

# 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](http://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

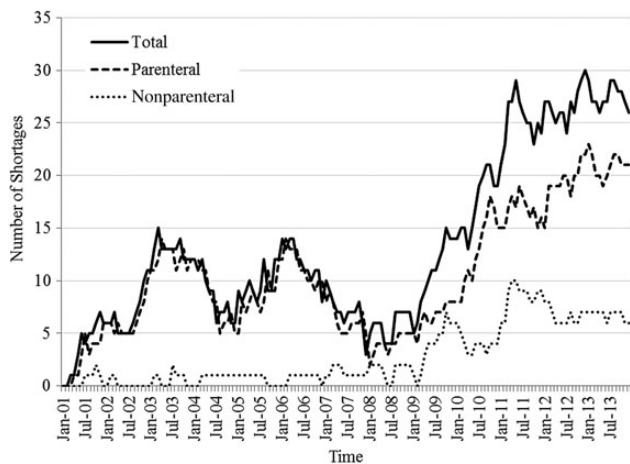
Data were described using standard descriptive statistics. Univariate analysis found that drug shortage time (measured in days) was not normally distributed (right skewed). Therefore, we used the nonparametric 2-sample Wilcoxon rank-sum (Mann-Whitney) test to compare shortage times and describe average 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/ $\beta$ -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	<b>1858</b>
Kanamycin injection	3	1682
Cefotaxime injection	3	<b>1542</b>
Doxycycline injection	3	1515
Erythromycin lactobionate	2	1245
Gentamicin injection, pediatric strength	2	1173
Meropenem	7	<b>1114</b>
Ampicillin-sulbactam	3	<b>1052</b>
Minocycline injection	2	944
Piperacillin sodium	2	942
Cefepime injection	3	801
Nafcillin	4	763
Azithromycin injection	4	<b>599</b>
Gentamicin injection	2	<b>574</b>
Cephalexin suspension	2	<b>535</b>
Imipenem-cilastatin	2	502
Ciprofloxacin 500 mg tablets	3	<b>442</b>
Ceftizoxime	2	405
Clindamycin injection	2	<b>394</b>
Vancomycin	3	<b>373</b>
Cefpodoxime	2	<b>344</b>
Colistimethate	2	255
Paromomycin (Humatin)	3	192
Cefuroxime injection	2	<b>185</b>
Sulfamethoxazole-trimethoprim injection	3	<b>165</b>
Methenamine	2	133
Dalfopristin/quinupristin (Synercid)	2	125
Ticarcillin-clavulanate	3	<b>123</b>
Ceftazidime	2	<b>69</b>
Spectinomycin	2	0

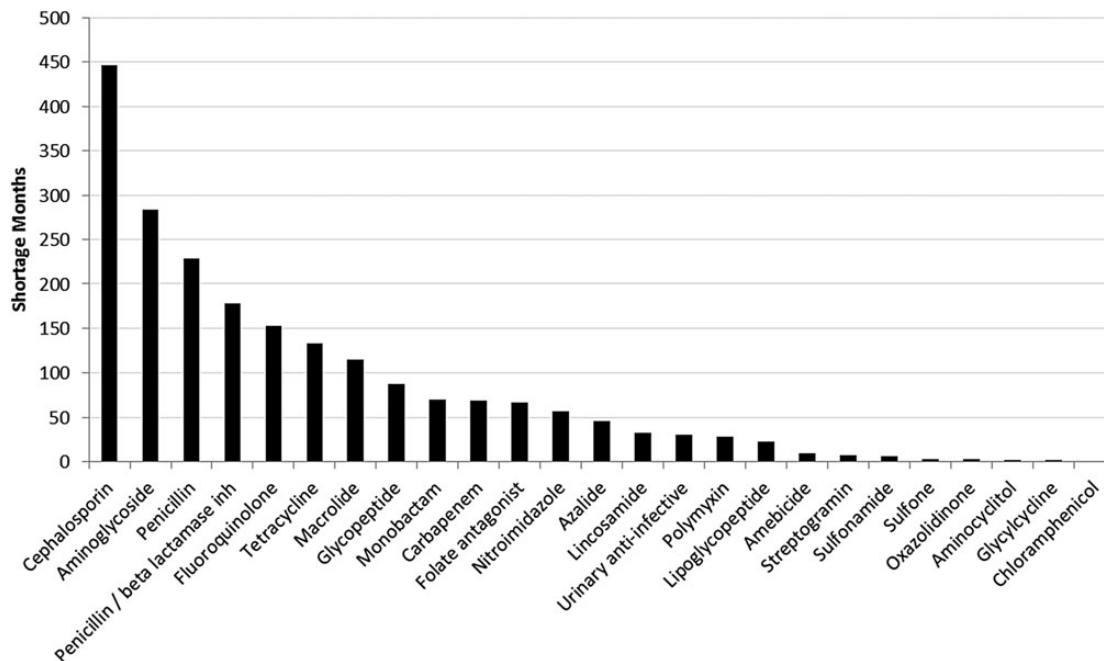
Includes both active and resolved shortages. Values in boldface indicate that the drug is currently experiencing a shortage.

Source: University of Utah Drug Information Service database.

Seven of the drugs treat extended-spectrum  $\beta$ -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,

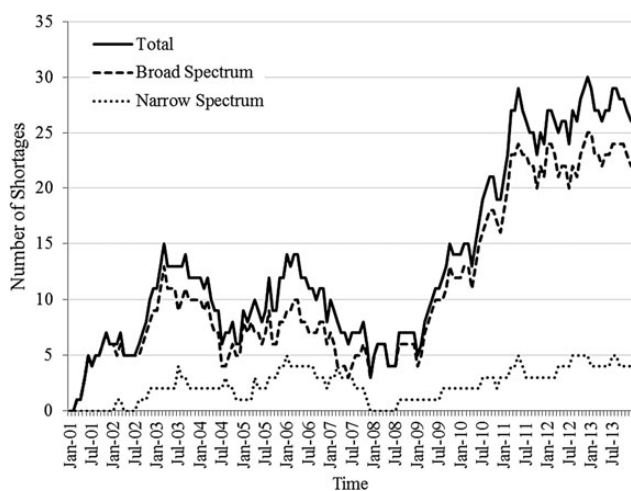


**Figure 2.** Drug shortages by drug class, 2001–2013.

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.

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



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

**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
<b>Total</b>	<b>148</b>

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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