide (77.8)
Endocrinology	8 (17.4)	9.7 (3.5–23)	dexamethasone (5)	hydrocortisone (31.6)
Fluids, electrolytes, nutrition	3 (6.5)	3.1 (0.1–44.6)	vitamin A (3)	vitamin A (44.6)
Gastroenterology	6 (13)	20.3 (12–29.1)	metoclopramide (4)	metoclopramide (40)
Infectious diseases	10 (21.7)	11.6 (7.6–26.7)	ampicillin (2) cefotaxime (2) gentamicin (2) vancomycin (2)	fluconazole (59.2)
Neurology	2 (4.3)	28.2 (1.7–54.6)	caffeine citrate (2)	caffeine citrate (54.6)
Pulmonary	3 (6.5)	0.9 (0.5–5.2)	albuterol (3)	albuterol (5.2)

Kruskal-Wallis equality-of-populations rank test: χ^2 with 7 df = 7.829; probability = 0.3479.

medications are FDA approved in these infants, and off-label knowledge only exists for a limited number of agents [9]. Threats for patient safety are inevitable, since alternative agents to established treatments might be less effective or carry a higher risk of adverse effects. In the NICU, no life-threatening consequences of drug shortages have been reported so far. During the 2011–2012 norepinephrine shortage, an association between the drug shortage and mortality due to septic shock was observed in adult patients [11].

Parenterally administered drugs were on shortage for a longer time period due to the higher manufacturing quality standards of sterile injectable agents compared to agents used for other routes of administration. The possibility to use nonparenteral routes of administration in the NICU is limited, since alternative routes of administration are never used in life-threatening conditions (e.g., sepsis).

The most frequent drug shortages occurred within the therapeutic classes of antimicrobial agents, cardiovascular agents, and anesthetic/analgesic agents, of which most can be considered drugs used for high acuity conditions. The pediatric gentamicin preparation was largely impacted by shortages. Using another than the usual formula-

Table 5. Mitigation strategies for drug shortages affecting medications used in the NICU

National level	Provider network level	Hospital level	Ward level
Early information about anticipated drug shortages	Anticipate (regional) drug shortages	Use pediatric/neonatal formulations for these patients ONLY	Share drugs among patients and minimize drug waste: administer the same medications at the same time in order to save vials
Follow recommendations of the respective professional society, such as AAP, ASPEN, ASHP and COG	Avoid overpurchasing and hoarding	Conserve resources for the most vulnerable patients, e.g. pediatric/oncologic/ immunosuppressed patients	Prioritize the sickest patients (e.g., ELBW infants) and use substitutes/compounded formulations for other patients
Import drugs	Expand current suppliers	Use substitutes in less vulnerable (e.g., adult) patients	Use substitute drugs of the same or a different class within the same indication
	Review available products	Adapt therapy (e.g., administration route) in less vulnerable (e.g., adult) patients	Use alternative ways of administration for non-life-saving indications (e.g., oral/enteral)
	Implement flexible supply strategies	Use compounded formulations in the hospital pharmacy (avoid constitution errors)	Avoid giving intravenous drugs via the oral/enteral route – use enteral formulations
	Evaluate replacement algorithms	Compound drugs centrally in the hospital pharmacy	Assess the indication of treatment every day
	Introduce clinical decision support tools for drug therapy	Use expired medications (only after regulatory approval)	

AAP, American Academy of Pediatrics; ASPEN, American Society for Parenteral and Enteral Nutrition; ASHP, American Society of Health-System Pharmacists; COG, Children's Oncology Group.

tion may lead to dosing errors. Compounding of pediatric formulations out of adult preparations may lead to inappropriate dosage, since additional dilution is needed, or microbial contamination [2].

Shortages of antibiotics are extremely critical in neonatal care due to limited alternative treatments, e.g. the use of ceftriaxone in term neonates is avoided due to the risk of kernicterus during neonatal hyperbilirubinemia.

Substitutes have been prescribed during previous drug shortages in children, e.g. doripenem replaced meropenem in the therapy of pediatric patients with cystic fibrosis [12]. This strategy cannot be 100% applied to neonatal care, since possible alternatives may not have been studied in neonates. Neonates have an increased doripenem exposure, a longer elimination half-life, and a lower clearance compared with infants >4 weeks [13], but pharmacokinetic data may not be present for other substitutes of drugs on shortage.

During the 2009–2010 shortage, erythromycin ophthalmic ointment, which had usually been used for neonatal ocular prophylaxis, was replaced by gentamicin sulfate ophthalmic ointment. As a complication, a higher rate of periocular ulcerative dermatitis was seen in treated newborns that likely resulted from the prophylactic use of this gentamicin ophthalmic ointment [5]. It was assumed that either gentamicin itself or an excipient (e.g., benzalkonium chloride) was responsible for this adverse drug reaction. It was recommended to resume erythromycin ointment use as soon as the shortage was resolved and to use caution when applying gentamicin ointment until then.

Thus, the quality assessment of the substitute should also consider the excipient, since that may cause toxicity in neonates. For example, propylene glycol, which is used as an excipient of intravenous vitamin E, led to serum hyperosmolarity and even lactic acidosis in neonates [14].

We found long shortage durations for drugs used as part of parenteral nutrition regimens. Preterm infants have special nutrient and vitamin requirements [15]. In the NICU, complications have occurred due to a shortage of intravenous selenium which is an additive to parenteral nutrition [16]. The American Society for Parenteral and Enteral Nutrition (ASPEN) issued recommendations regarding the management of parenteral nutrition product shortages during the peak of the 2010–2012 shortage [17]. The ASPEN recommended to use specific pediatric or neonatal products only for these patient groups [18]. If these are on shortage, however, parenteral nutrition should be saved for the patients in the NICU who need it most, such as very preterm or ELBW infants, or sick neonates with enteral obstruction, necrotizing enterocolitis, or after surgery.

The 2010–2012 vitamin A shortage actually led to reevaluation of therapy when the occurrence of chronic lung disease or death in ELBW infants appeared to be unaffected by the shortage [7].

Mitigation Strategies

Since the implementation of the FDASIA in 2012, manufacturers are required to notify the FDA of anticipated product shortages or discontinuations. While the notifications about anticipated drug shortages and the prevented drug shortages increased significantly, there was a decline in newly occurring drug shortages in 2012. However, the FDA cannot require a manufacturer to produce any product, no matter how lifesaving, and has no authority to require manufacturers to have redundancies or contingency plans in case of shortages [19]. Importing medications from other countries is an option to help mitigate shortages; however, this temporary strategy may only be used when a sufficient supply is available without creating a shortage in another country [20].

Specific mitigation strategies are required for the care of newborns. A general approach for rational drug use during shortages is to treat the patients who need the same drug at the same time or within the shelf-life after preparation in order to minimize drug waste which has already been practiced in oncology.

When other-than-usual preparations are used for reconstituting neonatal formulations, preventive measures should be taken (e.g., by storing the alternative preparation at another place, using different labeling and double-checking extemporaneous formulations) in order to avoid constitution errors. The NICU should be prioritized regarding delivery of drugs not containing toxic excipients [21].

The use of substitutes in the NICU regularly results in an increased off-label use (which was 65% as studied by Hsieh et al. [9]), which carries the risk of more adverse effects. Computer-based clinical decision support systems could impact the choice of the drug during a shortage and reduce the use of drugs on shortage [22].

For all mitigation strategies implemented in neonatal units, professional pharmaceutical and/or pharmacological advice should be sought [23]. The recommendations of the respective professional society should be followed, such as pediatric societies, the ASPEN, the Children's Oncology Group, and the ASHP, and in part, mitigation strategies can be adopted from adult recommendations (Table 5) [2, 17, 24–26].

Limitations of This Study

A limitation of this study is that this analysis is based on data from a single provider network (operating 305 NICUs) and from one single country, so perhaps not fully reflecting the situation in other countries. But, in terms of globalization and centralization of manufacturing, drug shortages in the USA may impact other countries as well, e.g., the 2018 shutdown of an ibuprofen manufacturing plant producing around a sixth of the global ibuprofen supply may have consequences on the ibuprofen availability worldwide [27].

This data set included infants with a gestational age of 33–38 weeks, therefore, the impact of drug shortages could be even severer in infants with a gestational age <30 weeks. Although there were no preterm infants <33 weeks included in that study, we still think that, because of the sample size, the study is a reliable source of information and that the studied ELBW infants are representative for this population.

Conclusion

Drug shortages affected a substantial number of the most common and high acuity agents used in the NICU, which can have quality and safety implications for patient care, especially in ELBW infants. Neonatologists must be aware of current shortages and implement mitigation strategies to optimize patient care.

Disclosure Statement

The authors declare no conflicts of interest.

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Antibacterial Drug Shortages From 2001 to 2013: Implications for Clinical Practice

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Background. Previous studies have described drug shortages; however, there has been no comprehensive evaluation focusing on US antibacterial shortages.

Methods. Drug shortage data from the University of Utah Drug Information Service database were analyzed, with a focus on antibacterial agents from 2001 to 2013. We used descriptive statistics to describe trends in drug shortages, analyze drug classes commonly affected, and investigate whether drugs experienced multiple periods of shortages.

Results. One hundred forty-eight antibacterial drugs were on shortage over the 13-year study period, with 26 drugs still active on shortage as of December 2013. The median number of new shortages per year was 10 (interquartile range [IQR], 7). The number of drugs on shortage increased at a rate of 0.35 additional drugs every month (95% confidence interval, .22–.49) from July 2007 to December 2013 ($P < .001$). The median shortage duration was 188 days (IQR, 366.5). Twenty-two percent of drugs experienced multiple shortage periods.

Conclusions. There were a substantial number of drug shortages from 2001 to 2013, with a dramatic rise in shortages since 2007. Shortages of agents used to treat multidrug-resistant infections are of concern due to continued transmission and limited treatment options.

Keywords. drug shortages; University of Utah Drug Information Service (UUDIS); National Drug Codes (NDC).

Drug shortages are an important issue in public health and medical care delivery [1]. The US Food and Drug Administration (FDA) defines a drug shortage as "a situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug product is inadequate to meet the projected demand at the user level" [2]. There are several reasons for drug shortages, including manufacturer mergers, facility consolidation, manufacturing quality issues, and narrow profit margin for generic drugs [3].

Anti-infective agents account for 15% of all drug shortages, with injectable antibiotics frequently impacted [4]. A majority of infectious disease physicians surveyed report having modified antimicrobial selection due to shortages [5]. Shortages have significant implications in the context of other factors that limit availability of effective antimicrobials, including a shrinking pipeline of new antibiotics and increasing drug resistance [6–8]. In this study, we evaluate antibacterial drug shortage trends in the United States from 2001 to 2013 and discuss clinical implications. A recent government report highlighted the public health crisis of drug shortages, but to our knowledge, ours is the first in-depth evaluation of antibacterial drug shortages [9].

METHODS

We conducted a cross-sectional study of antibacterial drug shortages using the University of Utah Drug Information Service (UUDIS) database from January 2001 to December 2013. UUDIS began collecting national drug shortage data in January 2001, and it publishes critical drug shortage information on a public website (www.ashp.org/shortages) hosted by the American Society of

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Health-System Pharmacists (ASHP). The UUDIS defines a shortage as a supply issue affecting how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent [10]. For this study's purpose, we used this definition for a shortage, which is more inclusive than the FDA definition. Detailed UUDIS methods have been previously published [11]. UUDIS receives voluntary drug shortage reports via the reporting feature on the ASHP website. Clinical pharmacists at UUDIS verify the existence of a shortage and determine all potential manufacturers of a drug reported to be in short supply using National Drug Codes (NDCs). Next, each manufacturer is contacted to determine which NDCs are in shortage at the national level. The manufacturers are also asked for reasons for the shortage and an estimated release date. UUDIS posts information at the ASHP drug shortage website, noting which products are affected, methods for accessing available products, reasons for the shortage, and estimated resupply dates. If applicable, patient care implications, safety concerns, therapeutic alternatives, and management strategies are also provided. UUDIS considers a shortage to be resolved when all suppliers have all NDCs (available strength and product size) available or have discontinued their products. UUDIS collects the following drug shortage data using Microsoft Excel: generic product name, therapeutic category, date shortage began (date UUDIS was notified), resolved date, duration, reason for shortage, and if the drug is an injectable product. Drug shortages that occur due to product discontinuation or withdrawal from the market are also included in the UUDIS database and marked as having shortage duration of zero days [10].

We analyzed drug shortage data from UUDIS from January 2001 to December 2013. Three investigators evaluated 1751 pharmaceutical products with reported shortages, focusing on antibacterial drugs. In addition, our dataset included information on whether the shortage was active or resolved, the reason for shortage, whether the product was an injectable product, whether the product was sole source (defined as a single-manufacturer product and determined by the investigator using FDA approval dates), and whether alternative drugs were available as a substitute.

The investigators further characterized each antibacterial drug in the data set to general pharmacologic class and whether the drug is broad spectrum or narrow spectrum in coverage (with broad-spectrum defined as treating both gram-positive and gram-negative infections). Further classification was conducted to determine special pathogen coverage (eg, for methicillin-resistant *Staphylococcus aureus* [MRSA] or *Pseudomonas aeruginosa*). We excluded topical and ophthalmic antibacterial agents. For example, tobramycin powder shortages were excluded because it is most commonly used in bone cement, although the product is labeled for injection. This is due to the increased time to reconstitute for intravenous use. Although it is possible that some hospitals reconstitute the powder for intravenous use, including this information would inaccurately account for the actual usage of systemic use. We also excluded antimycobacterial agents, such as rifampin, as this study's focus was to evaluate shortages for antibiotics used to treat acute bacterial infections and not tuberculosis. Shortage duration was calculated for resolved shortages. Because this study did not include human subject data, it was considered exempt by our institutional review board.

Data Analysis

Data were described using standard descriptive statistics. Univariate analysis found that drug shortage time (measured in days) was not normally distributed (right skewed). Therefore, we used the nonparametric 2-sample Wilcoxon rank-sum (Mann–Whitney) test to compare shortage times and describe average shortage time using median and interquartile range (IQR). Visual inspection of the drug shortages by month showed a distinct upward (positive) trend from July 2007 to 2014. A segmented regression analysis of drugs shortages before and after July 2007 was performed to assess this trend. Time was coded as a continuous variable in 1-month intervals from 1 (January 2001) to 156 (December 2013). We excluded the first year of data collection (2001) from the regression equation to adjust for a time lag for drugs to first appear on the shortage list. For the purposes of analysis, drugs that were on shortage for >1 time period are counted as separate shortages. The total number of antibacterial drugs on shortage was regressed on a constant, a linear trend term (x), a dummy variable equaling zero prior to July 2007 and 1 thereafter, and a post–July 2007 trend term (x-78) as described by Wagner et al [12]. A Durbin-Watson test indicated presence of serial autocorrelation and was corrected for by using the Cochrane-Orcutt transformation [13]. A P value of <.05 was considered significant. Data were collected in Microsoft Excel (Microsoft Corporation, Redmond, Washington), and analyses were conducted using Stata 13.1 (College Station, Texas).

RESULTS

Over the course of the study period, 148 antibacterial drugs went on shortage. Of those, 112 were resolved by the end of the study period (31 December 2013), 10 were discontinued by the manufacturer, and 26 remained active. Figure 1 presents the trends in shortages over time.

The median number of new shortages per year was 10 (IQR, 7) and ranged from a low of 6 in 2004 to a high of 18 in 2011. The median duration of a resolved shortage was 232 days (IQR, 373.5 days), or approximately 7.5 months.

We examined resolved shortage times for drugs with and without injectable administration, drugs with and without

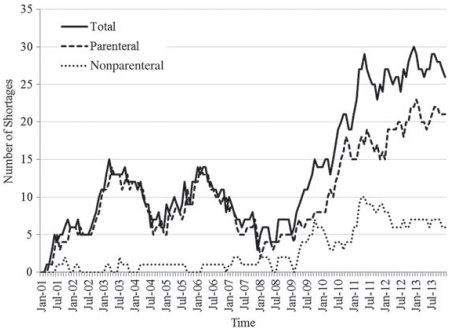

Figure 1. Trends in drug shortages, 2001–2013.

available alternatives, and broad- vs narrow-spectrum drugs. Drugs with injectable administration had a median shortage time of 250 days (IQR, 457 days) vs 129 days (IQR, 288 days) for drugs without injectable administration ($P = .06$).

Drugs without available alternatives had a median shortage of 149.5 days (IQR, 410 days) vs 262 days (IQR, 324 days) for drugs with an alternative ($P = .10$). Drugs classified as broad-spectrum had a median shortage of 232 days (IQR, 367 days) vs 199.5 days (IQR, 366 days) for narrow-spectrum drugs ($P = .74$).

Over the study period, an average of 14.2 drugs were on shortage per month (95% CI, 12.8–15.5). The number of drugs on shortage in a given month increased over time (Figure 1). On average, there were 9.7 drugs on shortage per month prior to July 2007 vs 17.9 from July 2007 through December 2013 ($P < .001$). From July 2007 to December 2013, the rate of increase was approximately 0.35 additional drugs every month (95% CI, .22–.49) and was significantly different from the trend prior to July 2007 ($P < .001$).

Thirty-two drugs (22%) experienced multiple shortages over the study period. The most commonly reported shortages were meropenem (7); cefotetan and piperacillin-tazobactam (5 each); and azithromycin, aztreonam, and nafcillin (4 each) (Table 1).

Cephalosporins were the most commonly reported drug class shortage, with 27 reported shortages for a total of 446 months over the study period. There were 11 aminoglycoside shortages for 284 months, 22 penicillin shortages for 229 months, and 11 penicillin/β-lactam inhibitor shortages for 178 months over the study period (Figure 2).

One hundred twenty of the 138 drugs (81%) were broad-spectrum antibacterial agents. Trends are displayed in Figure 3.

Sixty-eight of the shortages (46%) involved drugs used to treat high-risk pathogens, including 2 for *Clostridium difficile*, 1 for carbapenem-resistant Enterobacteriaceae (CRE), 1 for leprosy, 15 for MRSA, and 32 for *Pseudomonas aeruginosa*.

Table 1. Drugs With Multiple Shortages: Both Active and Resolved, 2001–2013

Drug Name	No. of Shortages	Total Days
Cefotetan	5	2141
Aztreonam	4	1990
Piperacillin-tazobactam	5	**1858**
Kanamycin injection	3	1682
Cefotaxime injection	3	**1542**
Doxycycline injection	3	1515
Erythromycin lactobionate	2	1245
Gentamicin injection, pediatric strength	2	1173
Meropenem	7	**1114**
Ampicillin-sulbactam	*3*	**1052**
Minocycline injection	2	944
Piperacillin sodium	2	942
Cefepime injection	3	801
Nafcillin	4	763
Azithromycin injection	4	**599**
Gentamicin injection	2	**574**
Cephalexin suspension	2	**535**
Imipenem-cilastatin	2	502
Ciprofloxacin 500 mg tablets	3	**442**
Ceftizoxime	2	405
Clindamycin injection	2	**394**
Vancomycin	3	**373**
Cefpodoxime	2	**344**
Colistimethate	2	255
Paromomycin (Humatin)	3	192
Cefuroxime injection	2	**185**
Sulfamethoxazole-trimethoprim injection	3	**165**
Methenamine	2	133
Dalfopristin/quinupristin (Synercid)	2	125
Ticarcillin-clavulanate	3	**123**
Ceftazidime	2	**69**
Spectinomycin	2	0

Includes both active and resolved shortages. Values in boldface indicate that the drug is currently experiencing a shortage.

Source: University of Utah Drug Information Service database.

Seven of the drugs treat extended-spectrum β-lactamase–producing organisms (ESBLs), and 4 treat human immunodeficiency virus–related opportunistic infections. Two drug formulations were specifically used to treat pediatric patients. The most common reason for shortage included manufacturing problems, with 35 reported shortages and 19 resulting from insufficient supply–demand ratio (Table 2)

DISCUSSION

There were several findings of concern in this study. First, there were a substantial number of drug shortages from 2001 to 2013,

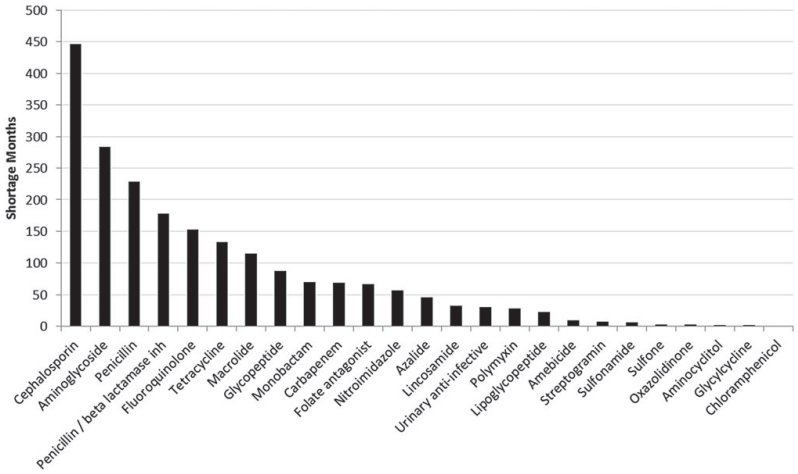

Figure 2. Drug shortages by drug class, 2001–2013.

with concerning trends over time. These shortages are often of very long duration, with a mean of nearly 9 months. Second, these shortages often impact clinicians' ability to treat infections, including multidrug-resistant pathogens for which there is a limited selection of effective antibiotics. Finally, we found that a substantial proportion of shortages (61 of 148) were for unknown reasons, suggesting a need for improved tracking and reporting.

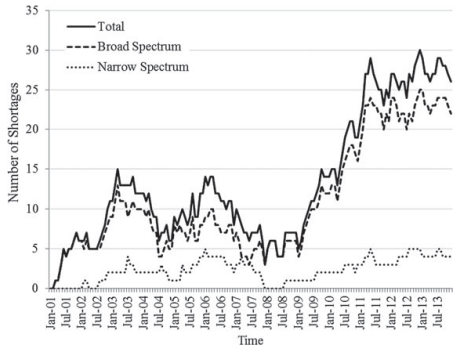

Figure 3. Trends in broad-spectrum vs narrow-spectrum shortages, 2001–2013.

A high proportion of recent drug shortages involved broad-spectrum agents, injectable drugs, medications with no alternative sources, or those used on pathogens with limited alternative treatment options or in pediatric patients. Although we were unable to determine the precise cause for the dramatic rise in antibacterial shortages after 2007, the shortage increase coincides with the downturn in the US economy, with the most common reasons for shortages being business related. Since 2011, drug shortages appear to have stabilized, but still remain high.

The upward trend in shortages of broad-spectrum agents is driving the total increase in shortages. We found especially

Table 2. Common Reasons for Drug Shortages, 2001–2013

Shortage Reason	No. of Drugs
General manufacturing/manufacturing delays or problems	35
Supply and demand	19
Raw material shortage	13
Discontinued	10
Regulatory issues/regulatory problems	5
Regulatory (import ban)	3
Natural disaster	1
Business decision	1
Unknown	61
Total	148

Source: University of Utah Drug Information Service database.

concerning the high shortage rates in antibacterial agents used to treat highly drug-resistant pathogens, including MRSA, CRE, and *Pseudomonas*. One hospital found that shortages occurred in 7 antimicrobials over a 3-month period, with 87% being generic products [14]. Treatment options for CREs are likely to become increasingly limited [15, 16].

Many shortages involve gold-standard therapies. For example, aztreonam treats life-threatening infections caused by gram-negative bacteria in patients allergic to penicillin and trimethoprim-sulfamethoxazole (TMP-SMX) for treatment of *Pneumocystis* pneumonia (PCP) [2]. TMP-SMX shortages are compounded because it is produced by a single manufacturer. Seventy-three drugs (49%) were listed as having no alternative production source. Use of therapeutic alternatives include lower efficacy rates and higher toxicity [1]. The shortage of TMP-SMX necessitating treatment with alternatives, such as clindamycin and primaquine, has led to delayed care, as well as refractory cases of PCP [13].

Implications for the clinical management of patients with critical infectious diseases in the setting of rising trends in drug resistance have been studied previously. A survey study of >600 infectious disease physicians found that 78% reported having to modify antibacterial choices due to shortages. In that study, clinicians reported the antimicrobials most commonly unavailable or in short supply as TMP-SMX (65%), amikacin (58%), and aztreonam (31%), which is supported by our findings. More than half felt that the shortage had a negative impact on patient outcomes, requiring the use of less effective, more toxic, or more costly alternatives. Most providers reported they learned of shortages after attempting to prescribe the medication through their pharmacy [5].

Alternatives may not be as familiar to clinicians and thus may lead to medication errors and adverse outcomes [1]. In a survey of the Institute for Safe Medication Practices conducted in 2010, clinicians reported adverse outcomes due to drug shortages in 20% of cases [17], as well as substantial resource utilization when developing an action plan (82%) and a lack of suitable alternatives (70%). Shortages may also lead to internal hoarding of medications, posing ethical challenges. Potential patient harm due to shortages includes medication overdoses, life-threatening side effects, cross-contamination, and even death [18]. For example, several patients with *Pseudomonas* infection only and amikacin sensitivity experienced morbidity or mortality when the drug could not be provided [13–15].

There are several ways to potentially mitigate the clinical impact of antibacterial drug shortages. One important strategy is through improved communication with providers. In half of cases, physicians and nurses learn about drug shortages from pharmacy staff, often when the pharmacy is unable to dispense the medication [13]. Institutions should consider prospectively tracking potential shortages and making recommendations for safe and appropriate use of therapeutic alternatives [19]. Strategies should also include keeping local inventory of critical antibacterial agents, anticipating the need for alternatives, and creating contingency plans. A multidisciplinary antimicrobial stewardship plan should include a stewardship pharmacist to help guide these efforts. One strategy would be guideline development, ensuring narrow coverage based on culture results, encouraging intravenous to oral conversion, ensuring ethical distribution to patients with the greatest need, educating clinicians, and developing protocols for when alternatives must be used, so as to prevent errors [15]. An interdisciplinary drug shortage task force can include physicians, pharmacists, nurses, ethics members, and patient representatives [20]. Optimization of utilization of the available supply and guidance regarding alternative agents are imperative, with guidelines available [17].

Although more than a dozen new antimicrobial agents have recently been developed against antibiotic-resistant pathogens, few act on new targets; thus, it is imperative to address the lack of agents, compounded by drug shortages, for these classes [21]. Many times, manufacturers do not report shortages until supplies are very low, and policy makers should advocate for mandatory earlier reporting of shortages.

Limitations included the inability to account for all possible shortages, lack of information on geographic disparities in shortages, and evidence of impact on clinical outcomes. Drug shortages may impact individual healthcare facilities at different times and with differing effects on clinical care. For example, not all facilities stock all drugs or all formulations. Small or rural facilities may have more difficulty accessing products that can only be purchased directly from the manufacturer. Inventory and delivery methods vary widely in the drug distribution chain. Furthermore, it is somewhat difficult to distinguish if the drug was completely unavailable, discontinued, or available but in short supply, so we cannot describe the severity of the shortage. We were also unable to measure the time and effort hospital staff spends attempting to mitigate shortages. Nonetheless, the database currently used represents the most comprehensive data source on trends and reasons for antibacterial and other drug shortages.

In summary, there were 148 reported antibacterial shortages, with 26 drugs still actively on shortage as of 31 December 2013, with nearly half reported as having no alternative production source. Given that 46% are used in the treatment of high-risk pathogens, such as MRSA, CRE, and *Pseudomonas*, it is imperative to develop a comprehensive strategy to mitigate the implications of shortages on clinical practice and patient outcomes, including improved communication, alternative algorithms, and antimicrobial stewardship policies.

Notes

Author contributions. F. Q. was responsible for the literature review, analysis of data, results, editing, and abstract. M. M.-A. was responsible for study design, data collection, data interpretation, and writing. E. R. F.

was responsible for data collection, data interpretation, and writing. K. L. H. was responsible for study design, data collection, and data interpretation. J. M. P. was responsible for study design, data interpretation, and writing. M. S. Z. was responsible for data analysis, figures, and editing. L. M. was responsible for study design, data analysis, data interpretation, literature review, writing, and editing. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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U.S. vaccine and immune globulin product shortages, 2001–15

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Purpose. Trends in shortages of vaccines and immune globulin products from 2001 through 2015 in the United States are described.

Methods. Drug shortage data from January 2001 through December 2015 were obtained from the University of Utah Drug Information Service. Shortage data for vaccines and immune globulins were analyzed, focusing on the type of product, reason for shortage, shortage duration, shortages requiring vaccine deferral, and whether the drug was a single-source product. Inclusion of the product into the pediatric vaccination schedule was also noted.

Results. Of the 2,080 reported drug shortages, 59 (2.8%) were for vaccines and immune globulin products. Of those, 2 shortages (3%) remained active at the end of the study period. The median shortage duration was 16.8 months. The most common products on shortage were viral vaccines (58%), especially hepatitis A, hepatitis B, rabies, and varicella vaccines (4 shortages each). A vaccine deferral was required for 21 shortages (36%), and single-source products were on shortage 30 times (51%). The most common reason for shortage was manufacturing problems (51%), followed by supply-and-demand issues (7%). Thirty shortages (51%) were for products on the pediatric schedule, with a median duration of 21.7 months.

Conclusion. Drug shortages of vaccines and immune globulin products accounted for only 2.8% of reported drug shortages within a 15-year period, but about half of these shortages involved products on the pediatric vaccination schedule, which may have significant public health implications.

Keywords: bacterial vaccines, immunization, immunoglobulins, supply and distribution, vaccines, viral vaccines

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Prescription drug shortages, defined by the Food and Drug Administration (FDA) as "a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug," have become increasingly prevalent over the past 2 decades.[1,2] Manufacturing and quality-control problems, as well as economic factors, have resulted in frequent supply disruptions.[2] Prescription drug shortages have affected multiple specialties, including oncology, emergency medicine, and infectious diseases.[3-5] Data have also revealed that sterile injectable products are more commonly in short supply compared with products for oral or topical administration.[2-5]

Millions of vaccinations are administered each year for infection prevention and control.[6] Vaccine shortages can have significant public health and clinical implications, as they may result in individuals not being fully vaccinated according to the recommended schedule, thereby compromising herd immunity and

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creating the potential for epidemic outbreaks of communicable diseases. Vaccine shortages may affect not only the health of adult patients seeking secondary vaccinations but that of vulnerable infants and children who are in need of primary vaccinations, with a potential significant effect on communicable disease morbidity and mortality due to reduced herd immunity.

In the case of a vaccine shortage, the Centers for Disease Control and Prevention (CDC) may recommend to postpone or omit a dose of a recommended booster vaccination in order to allow unvaccinated children to receive a first dose of the vaccine in short supply.[6] Data describing how drug shortages have affected vaccine and immune globulin availability are limited. Previous reports have focused on the availability of *Haemophilus influenzae* type b (Hib), pneumococcal, and influenza vaccines.[7-11] We assessed the shortages of vaccines and immune globulins in the United States from 2001 through 2015.

Methods

The University of Utah Drug Information Service (UUDIS) has been collecting national drug shortage data since January 2001 and publishes critical drug shortage information on a public website (www.ashp.org/shortage) hosted by the American Society of Health-System Pharmacists (ASHP). UUDIS defines a shortage as "a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent".[12] This definition differs slightly from, but is more inclusive than, FDA's definition of a shortage. For example, a shortage of prefilled syringes of a specific product may cause significant logistic and safety issues, even if the same medication is available in vials.

The Government Accountability Office (GAO) considers UUDIS data to be the most comprehensive and reliable source of drug shortage information and has used UUDIS data for 4 reports published on drug shortages.[2,13] Detailed methods describing UUDIS have been previously published.[14] Briefly, UUDIS receives voluntary reports of drug and vaccine shortages via the reporting feature on the ASHP website. Clinical pharmacists at UUDIS research each shortage reported to verify that the shortage actually exists. This research includes determining all potential manufacturers of a reported drug or vaccine in shortage and all drug presentation National Drug Codes (NDCs). Next, each manufacturer is contacted to determine which NDCs are in shortage at the national level. The manufacturers are also asked for a reason for the shortage as well as an estimated release date. If most manufacturers are having a national shortage, then UUDIS will post information on the ASHP drug shortage website noting which products are affected, which products are available, specific methods for accessing the product, reasons for the shortage, estimated resupply dates, and, if applicable, implications for patient care, safety concerns, alternatives, and management strategies. UUDIS considers a shortage to be resolved when all suppliers have all presentations available or have discontinued their products. UUDIS also follows FDA's drug shortage website and will generally list shortages as resolved when FDA considers the shortages resolved.

KEY POINTS

- From 2001 through 2015, half of the vaccine shortages affected the pediatric vaccine schedule.
- Nearly 90% of vaccines had multiple shortages during the study period.
- The mitigation of vaccine shortages is crucial for public health, especially shortages of products on the pediatric vaccination schedule.

UUDIS collects the following drug shortage data using Excel (Microsoft Corp., Redmond, WA): generic product name, therapeutic category, date shortage began (date UUDIS was notified), date shortage was resolved, duration of shortage, reason for the shortage, controlled substance schedule (if applicable), and whether the drug is an injectable product. Drug shortages that occur due to a product discontinuation or withdrawal from the market have the same start and stop dates for a duration of 0 days.

The data set was restricted to shortages that occurred between January 1, 2001, and December 31, 2015, and was analyzed in 2016. Members of the study team identified shortages that affected vaccines and immune globulins. All discrepancies were discussed until a consensus was reached. Shortage data were analyzed, focusing on the type of product, reason for the shortage, shortage duration, shortages requiring vaccine deferral, and whether the drug was a single-source product (produced by 1 manufacturer). Inclusion of the product into the pediatric vaccination schedule was also noted. The availability of a substitute therapy and whether the alternative was also affected by a shortage at any time during the study period, as well as multiple shortages (those that were resolved but then another shortage occurred) of the same vaccine were also noted. For some portions of the analysis, products were grouped together based on vaccine category, such as bacterial vaccines, viral vaccines, combination products, immune globulins, or toxoids. Shortage length was analyzed using Hodges-Lehmann median differences and the Kruskal–Wallis test for comparisons of more than 2 groups. Negative binomial regression was used to determine if the trend in new shortages observed each year was significant over the study period. Discontinued products were not included in analyses of shortage duration ($n = 3$). Data were analyzed using

Stata, version 14.0 (Stat Corp., College Station, TX). These data do not meet the definition of human subjects' research and therefore were exempt from institutional review board review.

Results

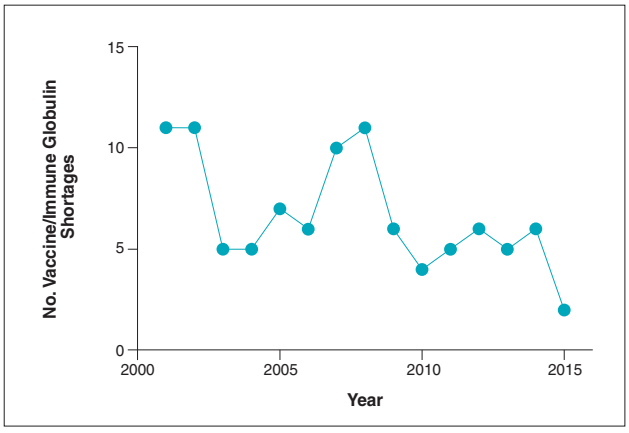
Number and duration of shortages. A total of 2,080 drug shortages were reported from January 2001 through December 2015, 59 (2.8%) of which involved vaccines or immune globulins. The number of products on shortage decreased from 11 in 2001 to 2 in 2015 ($p = 0.08$) (Figure 1). The median shortage duration was 16.8 months (interquartile range [IQR], 5.8–27.3 months). The median number of new shortages reported annually was 3 (IQR, 2–5). By the end of the study period, 2 products remained on active shortage (meningococcal vaccine for 230 days; yellow fever vaccine for 119 days). The median duration for the 57 resolved shortages was 18.3 months (IQR, 6.1–27.4 months). Fifty-three vaccines or immune globulins (90%) were the subject of multiple shortages during the study period. Rabies immune globulin had the longest shortage duration for any vaccine or immune globulin (2,717 days, from August 16, 2007, to January 23, 2015).

Thirty shortages (51%) involved vaccines on the pediatric schedule, with a median shortage duration of 21.7 months (IQR, 8.0–28.1 months). A vaccine deferral was required for 21 shortages (36%), and single-source products were on shortage 30 times. Single-source products were involved in 51% of shortages, with a median shortage duration of 19.8 months (IQR, 11.1–26.7 months). Shortage durations did not differ significantly among the product types examined.

Types of products involved in shortages. Of the 59 vaccine shortages during the study period, 34 (58%) involved viral vaccines, 18 (31%) involved bacterial vaccines, and 7 (12%) involved toxoids. Combination products accounted for 9 (15%) of reported shortages. Eight (14%) products affected by shortages were immune globulins (Table 1). Of all shortages, combination products had the longest median shortage duration (25.7 months; IQR, 16.3–36.8 months); however, this duration was not significantly different than that for other types of products ($p = 0.202$). The most common products with multiple shortages were viral vaccines, particularly hepatitis A, hepatitis B, rabies, and varicella vaccines, with 4 shortages each (Table 2).

Reasons for shortages. The most commonly reported reason for a shortage was manufacturing problems (51%), followed by supply-and-demand issues (7%) (Table 3). A reason was not provided for 18 cases (31%) of vaccine shortages. Shortage duration differed significantly depending on the reason given for the shortage ($p = 0.004$, Kruskal–Wallis test). The longest durations were for products on shortage due to manufacturing problems (median, 22.8 months; IQR, 16.8–31.1 months).

Figure 1. Total number of vaccine and immune globulin products in short supply from 2001 through 2015.



Discussion

Although the number of vaccine and immune globulin shortages (59 [2.9%]) was low compared with the total number of drug shortages (2,080) during the study period, shortages of these products can have far-reaching implications. Thirty (51%) of these shortages affected the pediatric vaccine schedule, and it is unknown how many children did not receive their full vaccination series due to these shortages. The National Immunization Survey reported that the vaccination coverage for diphtheria, tetanus, and acellular pertussis (DTaP) or measles, mumps, and rubella (MMR) was not affected by these shortages at a national level.[15,16] It is unknown whether vaccination rates for vaccines not on shortage remained stable, as any decrease in these rates would imply that the shortages had a causal role.

Nearly 90% of vaccines had multiple shortages during the study period, including important childhood vaccines such as varicella and hepatitis B (Table 2). Recurrent shortages of the same products suggest systematic errors in the manufacturing process. Vaccines and immune globulin products have more complex manufacturing requirements than do simple molecules and oral products. Problems with manufacturing these products

Table 1. Types of Vaccine Products Affected by Drug Shortages[a]

Product Type[b]	No. (%) Shortages	Median Shortage Duration in Months (IQR)	Median (95% CI) Difference vs. Other Product Types, in Months
All products	59 (100)	16.8 (5.8–27.3)	…
Bacterial vaccines	18 (31)	22.6 (11.1–27.4)	5.7 (–2.5 to 16.2)
Combination products	9 (15)	25.7 (16.3–36.8)	9.0 (–3.9 to 20.2)
Immune globulins	8 (14)	5.1 (3.7–13.9)	–6.8 (–17.6 to 0.0)
Toxoids	7 (12)	23.3 (4.1–36.8)	2.2 (–18.2 to 21.5)
Viral vaccines	34 (58)	16.6 (6.1–27.8)	–0.7 (–10.5 to 5.7)
Products on pediatric schedule	30 (51)	21.7 (8.0–28.1)	5.0 (–0.7 to 14.1)
Vaccine with deferral required during shortage	21 (36)	22.3 (11.1–27.4)	5.6 (–2.2 to 13.7)
Single-source products	30 (51)	19.8 (11.1–26.7)	3.5 (–3.5 to 11.9)

[a]IQR = interquartile range, CI = confidence interval.
[b]Some products may fit into more than 1 category.

accounted for 51% of the reported shortages (Table 3). Shortages of vaccines and immune globulin products usually take longer to resolve, and in many cases the actual manufacturing time of these products can take several months. This means that shortages of these products will be lengthy. The mean duration of shortage was well over 1 year (median duration of resolved shortages, 18.3 months), with the longest shortage durations of over 2 years for combination products (median, 25.7 months), including shortages for vaccines on the pediatric schedule, and almost 2 years for toxoids (median, 23.3 months) (Table 1). The advantage of combination vaccines is that they reduce the number of injections a child needs to in order to be fully immunized against several diseases. If individual vaccines are used due to a shortage of combination vaccines, the number of injections required for a child would increase, which might lead to objections against vaccinations in general.

Single-source products. Products manufactured by a single company or facility are at higher risk of a drug shortage, because any disruption in the manufacturing process typically results in a shortage.[17] GAO's latest report on drug shortages also notes that products with few suppliers are at greater risk of a drug shortage.[18] In this analysis, 51% of products on shortage were produced by a single manufacturer, and 5 products (8%) were affected by; at least 3 recurrent shortages (varicella, measles, mumps, rubella [MMR]; typhoid). Vaccines and immune globulin products are often single-source products or only supplied by 3 or fewer manufacturers. For example, in 2006, there was only 1 licensed manufacturer in the United States distributing MMR vaccine; varicella vaccine; tetanus and diphtheria vaccine; inactivated polio virus vaccine; meningococcal conjugate vaccine; and pneumococcal conjugate vaccines.[19]

Implications of deferrals. Shortages of vaccines have the potential to cause profound public health implications. The Advisory Committee on Immunization Practices (ACIP) recommends that clinicians evaluate vaccination status at each patient visit and avoid delaying vaccinations (e.g., deferral for mild illness).[6] Shortages of vaccines can result in deferrals and delays of over a year for vaccinations because many school-aged children only see a provider annually and most vaccine shortages last longer than 1 year. In this analysis, a vaccine deferral was required for 36% of shortages. In addition, multiple shortages might have a greater impact on children who get their first vaccination series because recommended vaccinations might be deferred more than once.

Shortages of vaccines have also resulted in changes to school vaccination requirements.[20] A publication describing 2 shortages of pneumococcal vaccine (heptavalent pneumococcal conjugate vaccine, PCV7) in 2001 and 2004 analyzed whether the vaccination behavior of pediatricians in Cincinnati was changed through the shortages. Only 66% of healthy children were documented as having received their first 2 doses of pneumococcal vaccine on time, compared with 74% of healthy children during nonshortage periods.[10] An analysis of the vaccination coverage rates of Hib during the 2008–09 vaccine shortage revealed 7.8–10.3% lower coverage rates compared with periods without a shortage.[9] Results of another study found a higher Hib carrier rate in Atlanta due to the vaccination deferral during the 2008–09 Hib vaccine shortage.[8]

Unfortunately, our data show that many of the problems highlighted in GAO's 2002 report on vaccine shortages still exist, such as manufacturing problems, demand exceeding supply, and a lack of redundancy in the manufacturing process.[20] In addition, vac-

Table 2. Characteristics of Vaccines and Immune Globulins Affected by Shortages, 2001–15

Vaccine or Immune Globulin	No. Shortages	Single Source?	Shortage Active on December 31, 2015?	Included on Pediatric Schedule?
Hepatitis A	4	No	No	No
Hepatitis B	4	No	No	Yes
Rabies	4	No	No	No
Varicella	4	Yes	No	Yes
Haemophilus influenzae type b	3	No	No	Yes
Measles	3	Yes	No	Yes
Mumps	3	Yes	No	Yes
Rabies immune globulin	3	No	No	No
Rubella	3	Yes	No	Yes
Typhoid	3	Yes	No	No
Cytomegalovirus immune globulin	2	Yes	No	No
Diphtheria, tetanus, and acellular pertussis	2	No	No	Yes
Hepatitis B immune globulin	2	No	No	No
Influenza	2	No	No	Yes
Meningococcal (MCV4)	3	Yes	Yes	Yes
Measles, mumps, rubella, and varicella	2	Yes	No	Yes
Pneumococcal (PCV7)	2	Yes	No	Yes
Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed	2	No	No	No
Diphtheria, tetanus, pertussis, and poliovirus antigens	1	No	No	Yes
Diphtheria, tetanus, pertussis, poliovirus, and *H.influenzae* type b antigens	1	Yes	No	Yes
Measles, mumps, and rubella	1	Yes	No	Yes
Pneumococcal (V23)	1	Yes	No	No
Yellow fever	2	Yes	Yes	No
Varicella immune globulin	1	No	No	No
Tetanus	1	Yes	Yes	No

Table 3. Reported Reasons for Vaccine and Immune Globulin Shortages[a]

Reason for Shortage	No. (%) Shortages	Median (IQR) Duration of Shortage, in Months
Discontinued product	3 (5)	NA
Manufacturing problem	30 (51)	22.8 (16.8–31.1)
Supply-and-demand issues	4 (7)	16.4 (5.8–22.1)
Other[c]	4 (7)	6.1 (4.5–15.5)
Unknown	18 (31)	7.8 (5.1–14.8)

[a]IQR = interquartile range, NA = not applicable.
[b]$\chi^2 = 13.199$ with 3 d.f. ($p = 0.004$), Kruskal-Wallis test.
[c]Natural disaster ($n = 2$), shortage of raw materials ($n = 1$), and product recall ($n = 1$).

cine shortages may have a disparate effect on vulnerable populations. For example, among children receiving vaccinations in public clinics, those living outside of urban areas, children in the South, and American Indian/Alaska Native children were less likely to have received the fourth dose of the DTaP vaccine during the shortage.[22,23]

Mitigation strategies. There are several potential strategies that may mitigate the impact of vaccine shortages, such as early notification about

foreseeable shortages, vaccine deferrals, vaccine stockpiles, and importation of commercial alternatives.[24]

Manufacturers should provide early notification about expected shortages to ensure that this information is included in current recommendations.[25] Providers should become more vigilant regarding anticipated shortages and proactively incorporate recommended strategies regarding existing supplies and future distribution. Unlike shortages of oncology or emergency drugs, vaccine shortages do not usually require institutional responses. Decisions on vaccine deferrals should only be made on an institutional basis in emergency situations (e.g., by vaccinating only high-risk patients) because vaccines are not usually used during emergencies. Instead, recommendations on deferrals should be issued on a state or national level. In the past, CDC, together with the American Academy of Pediatrics and the American Academy of Family Physicians, issued vaccine deferral recommendations, asking providers to withhold a third or fourth dose of PCV7 during the 2003–04 shortage.[21]

In another study, good adherence of pediatricians to vaccination recommendations was reported, with 91% of assessed care providers stating that high-risk patients were fully vaccinated. At the same time, pediatricians whose practice experienced no vaccine shortage were more likely to administer a fourth dose of PCV7 vaccine despite recommendations to the contrary.[26] This highlights the complexities of implementing vaccine deferrals when the vaccine supply is not distributed equally.

In order to keep track of patients who miss a vaccine booster during a shortage, proper surveillance measures should be implemented. During the 2003–04 shortage of PCV7, systems to track children who missed doses due to redistribution of vaccines at the national level were reported in approximately two thirds of the practices that deferred a vaccination.[21,26]

Influenza vaccine shortages were reported for patients at high risk during the 2004–05 influenza season. During this time, pediatricians prioritized vaccination of younger children and those with chronic medical conditions, such as chronic heart or kidney diseases and organ transplants or cancer.[11] Another strategy used in emergency medicine during a past shortage of tetanus vaccine was to provide tetanus boosters to patients with high-risk wounds only.[27]

Although the tracking of current vaccine stocks and early notification of when these stocks fall below certain levels do not prevent vaccine shortages, these methods could initiate early mitigation measures even before a vaccine shortage hits by issuing preventive deferrals or modifying immunization recommendations. The 2002 vaccine shortage resulted in multiple at-risk children not being vaccinated according to schedule.[20,22] In response, CDC used vaccine stockpiles for children to mitigate the risk of potential epidemics triggered by future shortages. One model suggested that while stockpiles were sufficient to meet future interruptions in manufacturing that last less than 6 months, the prolonged median shortages (5.1 months for immune globulins and 25.7 months for combination products) in this analysis (Table 1) suggest that such stockpiles may be inadequate to meet vaccination needs for children.[22] A 6-month stockpile is therefore unlikely to be effective due to the typically lengthy duration of vaccine shortages.

While FDA has imported medications from other countries in the past to help alleviate drug shortages (e.g., propofol, nitroglycerin, doxorubicin), no vaccine products have been imported to help alleviate vaccine shortages, and doing so could lead to extra costs due to the additional regulatory approval process. The importation of vaccines would be required if a U.S. vaccine product was discontinued without the availability of an adequate alternative.

It would be useful to assess whether drug shortages in the United States also occur globally; however, the United States is one of the few countries with such a robust system for tracking drug shortages. Other countries do not have a systematic way of tracking drug shortages or their systems are in the course of development. Manufacturers of vaccines in multiple countries do not provide information about vaccines marketed outside the United States to clinicians in the United States.[17] Despite this limitation, even if it is possible to know if a vaccine was marketed in another country, it is still impossible to know if there were shortages at that time in another country unless case reports were published in the literature, as it was for a shortage of bacille Calmette-Guérin vaccine in Europe.[28]

Ethical frameworks. Regardless of the type of vaccine implicated in a shortage, it is important to have an organized and ethical framework for the distribution of limited vaccine supplies. General ethical recommendations on the rationing of drugs respecting principles of justice and fairness include establishing an allocation committee for drugs on shortage to provide guidelines for patient prioritization.[29] For vaccines represented in pediatric schedules, ACIP and CDC have often provided recommendations for prioritizing patients. A strategy used for transferring ethical principles into oncology practice regarding drug shortages is the so-called "A4R" approach, which addresses relevance, transparency, revision, and enforcement.[30]

A key difference between vaccine and immune globulin shortages and other drug shortages is that there is typically no immediate harm due to a shortage, but future harm may be long reaching if sufficient vaccines are deferred to reduce overall herd immunity. There are also fewer available alternatives for a vaccine shortage.

Addressing reasons for shortages. The vaccine manufacturing process is complex and thus fragile.

A CDC publication described the vaccine shortages between 2000 and 2004 and the reason for the shortages in detail.[19] Factors disturbing the manufacturing process include production problems, adherence to quality-control measures, recommendations to remove the preservative thimerosal, and economic decisions.

Production problems as a cause of shortages is not unique to vaccines. A summary of drug shortages (not limited to vaccines) found that injectable drugs accounted for 73% of all shortages in 2011 and that quality issues accounted for 56% of shortages of sterile injectable drugs.[31] Quality issues for injectables were defined as bacterial or mold contamination and the presence of foreign particles in vials. These findings suggest that manufacturers should develop and expand their own quality-control measures in order to minimize these incidents.[32] FDA, GAO, and the International Society for Pharmaceutical Engineering have identified quality issues and manufacturing problems as the key causes of drug shortages. It has been proposed that the reason for problems related to quality is a lack of transparency, which results in few manufacturers devoting resources to ensure the highest quality manufacturing.[33]

Ultimately, a multifaceted approach involving stakeholders from government and industry will be required to address the underlying reasons for vaccine shortages. Suggested solutions include financial incentives for vaccine manufacturers, regulatory changes, and rotating vaccine stockpiles, particularly for pediatric vaccines.[20]

Implications for pandemic preparedness. Influenza vaccine shortages have significant implications for preparedness for influenza epidemics and pandemics, particularly given the small number of influenza vaccine manufacturers. Even with 5 manufacturers of influenza vaccine, the total number of influenza vaccine doses provides a dose for less than half the population of the United States.[34] In addition, the majority of influenza vaccine produced in the United States requires a lengthy egg-based manufacturing process.[35] Cell-based and recombinant influenza vaccines are made by 2 separate companies but represent a low volume of the overall influenza vaccine market.[34] Influenza vaccines were affected by 2 shortages during the observation period. While nonpharmaceutical interventions such as social distancing and postexposure prophylaxis will play a major role during a pandemic, vaccination remains an important strategy, particularly for at-risk populations.[36] Alternative strategies during shortages include targeting and prioritizing high-risk groups for vaccination as well as using modified formulations (i.e., split or whole virus formulations or adjuvants).[37]

Additional preventive measures. CDC maintains a national stockpile that includes a 6-month rotating supply of pediatric vaccines, which began as early as 1983 for some vaccines.[19] Since then, stockpiles have been used to cover vaccine demand on at least 8 occasions until 2004.[12] Optimization efforts concerning stockpiling pediatric vaccines were implemented in 2002.[19]

Several simulations exist to optimize vaccine stockpiling.[38,39] Planned stockpiling at a national level must be differentiated from individual physicians' practices to maintain vaccine stocks in their offices, which is better described as hoarding. Furthermore, SWOT analysis (strengths, weaknesses, opportunities, threats) may help public health partners address shortages of vaccinations, such as influenza vaccine, to help develop strategies for rationing vaccines during public health emergencies.[40]

Study limitations. The major limitation of this study was that we could not assess the actual effect of shortages on individual institutions or patient care (e.g., delayed or suboptimal therapy, resultant medication errors and adverse outcomes). We also could not describe the severity of shortages affecting a particular product (i.e., whether the product was in limited supply or completely unavailable) and how these were ultimately dealt with on a healthcare system level. However, CDC adjusted the vaccination schedule for multiple products due to shortages of MMR vaccine, Hib vaccine, PCV7, and varicella vaccine. CDC also recommended deferring preexposure prophylaxis vaccinations during the rabies vaccine shortage. We did not take into account additional costs or toxicity when considering the use of available substitutes. In addition, the duration of shortages that were active at the end of the study period would be underestimated. Finally, we could not account for the time and resources used by institutions to mitigate drug shortages as well as the effectiveness of mitigation strategies. These are all potential areas for additional prospective studies.

Conclusion

Drug shortages of vaccines and immune globulin products accounted for only 2.8% of reported drug shortages within a 15-year period, but about half of these shortages involved products on the pediatric vaccination schedule, which may have significant public health implications.

Disclosures

The authors have declared no potential conflicts of interest.

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Preface

Prescription drug shortages in the United States have reached critical levels and represent a major threat to public health. The consequences of these shortages come in the form of delayed or suboptimal care, medication errors, and increased healthcare costs. The investigations that comprise this thesis attempt to explore how drug shortages may impact different specialties, care settings, and age groups. This was accomplished primarily through retrospective studies of data from the University of Utah Drug Information Services, which is considered to be the most robust shortage data available.

General Discussion

The studies that comprise this thesis clearly demonstrate that prescription drug shortages are a major public health problem. We also describe some potential mitigation strategies, both in dealing with existing shortages and preventing future shortages from occurring. Mitigation strategies unique to each specialty and age group are presented in the individual chapters and a broader discussion is provided in Chapters 2 and 7. Ultimately, the optimal approach to managing shortages is complex and requires involvement from multiple stakeholders.

Governmental Interventions

On a governmental level, expanding the role of the FDA may help to mitigate shortages. With increased authority, the FDA could potentially require manufacturers to make products that are in critical need. This would limit the autonomy of pharmaceutical manufacturers and may impact profit margins, which could impact the prices of medications. Alternatively, incentives could be provided to encourage manufacturers to make products in need. These incentives could take the form of tax relief, rebates, or extended market exclusivity. Incentives can also be provided for manufacturers who keep their facilities in compliance with current good manufacturing practices. Although these interventions may make the supply chain more robust, there are some potential adverse consequences. Manufacturers may shift their production to make products that have incentives, precipitating shortages of medications that do not have incentives. In addition, extended exclusivity may increase drug prices and overall healthcare costs. For these reasons, incentives must be carefully balanced as to avoid unintended consequences. While the FDA does have a responsibility to ensure a stable drug supply, increased oversight would require more resources on the part of the agency, which would necessitate additional funding. A reasonable approach would be to expand the FDA authority in a some capacity short of requiring manufacturers to make specific products, and to provide some limited incentives to drug manufacturers in order to avoid driving up drug costs.

In addition to providing incentives, there are other actions that can be taken to deal with shortages. The FDA can expedite approvals for additional manufacturers who want to bring a product to market as well as help to facilitate reviews of sites that are currently not in compliance with good manufacturing practices. The authority of the FDA could

potentially be expanded to allow for civil or monetary penalties for manufacturers who do not provide adequate notification regarding shortages or who regularly have facilities that are in poor repair. Monetary penalties could potentially be used to subsidize the additional resources that would be required by the FDA. Currently, under FDASIA, the FDA can require notification but cannot penalize manufacturers who do not comply with notification requirements. Another potential solution is to more proactively manage quality control at production facilities and improve transparency in the manufacturing process with increased FDA oversight. The FDA has also implemented an emerging technology program, which helps to incorporate new technologies that might help to streamline the manufacturing process, decrease costs, or prevent quality problems at facilities. Although these programs will need to be subsidized, they will help to build a robust supply chain that produces quality products at facilities that are in compliance with current manufacturing standards.

Another potential option in mitigating shortages is to re-evaluate the pricing structure for generic drugs, which currently have limits on reimbursement, particularly as it relates to Medicare and Medicaid. We have demonstrated time and again, that shortages disproportionately impact generic injectable drugs. Removing some of the pricing constraints might help improve profit margins, attracting additional manufacturers and increasing redundancy in the supply chain. Once again, this must be a balanced approach as to avoid increasing healthcare costs; however, having fewer shortages may offset some of these costs, as shortages also increase healthcare costs.

For critical medications, such as saline solutions, another option would be to have the Department of Homeland Security consider them as part of the essential infrastructure, which would require manufacturers to develop business continuity plans. However, this would be costly and time consuming. As such, this would only be a feasible option for only the most critical of medications and supplies.

Temporary importation of drugs is a way to mitigate existing shortages; however, it does not address the underlying reasons why shortages occur. FDA has allowed for the importation of saline and other products during times of critical shortages. Importation has its limitations as well because importing an adequate amount of product to address a shortage in the U.S. may precipitate a shortage in the country of origin. The product to be imported should be up to current standards as set by the FDA. In addition, transportation of product, sometimes over long distances can increase healthcare costs. FDA has also allowed for extension of expiration dates and allowance of particulate matter if a filter needle is used in some instances. Overall, these are all feasible options to address current shortages if they can be done safely; however the ultimate goal is to prevent shortages from occurring in the first place.

Recently, the FDA has announced the formation of a Drug Shortages Task Force. The purpose of this task force is to address the underlying causes of why shortages exist. It is a multi-disciplinarily team of experts representing stakeholders from the FDA, the Centers for Medicare and Medicaid Services, and the Department of Veterans Affairs.

The ultimate role of this task force will continue to develop and evolve as it is currently in its infancy.

Non-Governmental Mitigation Strategies

Outside of the governmental initiatives, continued engagement of industry, state and local medical boards, healthcare organizations, and individual providers is also a critical component to solving the shortage problem. Pharmaceutical manufacturers should comply with current good manufacturing standards and federal and state regulations. Many professional societies and medical boards have also spoken out against drug shortages and should continue to play an active role in mitigation. At the institutional level, strategies to minimize waste, proactive substitution protocols, and development of an ethical framework for distribution of limited supplies will be required to minimize the impact of shortages at the bedside. In addition, emergency medical services will need to develop protocols that address shortages as well as incorporate shortages into their disaster planning efforts. Pharmacy staff must continue to continue to work to find alternative suppliers and to monitor stock. Information technology resources will also be required to update ordering platforms when products are substituted because of a shortage. All of the aforementioned interventions have to potential to mitigate or prevent shortages; however, their true impact has yet to be elucidated and represents an area of future prospective study.

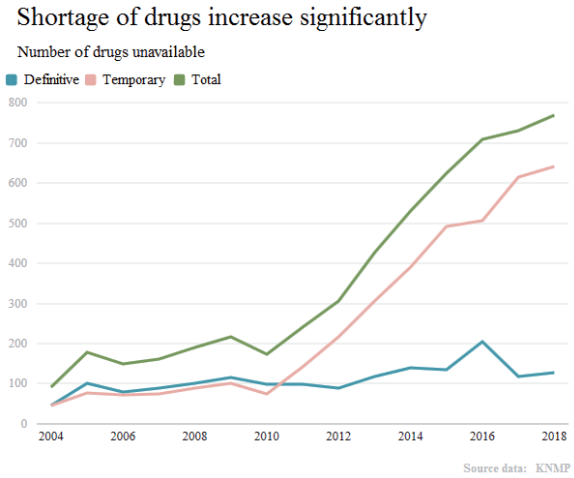
International Perspective

There is mounting evidence the problem of drug shortages are not unique to the US; however, the data pertaining to these shortages is much less robust. In Europe, there are some reporting systems in individual countries, including England, Belgium, the Netherlands, France, Spain, and Germany. These reporting systems are heterogeneous in nature and each has its own standards for reporting. One study demonstrated that brand name oral medications were more commonly impacted, in contrast to what has been documented in the US. Although data are more limited, production problems and market factors are thought to be the major drivers of shortages in Europe as well. More recently, the European Medicines Agency (EMA) has gotten involved in managing shortages, although the bulk of shortages are dealt with at the national level. The EMA will generally only get involved if several states in the European Union (EU) are impacted or if there is a serious safety issue related to a shortage. A task force has also been created in the EU to assist in managing drug shortages, with a similar focus as the US. Legislative efforts have also taken place in Canada in response to drug shortages. Finally, the global impact of shortages may be felt in other markets that are less studied, where profit margins are smaller. One potential example could be HIV and tuberculosis drugs in developing countries. Ultimately, additional data will be required in order to better understand the global footprint of drug shortages.

The situation regarding shortages of drugs in the Netherlands is highlighted in the textbox.

Shortages of drugs in the Netherlands

Shortages of drugs is not restricted to the situation in the USA. Based on information by the Dutch Ministry of Health as well as the Royal Dutch Society of Pharmacists (KNMP), alarming figures are published and a significant increase over the years of shortages of medication. In 2008 a total of 1390 reports were published on a potential shortages of a drug. In comparison to 2017, 536 reports were published of which 1000 different drugs were mentioned. This increase is not only due to a higher level of knowledge of this reporting agency but also due to real shortages. For instance in 2018, 769 drugs could not be delivered to the patients for at least a period of 2 weeks based on the figures of the pharmacists society KNMP Farmanco. The shortages were observed in a wide variety of drugs raging from anticonception; anti-hypertensive drugs; anti-epileptic medication and even levodopa with significant consequences for individual patients. At the back of this data, the origin of this problem is potentially due to problems with the production, as many of the active substances are produced in so called low-income countries such as China and India and in a very restricted number of factories. Any problems in the lines of production or other uncontrollable factors will have a major impact. This is also due to the low prices that insurance companies have negotiated with pharmacists and hospitals, leading to a low amount of storage in individual pharmacies. Insurance companies have identified one drug for an indication as the so called preference drug for that disease with serious consequences for the prescription of alternative drugs that will not be reimbursed by health insurance companies. Although the restriction in healthcare costs is appreciated and calculated to be more than one billion euro's the consequences for the individual patient are significant. In daily life 50% of all patients will not receive the prescribed drug directly from the pharmacist because it is not available. For this reason the ministry for Health (Minister B. Bruins) has now indicated that drugs storage is obligatory in the Netherlands for at least a period of 4 months. Which should result in a decrease of shortages with over 60%. This plan has not been approved so far by the European Union while the effect of Brexit in either way is hard to imagine. Another complicated point is the new European rules under the name of falsified medicine directive (FMD) that should prevent fraud of individual drugs because of every package of drugs one should be able to control the source and delivery with significant consequences for the way drugs are packed.



Limitations

There are some notable limitations to the dataset that we used for the majority of the studies presented in this thesis. The UUDIS data examined reported shortages, but the impact of shortages may vary depending on the geographic area or individual institution or practice. We did not examine the severity of shortages, such as whether a product was completely out of stock or just in short supply, only whether a shortage was present. Finally, we did not examine the impact on patient care or increased cost or resource utilization.

Future Directions

There is a great deal of room for additional studies pertaining to drug shortages. Future prospective studies should examine the impact of specific legislative interventions. In particularly, we should evaluate the total number of shortages, number of new shortages, duration of ongoing shortages, types of medications impacted, severity of shortages, and reasons the shortage occurred. It is important to determine which legislative interventions are effective and, as mentioned previously, what unintended consequences occur as a result. At the same time, it may be difficult to study the impact of individual interventions, as they will rarely occur in isolation. We must continue to refine and optimize interventions moving forward, as the proposed solutions are not without cost and resource expenditure.

In addition, it is critical that we evaluate the human costs of shortages. We should prospectively study the direct impact of shortages on patient care, in the form of delayed or suboptimal therapy. It would be useful for governmental agencies to provide research funding for institutions to actively study the impact of shortages rather to rely on passive reporting. In addition, we should have a mechanism in place for reporting adverse drug events or medication errors that occur as a result of shortages, similar to the MedWatch reporting system. In addition, we need pharmacoeconomic studies to determine the economic impact of shortages and to guide strategies to limit increased healthcare costs.

Conclusions

Prescription drug shortages are a major public health problem. This thesis contributes to the current body of knowledge pertaining to drug shortages in that it demonstrates the impact across multiple medical specialties and age groups. Shortages have the potential to impact countless lives by limiting access to care and causing harm. We have yet to determine the full human and economic burden of drug shortages. We must be vigilant in safeguarding access to medications for patients in need. While we have made some strides in mitigating the impact of shortages, additional interventions and studies are needed to determine the optimal strategies for mitigating and preventing shortages and to safeguard patient care.

Summary

Introduction

Chapter 1 provides a description of the history of prescription drug shortages from the late 1990s to the present day landscape. This chapter also introduces the clinical and public health implications of drug shortages, as well as mitigation shortages that have been implemented to date. Finally, this chapter outlines the methods and goals of the research conducted within the context of this thesis.

Adult Emergency Medicine/Acute Care

Chapter 2 discusses the clinical and public health implications of shortages as they apply to the practice of emergency medicine. Situations that may occur as a result of shortages, such as delayed or suboptimal therapy and medication errors are reviewed. Specific considerations to the specialty of emergency medicine are discussed and examples of how patient care is impacted are provided. For instance, we reviewed a case where a patient was given a fatal dose of methohexital when propofol was in short supply. We also explore how the healthcare system is impacted on a larger scale, such as increased cost and resource utilization, and increased pharmacy staff required to manage inventory during times of shortage. We discuss mitigation strategies to date at the governmental and non-governmental levels. We address challenges facing emergency medicine providers and offer strategies for bedside clinicians. Finally, future directions for mitigation and prevention are discussed. It should be noted that many of the situations and strategies presented are applicable to other specialties as well.

Chapter 3 is a retrospective study of the impact of shortages on drugs within the scope of adult emergency medicine from 2001-14. During the course of the study period, over a third of drugs impacted by shortages were within the scope of emergency medicine practice and there was an overall increase in shortages over time. Over 50% of the drugs on shortage were used for high-acuity or life-threatening conditions and 10% of these high-acuity drugs had no substitute available. Generic injectable drugs were most commonly affected by shortages and infectious disease drugs were the most common type of drug impacted, followed by analgesics and toxicology drugs. The median duration of resolved shortages was 9 months and the most common reason for shortage reported was manufacturing problems and delays. We discuss potential reasons for these findings and offer coping strategies for front line providers.

Chapter 4 is a study of drug shortages affecting medications used in adult intensive care units (ICUs) from 2001-2016. During the study period, there were nearly 2000 drug shortages and over 50% impacted medications used in the ICU. Nearly a quarter of medications on shortage were used for high-acuity or life-threatening conditions. Over 70% of shortages were for parenteral medications and nearly 40% were for single-source drugs. Generic drugs were also more commonly affected compared to their brand name counterparts. Therapeutic alternatives were available for the majority of the medications affected but nearly 25% of alternatives were also impacted during the study period. The median duration of resolved shortages was even longer than described for adult emergency medicine being13.6 months! The most commonly impacted medications, similar to prior studies were infectious disease drugs, which accounted for nearly 20% of

ICU shortages. We discuss specific implications for the ICU, which is a particularly high-acuity environment and close by offering mitigation strategies for intensivists.

Chapter 5 is a study of shortages for drugs used to treat poisoned patients from 2001-2013. We reviewed shortages of antidotes as well as medications used commonly in the management of poisoned patients. Toxicology shortages accounted for 8.1% of all shortages and shortages generally increased overtime, peaking in 2011. The median shortage duration was 5.5 months. Generic and injectable products were most commonly impacted and 41% of shortages involved single-source drugs. An alternative was available for 86% of drugs; however, 73% of alternatives were impacted at some point during the study period. The agent with the greatest number of shortages was naloxone. The most common class of toxicology drugs on shortage was sedative/hypnotics. Manufacturing problems was the most common reason for shortages. In the discussion, we draw attention to challenges faced by toxicologists and providers caring for poisoned patients, particularly with multiple naloxone shortages during the current opioid epidemic.

Chapter 6 examines shortages of sterile medical solutions, including normal saline, dextrose, lactated ringers, and sterile water for injection over time. We found a substantial number of sterile solution shortages. The median shortage duration was 13.9 months but the longest shortage lasted over 10 years. The most common product type involved was saline solutions. The most commonly cited reason for shortages was manufacturing problems. While there here was an overall increase in the number of sterile solutions over time, there was a significant increase at the end of 2017, which correlated with Hurricane Maria, which precipitated a critical saline shortage. We discuss the potential clinical impact of these shortages and coping strategies for providers and health systems.

Chapter 7 is a perspective piece from the New England Journal of Medicine that further examines the critical saline shortages precipitated by Hurricane Maria. We review the history of saline shortages and explore factors that contributed to the previously existing shortages, such as lack of manufacturing redundancy and transparency. These shortages were acutely worsened by the natural disaster. We review implications for patient care and discuss coping strategies for health systems and providers as well. Finally, we offer policy strategies to prevent future shortages.

Pediatric Drug Shortages

Chapter 8 is a study of drug shortages that impact the practice of general ambulatory pediatrics from 2001 to 2015. There were over 300 ambulatory pediatric shortages over the study period, with a median duration of 7.6 months. Similar to prior studies, infectious disease drugs were the most commonly impacted class of medications. Nearly 20% of shortages were for pediatric friendly formulations. An alternative agent was available for the majority of medications impacted; however, nearly 30% of alternatives were affected by shortages. In the discussion, we explore issues unique to pediatric shortages, such as a lack of safety and efficacy data for drugs in this population as well as a need for palatable formulations. We close by offering mitigation strategies for general pediatricians and suggesting policy solutions, in order to protect this particularly vulnerable population.

Chapter 9 examines shortages involving pediatric emergency medicine and critical care (ICU) drugs. During the study period from 2001 to 2015, there were nearly 800 shortages impacting pediatric emergency and critical care. There was an overall increase in shortages over time, peaking in 2011. The median shortage duration was 7.6 months and similar to prior trends, infectious disease drugs and sterile injectable products were the most commonly impacted. Over a quarter of shortages impacted drugs used for high-acuity or life-threatening conditions. While most drugs affected by shortages had an alternative, 43% of alternatives were impacted. Pediatric friendly formulations were impacted in 11% of shortages. In the discussion, we explore the safety issues unique to pediatric emergency and critical care, which is a particularly high-acuity environment and ways to mitigate the impact.

Chapter 10 examines shortages that affected the top 100 drugs used in the neonatal intensive care unit (NICU). Nearly 75% of the 100 most commonly used NICU drugs were impacted by multiple shortages. The median shortage duration was 8.8 months. Generic injectable medications were the most commonly impacted. A significant number of medications used in extremely low birth weight infants also experienced shortages. We discuss the potential consequences of these shortages in this particularly fragile population in the setting of critical illness. This is further confounded by the fact that medications have the least safety and efficacy data in neonates and some excipients are contraindicated in this age group, leaving few alternatives. In addition, dosing must be very precise, and as such, adult formulations may not be a suitable alternative and dilution and compounding may lead to medication errors.

Infectious Diseases

Chapter 11 focuses on shortages of the most commonly impacted drug class-antimicrobials. From 2001-2013, we found 148 antimicrobial shortages, with a median duration of 6 months. Over 20% of antimicrobials were impacted by multiple shortages. Shortages for broad-spectrum antibiotics were more common and nearly half of shortages involved medications used to treat high-risk pathogens such as methicillin-resistant *Staphylococcus aureus*. Cephalosporins and aminoglycosides were the most commonly impacted antimicrobial classes. We discuss mitigation strategies in the setting of increasing microbial resistance and a limited number of therapeutic options in the drug development pipeline.

Chapter 12 examines shortages for vaccines and immune globulins (agents used for passive immunity). There were 58 shortages noted, with a median duration of 16.8 months. Shortages for products that were for viral illnesses, such as hepatitis A, were more common. Thirty products on the pediatric schedule were on shortage and vaccine deferral was required for 21 shortages. Over half of the shortages were for single-source products. The most common reason for shortage was manufacturing problems. In the discussion, we focus on the public health implications in the setting of vaccine deferrals for primary immunizations, as this may impact herd immunity, as well as coping strategies for clinicians.

Samenvatting

Inleiding

Hoofdstuk 1 beschrijft de geschiedenis van de tekorten aan geneesmiddelen op recept van het eind van de jaren 90 tot op heden. Dit hoofdstuk presenteert ook en de gevolgen van geneesmiddelentekorten voor de klinische praktijk en voor de volksgezondheid, alsook de compenserende maatregelen die tot nu toe zijn genomen. Tot slot worden in dit hoofdstuk in het kort de methoden en doelstellingen van de studies die zijn uitgevoerd in het kader van dit proefschrift beschreven.

Spoedeisende geneeskunde voor volwassenen

Hoofdstuk 2 gaat in op gevolgen van geneesmiddelentekorten voor de spoedeisende geneeskunde. Situaties die kunnen ontstaan als gevolg van tekorten, zoals vertraagde of suboptimale therapie en medicatiefouten worden belicht. Specifieke overwegingen met betrekking tot het specialisme van de spoedeisende geneeskunde worden besproken en met voorbeelden wordt duidelijk gemaakt wat de impact is op de patiëntenzorg. Zo hebben we bijvoorbeeld een geval bekeken waarin een patiënt een fatale dosis methohexital kreeg toegediend bij een tekort aan propofol. We onderzoeken ook hoe het gezondheidszorgsysteem op grotere schaal wordt beïnvloed, zoals meer kosten en meer gebruik van middelen, en de noodzaak van meer apotheekpersoneel voor het voorraadbeheer in tijden van schaarste. We bespreken de huidige compenserende maatregelen door de overheid en niet-gouvernementele organisaties. We gaan in op de uitdagingen waarmee aanbieders van noodgeneesmiddelen worden geconfronteerd en bieden strategieën voor clinici aan het bed. Ten slotte worden mogelijkheden voor mitigatie en preventie besproken. Opgemerkt moet worden dat veel van de gepresenteerde situaties en strategieën ook van toepassing zijn op andere specialismen.

Hoofdstuk 3 is een retrospectieve studie naar de impact van tekorten op geneesmiddelen in het kader van de volwassen spoedeisende geneeskunde in de periode 2001-2014. In de loop van de onderzoeksperiode viel meer dan een derde van de door tekorten getroffen geneesmiddelen binnen de spoedeisende geneeskunde en was er in de loop van de tijd een algemene toename van de tekorten. Meer dan 50% van de geneesmiddelen waarvan een tekort was betrof zeer acute of levensreddende omstandigheden en voor 10% van de geneesmiddelen voor zeer acute omstandigheden was geen vervangend middel beschikbaar. Generieke injecteerbare geneesmiddelen waren het meest getroffen door tekorten en middelen tegen infectieziekten waren het meest getroffen, gevolgd door pijnstillers en antidota. De tekorten waren na een mediane duur van 9 maanden ongedaan gemaakt en de meest gemelde redenen voor het tekort waren productieproblemen en vertragingen. We bespreken de mogelijke redenen voor deze bevindingen en bieden copingstrategieën voor de eerstelijnszorg.

Hoofdstuk 4 betreft een onderzoek naar tekorten aan geneesmiddelen in intensive care units (ICU's) voor volwassenen in de periode 2001-2016. Tijdens de onderzoeksperiode waren er bijna 2000 geneesmiddelentekorten en dit betrof meer dan 50% van de geneesmiddelen die in de ICU’s werden gebruikt. Bijna een kwart van de geneesmiddelen waarvan een tekort was diende voor zeer acute of levensbedreigende aandoeningen. Meer dan 70% van de tekorten betrof parenterale geneesmiddelen en bijna 40% betrof geneesmiddelen waarvoor geen generiek alternatief was.

Generieke geneesmiddelen werden ook vaker getroffen dan de corresponderende merkproducten. Voor het merendeel van de getroffen geneesmiddelen waren therapeutische alternatieven beschikbaar, maar bijna 25% van de alternatieven werd ook beïnvloed tijdens de onderzoeksperiode. De mediane tijdsperiode waarna de tekorten waren opgelost was zelfs langer dan beschreven voor de volwassenen spoedeisende geneeskunde van 13,6 maanden! De meest getroffen medicijnen, vergelijkbaar met eerdere studies, waren geneesmiddelen voor infectieziekten, die goed waren voor bijna 20% van de tekorten op de ICU. Wij bespreken specifieke implicaties voor de ICU, die een bijzonder hoog spoedeisend karakter heeft, en presenteren ten slotte mitigatiestrategieën voor intensivisten.

Hoofdstuk 5 is een onderzoek naar tekorten aan geneesmiddelen voor de behandeling van vergiftigde patiënten in de periode 2001-2013. We onderzochten tekorten aan antidota en andere medicijnen die vaak worden gegeven aan vergiftigde patiënten. Tekorten aan antidota waren goed voor 8,1% van alle tekorten en de tekorten namen over het algemeen toe in de loop van de tijd en bereikten in 2011 een hoogtepunt. De mediane duur van de tekorten was 5,5 maanden. Generieke en injecteerbare producten waren het vaakst getroffen en 41% van de tekorten had betrekking op geneesmiddelen waarvoor geen generiek alternatief was. Een alternatief was beschikbaar voor 86% van de geneesmiddelen; aan 73% van de alternatieven was er echter op een bepaald moment tijdens de studieperiode een tekort. Het middel met het grootste aantal tekorten was naloxon. Sedativa/hypnotica vormden de meest voorkomende klasse van toxicologische geneesmiddelen waaraan een tekort was. Productieproblemen vormden de meest voorkomende oorzaak van tekorten. In de discussie vestigen we de aandacht op de uitdagingen waarmee toxicologen en zorgverleners van vergiftigde patiënten zich zien gesteld, vooral de meerdere perioden van tekorten aan naxalon tijdens de huidige opioïden-epidemie.

Hoofdstuk 6 onderzoekt de tekorten in de loop ter tijd aan steriele medische oplossingen, waaronder normale zoutoplossing, dextrose, Ringerlactaat en steriel water voor injectie. We vonden een aanzienlijk aantal tekorten aan deze middelen. De gemiddelde duur van het tekort was 13,9 maanden, maar het langste tekort duurde meer dan 10 jaar. De meest voorkomende productsoort betrof zoutoplossingen. De meest aangehaalde reden voor het tekort was productieproblemen. Terwijl er hier sprake was van een algemene stijging van het aantal tekorten aan steriele oplossingen in de loop der tijd was er eind 2017 sprake van een aanzienlijke toename, gecorreleerd met de orkaan Maria, die een kritiek tekort aan zout heeft veroorzaakt. We bespreken de mogelijke klinische gevolgen van deze tekorten en copingstrategieën voor zorgverleners en gezondheidzorgstelsels.

Hoofdstuk 7 is een ‘perspective piece’ uit het New England Journal of Medicine dat verder ingaat op de kritieke zout tekorten die door de orkaan Maria zijn ontstaan. We bekijken de geschiedenis van tekorten aan zoutoplossingen en verkennen factoren die hebben bijgedragen aan de eerder bestaande tekorten, zoals een gebrek aan redundantie en transparantie in de productie. Deze tekorten werden door de natuurramp acuut verergerd. We bekijken de gevolgen voor de patiëntenzorg en bespreken ook copingstrategieën voor zorgverleners gezondheidszorgstelsels en -aanbieders. Tot slot presenteren we beleidsstrategieën om toekomstige tekorten te voorkomen.

Tekorten aan geneesmiddelen voor kinderen

Hoofdstuk 8 betreft een onderzoek naar medicijntekorten die van invloed zijn op de praktijk van de algemene pediatrische ambulante gezondheidszorg van 2001 tot 2015. Er waren meer dan 300 van deze tekorten over de studieperiode, met een mediane duur van 7,6 maanden. , Geneesmiddelen tegen infectieziekten waren de meest getroffen klasse van geneesmiddelen, evenals in voorgaande studies. Bijna 20% van de tekorten betroffen pediatrische formuleringen. Een alternatief middel was beschikbaar voor de meeste van de betrokken geneesmiddelen, maar er ontstond ook een tekort aan bijna 30% van de alternatieven. In de discussie gaan we in op kwesties die uniek zijn voor pediatrische tekorten, zoals een gebrek aan gegevens over de veiligheid en werkzaamheid van geneesmiddelen in deze populatie, en behoefte aan smakelijke formuleringen. Ten slotte presenteren we mitigatiestrategieën voor algemene kinderartsen en stellen beleidsmaatregelen voor ter bescherming van deze kwetsbare groep patiënten.

Hoofdstuk 9 gaat in op tekorten aan geneesmiddelen die worden gebruikt in de pediatrische spoedeisende hulp en kritieke zorg. In de bestudeerde periode van 2001 tot 2015 waren er bijna 800 tekorten aan deze middelen. In de loop van de tijd namen de tekorten in het algemeen toe, met een piek in 2011. De gemiddelde duur van de tekorten bedroeg 7,6 maanden en – vergelijkbaar met eerdere trends – geneesmiddelen tegen infectieziekten en steriele injecteerbare producten waren het meest getroffen. Meer dan een kwart van de tekorten betrof geneesmiddelen die gebruikt worden bij zeer acute of levensbedreigende omstandigheden. Terwijl er voor de meeste middelen waaraan een tekort ontstond een alternatief was, was ook 43% van de alternatieven onderhevig aan tekorten. Kindervriendelijke formuleringen vormden 11% van de tekorten. In de discussie gaan we in op de veiligheidsaspecten die uniek zijn voor de pediatrische spoedeisende hulp en kritieke zorg, en mogelijkheden om de gevolgen te verzachten.

Hoofdstuk 10 onderzoek tekorten aan de top-100 geneesmiddelen die worden gebruikt in de neonatale intensive care unit (NICU). Bijna 75% van de 100 meest gebruikte NICU-geneesmiddelen werden getroffen door meerdere tekorten. De gemiddelde duur van het tekort bedroeg 8,8 maanden. Generieke injecteerbare medicijnen werden het meest getroffen. Een aanzienlijk aantal medicijnen die worden gebruikt bij baby's met een extreem laag geboortegewicht hadden ook te kampen met tekorten. We bespreken de mogelijke gevolgen van deze tekorten in deze bijzonder fragiele populatie in de context van kritieke ziekten. Dit wordt nog verder vertroebeld door het feit dat er voor geneesmiddelen bij pasgeborenen de minste gegevens over veiligheid en werkzaamheid beschikbaar zijn en dat sommige hulpstoffen in deze leeftijdsgroep gecontra-indiceerd zijn, waardoor er weinig alternatieven overblijven. Bovendien moet de dosering zeer nauwkeurig zijn, en als zodanig kunnen formuleringen voor volwassenen geen geschikt alternatief vormen en kunnen verdunningen en samenstellingen tot medicatiefouten leiden.

Infectieziekten

Hoofdstuk 11 richt zich op de tekorten aan de meest getroffen medicijnklasse – antimicrobiële middelen. Over de periode 2001-2013 vonden we 148 tekorten aan deze middelen, met een mediane duur van 6 maanden. Meer dan 20% van de antimicrobiële stoffen had te kampen met meerdere tekorten. Tekorten aan breedspectrumantibiotica kwamen vaker voor en bij bijna de helft van de tekorten ging het om middelen voor de behandeling van pathogenen met een hoog risico, zoals meticilline-resistente Staphylococcus aureus. Cephalosporinen en aminoglycosiden waren de antimicrobiële klassen die het meest waren getroffen. We bespreken mitigatiestrategieën in de context van de verhoogde microbiële resistentie en een beperkt aantal therapeutische opties in de pijplijn.

Hoofdstuk 12 gaat in op tekorten aan vaccins en immuunglobulinen (middelen die worden gebruikt voor passieve immuniteit). Er werden 58 tekorten vastgesteld, met een mediane duur van 16.8 maanden. Dit betrof het meest middelen tegen virale ziekten, zoals hepatitis A. Er waren tekorten aan 30 producten op het pediatrische programma en vaccinatie-uitstel was nodig voor 21 tekorten. Meer dan de helft van de tekorten betrof middelen waarvoor geen generiek alternatief was. Productieproblemen vormden de meest voorkomende oorzaak van het tekort. In de discussie concentreren wij ons op de implicaties voor de volksgezondheid van het vaccinatieuitstel voor primaire immunisaties, omdat dit invloed kan hebben op de collectieve immuniteit, en richten ons ook op de copingstrategieën voor clinici.

Curriculum Vitae

Maryann Elizabeth Amirshahi was born on October 20, 1975 in Toms River, NJ. She graduated with honors from Jackson Memorial High School in Jackson, NJ in 1994. Her work experience as a pharmacy technician inspired her to pursue a career in pharmacy. She completed her Bachelor of Science degree in pharmacy at the University of the Sciences in Philadelphia in 2000, followed by a Doctor of Pharmacy degree in 2001 (cum laude). During her time in pharmacy school, she worked full-time as a pharmacy intern for CVS/Pharmacy, but ultimately decided to pursue a career in medicine. From 2001-2002, she continued to work for CVS while studying for the MCAT. In 2002, she enrolled at Temple University School of Medicine in Philadelphia, PA. During medical school, she continued to work as a pharmacist in the retail and inpatient settings. Upon graduating medical school with honors in 2006, Maryann matched in a four-year emergency medicine residency at the Hospital of the University of Pennsylvania.

During internship and residency, Maryann not only continued to work part-time as a pharmacist, but began pursing research focusing on medical toxicology and medication safety, which led to several publications. She finished her residency in 2010 and moved to Washington DC to start fellowship. She completed her medical toxicology fellowship from 2010 to 2012 at the George Washington University and National Capital Poison Center. During fellowship, she also worked as a Specialist in Poison Information at the National Capital Poison Center and as an attending physician in emergency medicine at the George Washington University Hospital, Prince George's Hospital Center and Children's National Medical Center. In addition, she enrolled in the Master of Public Health program at the George Washington University, with a concentration in environmental and occupational health. Upon completion of her medical toxicology fellowship in 2012, she began a clinical pharmacology fellowship at Children's National Medical Center under the mentorship of Dr. John van den Anker. During this time, she focused on research pertaining to pharmacology, toxicology, and medication safety. In addition, she became interested in studying the prescription opioid epidemic as well as prescription drug shortages. She continued to work as an emergency medicine attending. In 2013, she completed her MPH degree from the George Washington University.

Upon completion of her fellowship in 2014, Maryann took a position as an emergency medicine attending at MedStar Washington Hospital Center, which is affiliated with the Georgetown University School of Medicine. In her current role, she works clinically at MedStar Washington Hospital Center and Children's National Medical Center. As a pharmacist, she is currently a Board Certified Pharmacotherapy Specialist. As a physician, she is board certified in emergency medicine, medical toxicology, addiction medicine, and clinical pharmacology. She is an Assoicate Professor of Emergency Medicine at the Georgetown University School of Medicine

and an Adjunct Assistant Clinical Professor of Pediatrics at the George Washington University. She serves as a toxicology consultant for the Mid-Atlantic Center for Children's Health and the Environment and the National Capital Poison Center. She is an active member of the American College of Medical Toxicology, as chair of the Research Committee and a member of the Positions and Guidelines Committee. She is also a member of the Board of Directors for the American Board of Clinical Pharmacology. Maryann periodically serves on U.S. Food and Drug Administration Advisory Panels. She teaches medical toxicology to pharmacy and medical students, residents, fellows, and paramedics. She also serves a research mentor and faculty member for the Georgetown/MedStar Washington Hospital Center emergency medicine residency program. Finally, she continues to focus on her own research interests, particularly prescription drug shortages. She has continued to work with Dr. John van den Anker as her primary mentor for her PhD thesis at Erasmus University. Maryann currently resides in Bethesda, Maryland with her two children.

ECTS for PhD of Maryann Amirshahi

Courses	Date	Location	ECTS
DATA 2000 for Buprenorphine Prescribing	2015	Online course	1
Principles and Practice of Practice of Clinical Research, NIH	2012-2013	Bethesda, MD, USA	2
Principles of Pediatric Clinical Pharmacology, NIH	2012-2013	Bethesda, MD, USA	2
Principles of Clinical Pharmacology, NIH	2010-2011	Bethesda, MD, USA	2

Conference Presentations	Date	Location	ECTS
Society of Academic Emergency Medicine Annual Meeting-20 abstracts	2010-2018	Various	10
American College of Medical Toxicology Annual Scientific Meeting-16 abstracts	2012-2018	Various	8
American College of Emergency Physicians Research Forum-2 abstracts	2016	Various	1
North American Academy of Clinical Toxicology Annual Meeting-4 abstracts	2015-2018	Various	2
Pediatric Academic Society Annual Meeting-2 abstracts	2013-2014	Various	1
American Society for Clinical Pharmacology and Therapeutics-7 abstracts	2012-2018	Various	3.5
American College of Clinical Pharmacology Annual Meeting-1 abstract	2013	Bethesda, MD, USA	0.5
European Society for Developmental Perinatal and Paediatric Pharmacology -1 abstract	2013	Salzburg, AU	0.5
European Association of Poison Centres and Clinical Toxicologists Annual -2 abstracts	2012	London, UK	1
ACMT Lecture: Opioid Epidemic: Best Prescribing Practices and the Role of Toxicologists	2017	Washington, DC	0.5
SAEM Lecture: Ten Commandments of NSAID Use in the ED	2017	Orlando, FL	0.5
National Academy of the Sciences: Medical Product Shortages During Disasters	2018	Washington, DC	0.5
Massachusetts ACEP: Advanced Pain Management in the Emergency Department, 3 lectures	2018	Waltham, MD	1.5
Coverys Webinar: Coping with Medications Shortages: Strategies for Healthcare Providers	2018	Webinar	0.5

Teaching	Date	Location	ECTS
Semi-annual toxicology lectures, Georgetown EM Residency	2014-2018	Washington, DC	4
Monthly toxicology teaching rounds, National Capital Poison Center	2012-2018	Washington, DC	6
Preceptor, Georgetown University School of Medicine Ambulatory Care Course	2014-2018	Washington, DC	1
Preceptor, Georgetown University School of Medicine Independent Scholarly Project	2014-2018	Washington, DC	1
Preceptor, Georgetown-MedStar MedStar Summer Research Program	2014-2018	Washington, DC	1
Faculty, Emergency Medicine Clerkship Georgetown University School of Medicine	2014-2018	Washington, DC	4
Faculty, Emergency Medicine Residency Georgetown University School of Medicine	2014-2018	Washington, DC	4
Instructor for Practice of Medicine IV Course, Medication Safety and Medical Toxicology Electives, George Washington University School of Medicine	2012-2015	Washington, DC	2
Preceptor, Clinical Apprenticeship Program, George Washington School of Medicine	2012-2014	Washington, DC	2

Total ECTS: 63

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To my husband Babak. I thank you for your endless love and for every time you said "no baby, that isn't crazy-I support you" whenever I decided on another academic pursuit. I am so blessed to share this crazy life with you. Fadat sham azizam.