Project Report

# Impact of Drug Shortages on Consumer Costs

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# About This Research Report

Prescription drug shortages are an ongoing concern in the United States. While prior analyses explore the frequency of drug shortages in the United States, little is known about the extent to which U.S. shortages are associated with changes in costs to consumers specifically. In this report, we identify and describe potential costs to patients from drug shortages, empirically measure the impacts of shortages on available indicators of changes in costs to patients, and examine how shortage effects on patient costs vary by drug and patient characteristics. This research was conducted in 2021 and was funded by the U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation under Contract Number HHSP233201500038I and carried out within the Payment, Cost, and Coverage Program in RAND Health Care.

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# Summary

Drug shortages occur when the demand from patients and prescribers is not met by supply for a particular drug. Drug shortages can have a range of root causes, including disruptions in supply chains, quality concerns, manufacturer decisions to cease production for financial reasons, and sudden increases in demand. The effects of drug shortages on consumers are complex, and while there are several studies documenting the effects of insurer payment for drugs, their effects on consumer costs are largely unknown. The goal of this study is to describe consumer costs associated with drug shortages.

## Background and Framework

The U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation (ASPE) asked RAND to address the following research questions related to associations between drug shortages and consumer costs:

(1) how many Americans face drug shortages?
(2) what types of costs do consumers incur related to drug shortages?
(3) how have trends in these costs varied over time?
(4) are there differences in shortage costs for generic versus brand shortage drugs, between dispensing locations, or across consumers with different characteristics?
(5) what policy options can address drug shortages?

To answer these questions, we first conducted a literature review to assess the evidence base and to inform the development of a conceptual framework. Prior studies have found that drug *list prices* increase by 20 percent (Hernandez et al., 2019) and *payments by insurers* increase between 4.3 to 14.2 percent on average through drug shortages (Alevizakos et al., 2016; Dave et al., 2018). Our own prior study for ASPE found slight increases in *manufacturer prices* through shortages, although the direction and magnitude of prices changes were highly variable (Mulcahy et al., 2021). Surprisingly, we found very little prior research on associations between shortages and *out-of-pocket costs* which are most immediately relevant to consumers. Other studies assess the impact of poor prescription drug adherence and other sub-optimal use of drugs, although these studies rarely focused on effects due to shortages per se.

Based on findings from our review, we developed a framework to organize conceptual links between shortages and consumer costs. We identified several broad categories of consumer costs that could increase or decrease through drug shortages, including direct costs (i.e., out-of-pocket costs associated with purchasing shortage and substitute drugs, if available), indirect costs (time and other costs involved in acquiring drugs and other treatment), and costs associated

with changes in health outcomes and related care due to shortages (i.e., delays in treatment, receiving a suboptimal substitute, or not receiving treatment at all).

We also outlined reasons why changes in list prices or insurer payments are unlikely to increase consumer costs directly and in the short-term. Many patients with drug coverage pay fixed co-pays for pharmacy-dispensed and mail-order prescription fills. These copays often only change at the start of a new plan year (typically January 1). Medicare and other payers' approaches to pay for certain types of drugs (e.g., physician-administered drugs covered by Medicare Part B) and broader services like inpatient hospital stays that cover related drugs use lagged data on acquisition costs to set payment rates. As a result, even if hospitals, physician practices, and other providers face higher acquisition costs for shortage drugs, patients would not immediately see higher out-of-pocket costs.

We identified several consumer groups where shortages are more likely to directly affect costs, including those without drug and/or medical coverage, those with relatively less generous coverage (e.g., commercial plans with high deductibles), and those responsible for a fixed share of prices charged by pharmacies (e.g., through coinsurance). In addition, shortage drugs that have few close substitutes and that are used to treat serious conditions will likely have more direct and more severe implications on patient health, with likely implications for downstream spending on medical care, declines in health, and potentially on patient mortality. Ultimately, higher insurer and payer expenses could result in higher premiums. Ideally, researchers would use pharmacy and medical claims data and premium data to empirically assess the longer-term implications of drug shortages on consumer costs. While we did not use claims data to directly measure changes in out-of-pocket costs or downstream health care spending associated with shortages in this study, we think this is a promising area for future research.

## Empirical Data and Methods

We used an extract from the FDA drug shortage database listing ongoing or recently resolved drug shortages as of March 2020. We linked these shortage drugs to 2016-2020 IQVIA's National Sales Perspective (NSP) data containing estimates of drug-specific monthly volume and payments to manufacturers. We also linked shortage drugs to IQVIA's Total Patient Tracker (TPT) data which includes estimated counts of unique patients with fills for specific pharmacy-dispensed drugs (30 of 117 shortage drugs were primarily pharmacy-dispensed). Separately, we identified a set of 26 shortage drugs for in-depth analysis, including identification of substitutes. We rely on the case studies to illustrate potential, but not necessary average or typical, changes in volume, prices, and other outcomes through drug shortages.

We calculated changes in volume, prices, and unique patient counts over several intervals anchored on the shortage start date month, which we defined as the date a shortage was first reported to FDA. For our main results, we compared changes in volume, prices, and patient

counts around the start month of the shortage, and more specifically over 12 months in either direction with a washout period excluding the shortage start month.

## Results

Our results suggest shortage drugs typically experience declines in volume, modest increases in manufacturer price, and reductions in the number of patients treated (Table S.1). These general findings do not apply to every shortage: volume increased and prices decreased through some shortages. Across all study drugs, annual spending *decreased* by $1.2 billion (from $4.1 billion) when measured around the shortage start month because decreases in volume were proportionally larger than increases in prices.

**Table S.1: Changes in Volume, Price, and Unique Patient Measures Around Shortage Start Month**

| | Pre-shortage median | Pre-shortage mean | Median change (%) | Mean change (%) | 95% C.I. (%) |
|---|---|---|---|---|---|
| **Volume (mil. SUs)** | 8.8 | 124.2 | -35.4 | -27.8 | (-37.7, -17.8) |
| **Manuf. price per SU** | $1.5 | $53.4 | 7.2 | 16.6 | (9.7, 23.4) |
| **Unique patients/mo.** | 214,000 | 652,100 | -6.7 | -10.8 | (-25.4, 3.8) |

Source: Authors' analysis of IQVIA NSP and TPT data for study FDA shortages. Note: Analysis reflects 117 shortage drugs for volume and price results and 30 primarily retail pharmacy-dispensed shortage drugs for mean unique patient results. Only specific NDCs in shortage contribute to volume and price results. Patient counts are likely biased upward due to patients filling multiple prescriptions across shortage drugs. "Manuf." is manufacturer. "SU" is standard units.

While we were not able to systematically estimate the total number of Americans affected by drug shortages, the reduction in patients across the 30 retail-dispensed study shortage drugs amounted to approximately 510,000 fewer patients with fills monthly (an average of 17,000 fewer patients per month per shortage drug, with a median of 1,500 fewer patients per month per shortage drug).[1]

We found some differences in volume, price, and patient measures across different groups of drugs and patients. Generic shortage drugs typically had larger relative increases in prices (median of 14.6 percent) than brand-name drugs (median of 0 percent). Shortage drugs that were primarily retail-dispensed experienced greater increases in price (14 percent) and decreases in volume (66 percent) compared to drugs that were primarily hospital-dispensed (1 percent increase in price; 55 percent decrease in volume) or primarily dispensed through another channel (5 percent increase in price; 29 percent decrease in volume).

[1] Some patients are double counted because they fill prescriptions for multiple shortage drugs in the same month.

We also found that older consumers (ages 65-85) represented 31 percent of unique patients that were filling prescriptions for retail-dispensed drugs that went into shortage, larger than any other age group. However, adults aged 45 to 54 were the only age group with a statistically significant reduction in monthly unique patient fills for shortage drugs (at 14%); other age groups had smaller declines that were not distinguishable from zero. We were not able to systematically assess trends in the number of shortages or outcomes associated with shortages due to limitations related to the drugs included in the publicly available FDA shortage database.

Our 5 illustrative case studies help describe the wide range of potential shortage impacts. The shortage for belatacept (brand-name Nulojix, an immunosuppressant used to prevent rejection in patients receiving kidney transplants) stemmed from increasing demand and issues around a manufacturing change. We found volume increased over time through the onset of the shortage and over the long-term, which is consistent with increasing demand, while manufacturer prices remained flat. For carbidopa/levodopa (a generic drug used to treat Parkinson's disease), prices for both shortage and substitute drugs were flat or decreasing over time. We observed substantial increases in manufacturer price (by roughly two-thirds) for heparin national drug codes (NDCs) in shortage and large changes in manufacturer prices for non-shortage heparin NDCs. However, most heparin is used in the inpatient setting where consumers are typically shielded from immediate cost increases.

Across our analysis of 26 broader case studies, the volume of substitutes increased over most intervals, most notably by 13 percent measured over a 12–month period starting after the onset of a shortage. This suggests patients are switching to substitute drugs in at least some cases. We found manufacturer prices for substitutes remained about the same as prior to the shortage, except for a decrease during the recovery period. Pre-shortage prices for substitutes ($101) were about half of pre-shortage prices for the drugs in shortages themselves ($190).

## Discussion and Conclusion

While there are many conceptual links between drug shortages and patient costs, we expect the likelihood and magnitude of these effects are modest for most shortages. We found that average manufacturer prices increased slightly for shortage drugs, and we expect that drug supply chain, payment, and coverage factors will shield most patients from these increases in the short term. We also found an average 11 percent reduction in the overall number of patients with fills for retail-dispensed shortage drugs around the shortage start date, although this change was not statistically significant.

However, in some cases prices for shortage drugs increased substantially, while in others, the price of substitutes was higher than the pre-shortage price for the shortage drug. These specific scenarios could have more-direct impacts on patient costs.

While the data available for this study are useful for tracking national trends in drug utilization and spending at manufacturer prices, they have relatively limited utility in quantifying

the full range of shortage impacts on consumer costs. More specifically, these data cannot directly assess patient-level responses to shortages, such as delayed fills, reductions in adherence, or switches to alternative drugs, or changes in indirect costs. We recommend further research, including analysis of comprehensive claims data, to better elucidate associations between drug shortages and consumer costs.

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# 1. Introduction

## Background and Introduction

Prescription drug shortages are an ongoing concern for patients, prescribers, and policymakers. Conceptually, drug shortages are cases where the demand from patients and prescribers is not met by supply for a particular drug. In practice, there are several approaches to defining and identifying drug shortages. As of September 2021, the U.S. Food and Drug Administration (FDA) tracked 107 "market-wide" drug shortages where the agency determined that manufacturers could not meet U.S. market demand (U.S. Food and Drug Administration, 2021). Other organizations, such as the American Society of Health-System Pharmacists (ASHP), define shortages as disruptions and delays facing pharmacists and others working to procure drugs.

Regardless of definition, drug shortages have important implications on the U.S. health care delivery system. Pharmacies and health care systems must devote resources (e.g., staff time) to address shortages and may face higher prices to buy shortage drugs (Vizient, 2019; FiercePharma, 2011). The effects of drug shortages on consumers are complex, with potential implications on costs to consumers. Consumers may face higher or lower *direct* (i.e., out-of-pocket) costs through drug shortages as prices for shortage drugs fluctuate and, to the extent practical, they and their prescribers switch to alternate treatments. Consumers may also incur *indirect* costs from shortages as they invest time and effort to locate an available supply or substitutes. Shortages may also increase spending by consumers on medical care if the direct effects of shortages, such as abandonment of therapy, medication errors, delays, or substitution to suboptimal treatments, lead to adverse health outcomes and/or the need for additional services. Finally, net increases in payments by insurers as a result of shortages may lead to higher premiums for prescription drug and medical coverage for consumers.

The potential for a drug shortage to affect consumer costs likely varies with the cause and other characteristics of the shortage, the availability of substitute drugs and other alternative treatments, the relevant health care settings and related payment systems, and the characteristics of the patient population in need of the shortage drug. Drug shortages can have a range of root causes, including disruptions in supply chains, quality concerns, manufacturer decisions to cease production for financial reasons, and increases in demand that cannot be immediately met by manufacturers. Many shortage drugs are sterile injectables where both quality and manufacturer financial incentive concerns are of particular concern (Woodcock and Wosinska, 2012; Drug Shortages Task Force, 2020). However, even shortages with these shared characteristics may play out very differently depending on context.

Despite numerous studies documenting the effects of shortages on the health care system and pharmaceutical spending, their effects on consumer costs are largely unknown. This report describes work done for the U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation (ASPE). The goal of the study and report is to present as full a description of consumer costs associated with drug shortages as possible given the time, resources, and data at hand. ASPE posed several specific research questions, including:

(1) how many Americans face drug shortages?
(2) what types of costs do consumers incur related to drug shortages?
(3) how have trends in these costs varied over time?
(4) are there differences in shortage costs for generic versus brand shortage drugs, between dispensing locations, or across consumers with different characteristics?
(5) what policy options can address drug shortages?

To that end, we

- reviewed the available literature and resources related to links between drug shortages and consumer costs
- identified and described potential consumer costs related to drug shortages
- summarized the ways in which consumers may be insulated from costs associated with shortages, and the conditions where they may not be
- analyzed the available data related to, but not directly measuring, how consumer costs change through drug shortages by measuring changes in manufacturer prices, total U.S. volume, and total U.S. patients with fills
- explored how shortage effects on indicators related to consumer costs vary over time, by drug characteristics (e.g., brand versus generic status), and by consumer characteristics (e.g., by age).

## Literature Review Approach

We reviewed the literature both on drug shortages in general and that specifically linked U.S. drug shortages to consumer costs. We included both peer-reviewed journal articles and reports from government, industry, and other organizations in our review. While we focused on more recent publications, we did not impose a specific date range for our search. We reviewed studies for results and relevant discussion points. Drawing on the results of our review, we developed a conceptual framework of the potential consumer costs associated with drug shortages, including costs that we did not or could not address directly with available data, such as costs associated with downstream medical care resulting from unavailable or suboptimal prescription drugs. Separately, we assessed the papers and reports identified in our review and distilled main concerns and limitations of prior studies in terms of identifying and estimating associations between drug shortages and patient costs.

## Empirical Analysis Approach

We used the FDA's Center for Drug Evaluation and Research (CDER) shortage database[2] to identify a cohort of recent drug shortages and linked these data to IQVIA's National Sales Perspective (NSP) and Total Patient Tracker (TPT) data. The NSP data report estimates of total U.S. volume and average price for drugs while the TPT data include estimates of unique patients with retail prescription fills for drugs. Chapter Three describes our data and methods in detail. In brief, we

- identified 154 shortage drugs from the FDA's drug shortage database as of March 2020
- linked these shortage drugs to IQVIA NSP and TPT data
- calculated national (U.S.) changes in volume and price around the start month for these shortages using IQVIA NSP data
- calculated changes in estimated unique U.S. patient counts receiving fills for shortage drugs using IQVIA Total Patient Tracker (TPT) data
- identified 26 case study shortages covering a range of shortage types and prescription drug categories and identified major substitutes for these case study shortages
- measured national changes in volume and price for substitutes of the 26 case studies through the start of the shortage period.

While we ideally would have analyzed claims data to assess the implications of drug shortages on patient costs, claims data were not available for the current study. Chapter Five below includes our recommendations on the types of claims-based analyses that would be useful to explore associations between drug shortages and consumer costs more fully.

## Report Overview

The next chapter (Chapter Two) describes findings from our literature review, including a summary of all identified potential links between drug shortages and consumer costs. Chapter Three describes data and methods for our empirical analysis. Chapter Four summarizes results from our analyses of market-level data. Chapter Five discusses our findings and policy recommendations. Appendices A, B, and C present additional methodological details, supplemental results, and findings from illustrative case studies, respectively.

[2] Within FDA, both the CDER and the Center for Biologics Evaluation and Research (CBER) maintain lists of shortage drugs under the purview of their respective centers. CDER regulates small-molecule drugs and therapeutic biologics, while CBER regulates blood products and other biologics. The FDA CBER database is not readily available in a format to be used by researchers. As a result, we used only the FDA CDER database and we refer to this database as *the FDA database* throughout.

# 2. Literature Review Findings

This chapter describes findings from our literature review, and includes:

1.) a taxonomy of the types of consumer costs associated with shortages and the typical timing of these costs relative to when the shortage occurred
2.) a summary of prior research on drug shortages with relevance to consumer costs;
3.) our assessment of the limitations of these prior studies
4.) a discussion of how consumers may be shielded from certain costs associated with drug shortages and specific cases where consumers may be more directly affected.

## Taxonomy of Potential Consumer Costs Associated with Drug Shortages

We present a taxonomy of the different ways that drug shortages could affect consumer costs in Figure 2.1. The columns in Figure 2.1 describe broad categories of consumer costs, including direct costs (out-of-pocket costs associated with purchasing drugs), indirect costs (other costs incurred by consumers as they fill prescriptions, for example travel time), and costs associated with changes in health outcomes and related care stemming from the shortage. Consumers may experience changes in costs in any or all of these categories. The net change in consumer costs will depend on that magnitude of the costs (or savings) across these cost categories.

**Figure 2.1. Consumer Responses to Shortages and Their Costs**

| | Direct Costs | Indirect Costs* | Health Outcomes/Related Costs* |
|---|---|---|---|
| I. Shortage drug received | Potentially higher out-of-pocket costs | Potentially higher premium<br>Potential search costs | N/A |
| II. More expensive alternative received | Potentially higher out-of-pocket costs | Potentially higher premium<br>Potential search costs | Potential adverse outcomes and higher costs if alternative is sub-optimal relative to the shortage drug |
| III. Less expensive alternative received | Potentially *lower* out-of-pocket costs | Potentially *lower* premium<br>Potential search costs | Potential adverse outcomes and higher costs if alternative is sub-optimal relative to the shortage drug |
| IV. Delayed or no treatment | Potentially *lower* out-of-pocket costs | Potentially *lower* premium<br>Potential search costs | Likely adverse outcomes and higher costs relative to the shortage drug |

Shortage

Source: Author summary of findings. NOTES: *Indicates that the response will be delayed from when the shortage occurred. Search costs are defined as the time and resources that consumers spend to locate the shortage drug. N/A = not applicable.

To better highlight relevant costs, we include a separate row (I–IV) in Figure 2.1 for each of four scenarios:

I. Patient receives the shortage drug
II. Patient receives a more expensive substitute drug
III. Patient receives a less expensive substitute drug
IV. Patient delays or does not receive treatment

The following sections walk through the direct, indirect, and long-term health and related costs for each of these four scenarios.

### *Direct costs*

Based on microeconomic theory and the prior empirical research, drug list prices (i.e., prices set by manufacturers) on average increase following a shortage occurrence (Drug Shortages Task Force, 2020; Mulcahy et al., 2021). Several studies found that shortage drugs in the United States on average were more likely to experience price increases compared to non-shortage drugs (Alevizakos et al., 2016; Dave et al., 2018; Hernandez et al., 2019; Yurukoglu, Liebman and Ridley, 2017). Furthermore, prior RAND and FDA studies (Drug Shortages Task Force, 2020; Mulcahy et al., 2021) found that, while prices for shortage drugs increased slightly, on average, there was a wide range of price changes over time during drug shortages, and prices for shortage drugs *decreased* about as often as they increased.[3]

To the extent to which these list prices are passed on to consumers depends on several factors, including whether consumers have drug coverage; if so, the details of their benefit design; and whether consumers receive a relatively more or less expensive substitute in lieu of the shortage drug. In some cases, as we discuss in the next section, consumers may experience greater direct costs. Despite discussions of this mechanism in the literature (Davies, Hwang and Kesselheim, 2017; Boulis, Goold and Ubel, 2002; McLaughlin et al., 2013), there is very limited empirical research to support whether higher manufacturer prices are passed on to consumers.

To our knowledge, there is only one study that has estimated changes in direct consumer costs due to shortage in the United States. In response to the shortage of the drug leucovorin, which treats megaloblastic anemia, Hayes and colleagues estimated that 6.6% of patients substituted the shortage drug with levoleucovorin. On average, patients who switched to

[3] In a 2021 RAND study for ASPE comparing drug shortage trends in the United States to other OECD countries, Mulcahy and colleagues found heterogeneous responses to drug shortages in the United States (Mulcahy et al., 2021). Using IQVIA MIDAS data covering the entire U.S. prescription drug market, they found that shortages listed in FDA's Center for Drug Evaluation and Research (CDER) database and the American Society of Health-System Pharmacists (ASHP) databases were associated with modest decreases in U.S. volume (about 8 percent) and modest increases in U.S. prices (about 7 percent) on average with outcomes measured from the quarter prior to the quarter after the onset of each shortage. In comparison, neither volume nor price significantly changed over time for a comparison group of non-shortage drugs weighted to resemble shortage drugs in terms of observable characteristics (formulation, pre-shortage volume, and brand vs. generic status). While volume decreased and price increased on average for shortage drugs, there was substantial variation for both measures, and nearly as many shortage drugs experienced increases in volume and decreases in price compared to changes in the other (expected) directions.

levoleucovorin experienced annual increases in out-of-pocket costs of between $167 to $716. As levoleucovorin is similar to leucovorin in terms of efficacy, this increase in spending did not correspond to improvements in health for these consumers (Hayes, 2014).

There is no reason to believe substitutes to shortage drugs would be systematically more or less expensive than shortage drugs themselves. Should a substitute drug (or other health care service) be less expensive than the shortage drug, the potential savings to the health care system could correspond to lower out-of-pocket costs to patients. For example, when intravenous pantoprazole went into shortage, Gupta and colleagues found that providers replaced the drug with an oral version that amounted to a savings of $200,000 per hospital. Though this study does not include patient-level estimates, it suggests that drug shortages may offer an opportunity to identify and switch to more-affordable alternatives (Gupta et al., 2017). An overall cost-benefit or cost-effectiveness analysis of these situations hinges on the clinical and quality implications of the switch in addition to the change in cost.

Another short-term response that would lower out-of-pocket costs to consumers is delaying or ending treatment with the shortage drug. As estimated in an earlier RAND report to ASPE, the volume of shortage drugs purchased decreased by 8.4 percent on average from the quarter prior to the quarter after the start of a given shortage (Mulcahy, et al. 2021). The findings of the RAND report are consistent with those from prior drug shortages studies. For example, in an analysis using IQVIA's National Sales Perspective (NSP) database from 2010 to 2018, the FDA Task Force report found that only 30 percent of shortage drugs recovered from declines in volume to pre-shortage levels by the end of the shortage or 12 months of the start of the shortage, whichever was earlier. In terms of changes in price, 18 percent of shortage drugs experienced sustained price increases of 50 percent over six months or longer (Drug Shortages Task Force, 2020). Though these studies do not estimate the consumer savings from these delays of care, if consumers were subjected to cost sharing for drugs or services that they are delaying, they would save in direct costs as a result. Of course, as described below, there are other important costs of decreased utilization of necessary prescription drugs, including likely impacts on health outcomes.

### *Indirect costs*

In addition to out-of-pocket costs, consumers may devote more time and effort to address medical concerns in response to drug shortages. Few prior studies address these indirect costs head-on. In a survey of directors of pharmacy, some respondents reported that shortages sometimes resulted in patient transfers to other facilities {McLaughlin, 2013 #180}. In the same survey, some respondents reported patients had to provide their own medication in some cases. Both of these outcomes could involve indirect travel and time costs for patients, their families, and their caregivers In cases where patients must provide their own medication or identify an alternate source of care, they may face higher "search costs" related to more frequent visits to prescribers, contacting additional pharmacies, and travelling greater distances to fill a

prescription. More generally, the time patients spend on these activities incurs an opportunity cost, for example time that could have been spent working or on leisure. Despite the strong conceptual basis for assuming these indirect costs exists, we did not find any empirical estimates of their magnitude.

### *Costs associated with shortage-related changes in health outcomes*

As a result of the decreased prescription fills of the shortage drug and/or switches to substitutes, some consumers may experience worse health outcomes, resulting in greater health care costs to manage these outcomes {Phuong, 2019 #221}. A multitude of studies have estimated that delays in care and reductions in medication adherence are subsequently associated with increased hospitalizations and emergency department visits (Benner et al., 2002; Roebuck et al., 2011; Aitken, 2013). In a report by the IMS Institute for Healthcare Informatics, they estimated that medication non-adherence and delays in care led to an additional $105.4 billion and $39.5 billion, respectively, in avoidable health care costs in the United States in 2012 (Aitken, 2013). At the patient level, Roebuck and colleagues estimated that those who were non-adherent to medications spent between $1,860 and $8,881 higher (in 2008 dollars) on their average medical expenses per year compared with patients who were adherent to their medications (Roebuck et al., 2011). The extent to which shortages affect adherence and these costs are, however, generally unclear (Tucker et al., 2020). Studies surveying pharmacy directors and providers reported delays in treatments, including procedures, surgeries, and chemotherapy infusions because of shortages, all of which might have clinical implications (McLaughlin et al., 2013; Kehl et al., 2015; Baumer et al., 2004).

There are also likely to be health complications if the substitute treatment is less effective or has worse side effects than the shortage drugs. Surveys of pharmacy directors and providers have found that switching from a shortage drug to substitutes led in some cases to increases in adverse drug reactions, hospitalizations, and mortality rates (Baumer et al., 2004; McLaughlin et al., 2013). Insured patients would likely be subjected to cost-sharing for these services. On the other hand, in some instances, there may be no practical health implications of switching to a substitute. As noted above, substitutes may be relatively more or less expensive than shortage drugs. On balance, the value implications of switching to substitutes given differences in health outcomes and cost must be assessed on a case-by-case basis. Under different scenarios, shortages may catalyze changes in prescribing patterns leading to either lower- or higher-value care.

### *Dynamic effects on premiums*

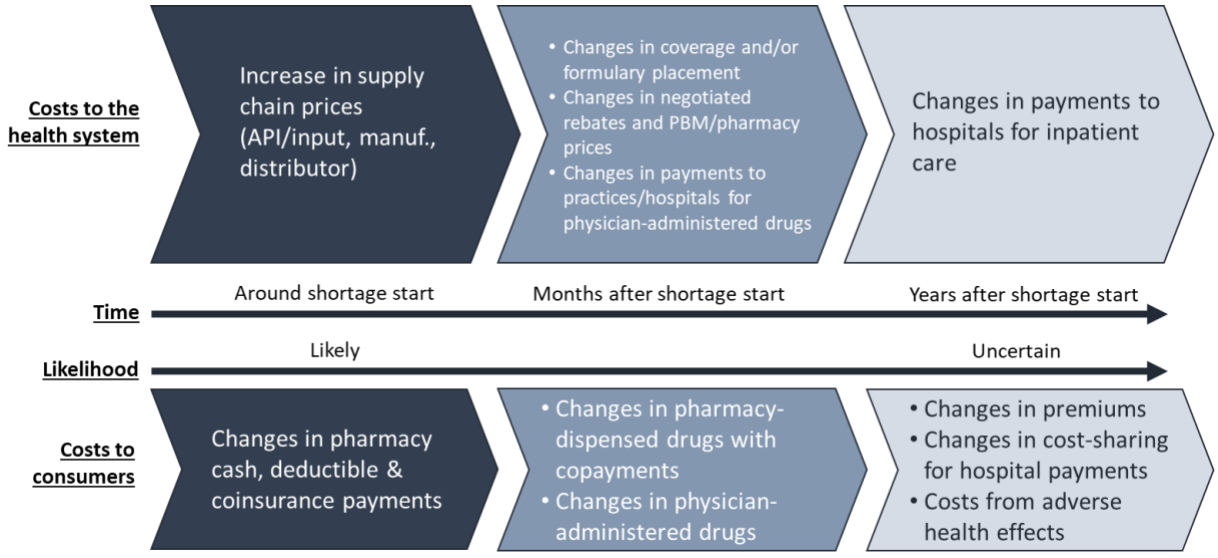
Across all four scenarios, should a drug shortage have an impact on drug costs or overall health care spending, then it could conceivably change insurance premiums paid by patients (and often their employers) for insurance plans in subsequent years. When drugs go into shortage, health care systems spend considerable labor managing the shortage, either through searching for the shortage product, identifying substitutes, and increasing their monitoring of patients.

According to a Vizient Drug Shortages Impact Report, these activities amount to at least $359 million annually in additional spending throughout the United States (Vizient, 2019). In order to cover these additional labor costs, providers may over time increase prices for broader health care services where drugs are bundled, such as with inpatient stays and certain outpatient visits. To the extent providers are able to pass these costs on to payers, such expenses could then increase an insurer's projections of future medical spending for their enrollees, which insurers would then account for by increasing premium rates for consumers (American Academy of Actuaries, 2020; Cantor and Monheit, 2016).

## Timing and Mitigating Factors

We present a framework in Figure 2.2 to describe costs to the health care system (top-half of the figure) and to consumers (bottom-half of the figure) based on timing relative to the start of the shortage, which we classify in three stages: (1) around the shortage start date, (2) months after the start of a shortage, and (3) years after the start of a shortage. The likelihood of shortage-related costs to consumers or the health systems becomes more uncertain as more time elapses after the start of the shortage because patients, prescribers, and policymakers will be better able to respond to some shortages than to others.

**Figure 2.2. Costs of Drug Shortages by Time and Likelihood**




### *Around shortage start date*

As noted above, prior studies find that price decreases are about as common as price increases for shortage drugs. For the slightly more than half of cases experiencing price increases, the specific price that increases through a shortage is the price charged by manufacturers to buyers of drugs (including, depending on the context, distributors, pharmacies,

and hospitals and other health care providers). Depending on where the immediate purchaser is located in the prescription drug supply chain, there may be additional markups on this "manufacturer" price.[4] However, the speed at which these price adjustments flow through prescription drug supply chains depends on the contractual arrangements between manufacturers, distributors, and the ultimate drug buyers (e.g., pharmacies and hospitals), which vary significantly.

As described above, the prices as drugs flow through the supply chain, with markups along the way, are neither (a) the net prices that health plans pay for drugs; nor (b) the prices that patients pay for drugs. For brand-name drugs dispensed via retail and mail pharmacies in particular, insurers and their pharmacy benefit managers (PBMs) receive manufacturer rebates that lead to lower net prices. Patients with drug and/or medical coverage typically pay a fixed-amount copay (e.g., $25) that does not vary immediately with the manufacturer price or other prices as drugs flow through supply chains. Patients who receive drugs in a physician's office or hospital outpatient department are more likely to pay a percentage of a drug's acquisition price, or coinsurance, rather than a fixed-amount copay.

There are a few narrow cases where patients are more exposed to manufacturer and related prices around the onset of a shortage. Patients without drug and/or medical coverage, patients with coverage to fill a prescription for a non-covered drug, or patients in the deductible phase of their coverage benefit may be responsible for paying the amount the pharmacy charges, which could reflect shortage-related increases in price. In addition, patients responsible for paying coinsurance, i.e., a share of the cost of a drug rather than a fixed-dollar amount, may be more exposed to shortage-related increases in price because the patient's share is also calculated using the amount the pharmacy charges. In general, coinsurance is more common for expensive specialty drugs, so the impact on patients in monetary terms may be substantial. Note that while Medicare beneficiaries are responsible for 20% coinsurance on Part B drugs administered by practitioners, for reasons described below, out-of-pocket costs would likely not increase immediately for these patients.

### *Months after shortage start date*

Several months after the start of a shortage, there may be broader implications on consumer costs, regardless of whether the shortage is resolved or ongoing. Insurers can often update formulary placement and cost-sharing arrangements annually when plans renew. Depending on when a shortage starts during a plan year and the time elapsed, it is more likely that any additional cost facing insurers and PBMs will be partially shifted to patients, even in cases where

[4] Manufacturers are free to set their own "list" prices in the United States. These list prices are often closely related to the actual prices charged by manufacturers to distributors and other purchasers. However, actual manufacturer prices as we measure for our analysis reflect certain discounts appearing on invoice, such as prompt-pay discounts. This results in an important technical distinction between list and manufacturer prices.

patients pay a fixed-dollar copay (e.g., a $25 copay may increase to $50). Agreements between manufacturers and insurers and their PBMs also renew over time (e.g., annually), and it is possible that the net price may increase or decrease depending on circumstances.

Changes in prices for physician-dispensed drugs would also take several months to affect consumers. As noted above, Medicare Part B covers physician-administered drugs. Part B payment rates for drugs are based on the average volume-weighted price paid by providers to acquire the drug, or the "Average Sales Price" (ASP), plus a small markup. ASP data are updated quarterly, drawing on pricing data from drug manufacturers submitted six months prior to the update (National Academies of Sciences, 2018). Patients or patients' sources of supplemental coverage, such as Medigap plans, are responsible for 20% of the cost for Part B services including drugs. Thus, consumers would only face higher out-of-pocket costs for Part B drugs after this six-month delay. Interestingly, some shortages resulting in price increases may be resolved within this six-month period, which means that patients who face increased costs may not be the same patients that were directly affected by the drug shortage.

### *Years after shortage start date*

Medicare and may other health care payers use prospective payment systems or fee schedules to pay for inpatient hospitalizations and outpatient facility services (e.g., procedures performed in a hospital's outpatient departments). Most drugs used during inpatient stays and some drugs used during outpatient procedures are bundled into the payment for the stay or procedure rather than paid separately. Payment rates for these stays and procedures are updated regularly, typically using lagged data on the resources required to provide the service. In the case of Medicare's payment for inpatient stays, prospective payment rates are based on cost information lagged by two years. As a result, higher prices for shortage drugs could eventually increase payment rates for these services, although the effects would be felt by all patients using the bundled service, even those who were not using the shortage drug and even those receiving care after the shortage is resolved.[5]

Relatedly, if drug shortages result in poorer health outcomes due to delayed treatment, lack of treatment, or substitution of suboptimal treatments, then it is possible that the costs of treating patients may increase over time, and these increased costs could feed back into higher payment rates and cost-sharing for all patients. For example, if hospitals face higher labor, supply, or other costs to address the health implications from a drug shortage during an inpatient stay, these higher costs would in the long-term result in higher payment rates and potentially higher cost-sharing.

Another delayed effect of shortages on consumer costs is changes in premium rates for insurance plans. Actuaries calculate annual premiums using projections of health care spending of enrollees in a given year (Congressional Budget Office, 2016; American Academy of

Actuaries, 2020; Cantor and Monheit, 2016). As noted above, drug shortages have the potential to, but may not always, increase spending through higher prices for shortage drugs or substitutes, increased hospitalizations because of either delayed treatments or suboptimal substitutes, or eventually, increased payment rates for broader services like inpatient hospitalizations. Actuaries would use these expenses to inform their projections of future spending for their enrollees, which would be passed on as increased premiums and/or increased costs to taxpayers to fund public insurance programs.

## Challenges in Assessing Links Between Shortages and Consumer Costs

Several of the papers and reports that we reviewed noted data limitations that prevent the full characterization and evaluation of the implications of drug shortages. Ideally, researchers would have access to the following information when studying associations between shortages and consumer costs:

- the prescriber's and patient's choice of optimal treatment in the absence of a shortage (including choice of drug, quantity, and timing)
- the drugs prescribed, if any (including choice of drug, quantity, and timing)
- patient time, travel, and other indirect costs associated with the shortage
- receipt of any health care services associated with delays in treatment, use of a substitute, or no treatment
- the costs to the patient and, if the patient has drug and/or medical coverage, the insurer for that care
- the extent to which changes in costs of care translate into higher payment rates for services like inpatient stays over time and the utilization of affected services
- the extent to which changes in costs of care translate into higher premiums for coverage and contributions from taxpayers to finance public insurance programs.

Unfortunately, only a fraction of this information is routinely available to researchers. Instead, the body of studies described in this chapter largely relies on two sources of data, either samples of claims data recording prescription fills and (in some cases) the amount the patient paid out of pocket, or national summaries of volume and average invoice prices paid to manufacturer prices (e.g., from the IQVIA MIDAS or NSP databases). Neither type of data is ideal to understand the full impacts of drug shortages on consumer costs.

The fragmented and often incomplete nature of claims data creates challenges for assessing the holistic impacts of shortages on patient costs. These challenges include the following:

- An often-incomplete picture of prescribing. Researchers do not always have access to comprehensive claims covering all channels for drug distribution (including pharmacies, physician offices and outpatient hospital settings, and inpatient hospital settings). For example, many studies rely on pharmacy claims only. However, some shortage drugs or

their substitutes are administered in outpatient facility settings and are therefore billed on medical rather than prescription claims.

- Scope limited to one payer. Some patients pay cash for prescriptions even if they have health insurance. Other patients may have multiple sources of health care coverage (e.g., via Medicare and the Veterans' Health Administration), and examining data from a single payer may not provide a full picture of all prescriptions filled by a given patient. Pursuing atypical routes to fill prescriptions may be more common during shortages when drugs are in short supply.
- Incomplete information on patient out-of-pocket costs. Many shortage drugs are administered in physician offices or in facility settings (e.g., hospitals), and providers typically bill for these drugs using medical rather than pharmacy claims. Some common sources of medical claims, such as Medicare claims, include the amount patients are responsible for paying but do not indicate whether some or all of this amount is covered by sources of supplemental coverage (such as Medigap policies). As a result, the reported out-of-pocket costs to patients may be biased upward.
- Limited insight into inpatient drugs. Other shortage drugs are commonly used in the inpatient setting where records of which specific drugs were administered to patients is likely incomplete because drugs are typically not billed separately from broader inpatient hospital stays.
- Incomplete clinical context. Claims data include information on diagnoses and claims submitted and paid for health care services. They do not indicate cases where prescribers or patients faced difficulty accessing a shortage drug. Electronic health record data may provide more insight into the context around treatment choices and the implications of drug shortages on health outcomes.

Studies using national market data (e.g., Mulcahy, et al., 2021; FDA 2020) face a different set of challenges:

- Inability to assess patient-level shortage impacts. IQVIA's MIDAS and NSP data estimate total national volume and sales amounts based on IQVIA's audits of invoices between manufacturers, distributors, pharmacies, and hospitals. While these data offer the most complete view of total national volume of prescription drugs, they are not well-suited to assessing patient-level effects of shortages. Because purchases by distributors, pharmacies, and hospitals ultimately serve many patients with different conditions and sources of coverage, it is impossible to link information from invoices to individual patients. As a result, flagging certain patient-level changes in response to shortages (e.g., switching from a shortage drug to a substitute) is impossible. This kind of longitudinal analysis is more feasible with claims data, provided that complete data are available as discussed above.

- Lack of information on patient costs. The IQVIA MIDAS and NSP data focus on amounts reported in invoices for sales between manufacturers, distributors, pharmacies, and hospitals, but not patients. Although other IQVIA data sources track out-of-pocket spending from claims, these two market-level data sets do not.

In addition, both claims and market-level data lack information on the net prices ultimately paid by prescription drug and medical plan sponsors. This is particularly problematic for brand-name drugs where off-invoice negotiated rebates and other discounts between pharmacy benefit managers (PBMs) or plan sponsors and drug manufacturers are common. As a result, these data cannot be reliably used to assess how shortages affect prices paid by health plans or the downstream effects on consumer insurance premiums.

## Linking Conceptual Costs to Empirical Analysis

We had access via ASPE to several national-level U.S. prescription drug market data sets from IQVIA (NSP and TPT). These data sets provide a window into some of the consumer costs of shortages described above, although in most cases via inference, from the following metrics:

- the number of unique patients with prescription fills for shortage drugs in a given month (pharmacy-dispensed prescription fills only)
- changes in U.S. volume for shortage drugs and substitutes
- changes in U.S. manufacturer prices for shortage drugs and substitutes.

As noted above, the prices in market-level data like the NSP data are manufacturer prices and not amounts actually paid by consumers. We analyze these market-level data using methods described in the following chapter.

# 3. Summary of Empirical Analysis Data and Methods

This chapter briefly describes our sample of drug shortages, two IQVIA data sets used for empirical analysis, our approach to select case studies, and our empirical methods. Appendix A includes additional details on our data and approach.

## FDA Drug Shortage Database and Sample

The FDA drug shortage database (FDA, 2021) lists drugs that have experienced production disruptions that are "market wide," meaning that manufacturers cannot meet the current market demand for the drug. In order to make this determination, FDA considers the following factors: the market share of the forms in disruption, manufacturers' inventory, monthly rate of demand, manufacturing schedules, and changes in ordering patterns of the products of interest. The FDA database includes information on the National Drug Codes (NDCs) in shortage, the dates on which shortages were reported and last updated, and, in some cases, the reason for the shortage.[6] The database is publicly available for download on the FDA's website.

The FDA database includes drugs that are currently in shortage, drugs that were in shortage but were resolved within the past six months, and NDCs that were discontinued within the past 12 months. We used an extract from the FDA database downloaded in March 2020. As a result, our data include records of shortages that were either ongoing in March 2020, were resolved prior to or during October 2019–March 2020, or were discontinuations from April 2019 through March 2020.[7] The initial file included 2,293 records.

We excluded most entries in the FDA database for discontinuations, which we did not consider to be shortages per se. These entries appeared to report specific NDC-level discontinuations reported by manufacturers rather than broader drug shortages. Discontinued products can in some cases have important implications for prescribers, health systems, and patients. However, manufacturers often discontinue specific package-level NDCs (e.g., 1000-tablet bottles of a drug) while supplying related package-level NDCs (e.g., 100-tablet bottles of the same drug). After separating unique NDCs into individual rows and excluding these discontinuations, the final FDA analytic dataset included 1,650 NDC-level records.

We use the "initial posting date" in the FDA database as a proxy for the shortage start date. The initial posting date is based on when manufacturers reported a shortage to FDA. The practical effects of a shortage may first be felt weeks or even months prior to or after this date. In

[6] About 60 percent of shortages lack any description of the reason for the shortage. Most of those that do have a description lack detail.

[7] Some of the shortages in the extract started many years prior. We address these older shortages below.

some cases, there may be a lag after the effects of a shortage are first felt and when the shortage is reported to FDA and entered in the database. In other cases, manufacturers may report a shortage months before the effects are observed in market-level data (e.g., as existing stocks are used). We used FDA initial posting dates as a proxy for shortage start dates because we are not aware of an alternative data source for shortage start dates. We developed specifications for our outcome measures that try to accommodate some uncertainty in the actual start date as described below.

## IQVIA National Sales Perspective Data

The IQVIA NSP data estimates the volume and sales of U.S. pharmaceutical products purchased by retail, mail, long-term care, and other channels across all payers. IQVIA captures approximately 90% of the total retail pharmaceutical market in the United States and projects the NSP data to approximate U.S. total volume and sales using a proprietary approach. Importantly, NSP lists total payments for drugs from distributors, pharmacies, hospitals, and other buyers to manufacturers at invoice prices. These "manufacturer prices" are not (a) net prices paid by PBMs or insurers, or (b) the amounts paid directly by patients.

We analyzed an NSP extract spanning January 2016 through December 2020 provided under contract with ASPE and containing all prescription drug NDCs. Of the 1,650 NDCs from the FDA database, 1,291 (78.2%) matched to an NDC in the NSP data. The remaining (n=359) may represent NDCs not sold via a channel contributing to IQVIA's NSP data (e.g., drugs used in inpatient hospital settings or administered by practitioners), NDC errors in the FDA database that we did not immediately identify and correct, or other factors.

Separately, for a set of 26 illustrative case studies (described below), we manually linked the NSP data to substitutes for shortage drugs. We identified substitutes as described below.

## Study Shortage Observations

After combining FDA database with the NSP data, the 1,291 NDCs were from 132 unique active ingredients. For our main analyses, we collapsed these data to the active ingredient level with separate records for

- shortage NDCs
- NDCs not in shortage but for the same form as the shortage NDCs
- all other forms for the same active ingredient.

We used the New Form Code (NFC) values in NSP data to determine form. In most cases, we combined oral solids into one category (NFCs beginning with "A" or "B"), oral liquids into a second category (NFCs beginning with "D" or "E"), injected and infused drugs into a third

category (NFCs beginning with "F" or G"), and all other NFCs as a fourth category. We sometimes refer to "detailed forms" that are the specific three-digit NFC values.[8]

We separated cases where the same active ingredient had a shortage for multiple forms, for a total of 142 active ingredient-forms. For simplicity, we refer to a combination of an active ingredient and form in shortage as a "shortage drug." In the context of our analyses, a shortage drug may include some NDCs that themselves were not in shortage. However, other formulations are not considered as part of same shortage drug. Results are, depending on the table or figure, calculated at the shortage drug level (i.e., including specific NDCS in shortage and not in shortage), for the specific NDCs in shortage within a shortage drug, or for the specific NDCs not in shortage within a shortage drug.

We excluded shortage drugs where there was no shortage start date listed in the FDA database (n=5), shortages starting within the first 12 months of our NSP data extract (n=8), and shortages starting within the last 15 months of our NSP data extract (n=12 active ingredients). We made these exclusions because we needed to know the shortage start date and have sufficient data to calculate changes in volumes and prices as described below. There were 117 remaining shortage drugs after these exclusions.[9]

Using the distribution channel information in the NSP data, we calculated the share of total volume for these shortage drugs via the pharmacy channel, the office or clinic channel, hospitals, and an "other" category that combined all other distribution channels. We also flagged shortage drugs with greater than 50 percent of volume categorized as "generic" in the NSP data set as generic drug forms, and all others as brand-name drug forms.

## Linking to IQVIA Total Patient Tracker Data

IQVIA's Total Patient Tracker (TPT) data estimates the number of unique patients in the United States with monthly prescriptions for specific drugs filled through retail or mail channels. IQVIA estimates these patient counts using its "LRx" prescription claims data, which are aggregated from a large convenience sample of prescription claims processors covering an estimated 90 percent of retail prescription fills and a substantial (although smaller) share of mail-order prescription fills. IQVIA uses information submitted on prescription claims, including patient ZIP code, patient date of birth, and patient gender, to construct unique patient IDs and project observed prescription fills to national levels. The TPT data are updated monthly.

The TPT data do not include patients who had drugs administered in a physician's office, facility, hospital, or other settings, or who received prescription fills in long-term care or home health settings. As a result, we analyzed TPT data for a subset of 30 shortage drugs that had at

[8] NFC is a hierarchical system where the first digit is the most general and the third is the most specific.

[9] In most cases, the shortage for an active ingredient covered just one broad form category. The shortage for one active ingredient, sildenafil (brand-name Viagra), extended to three broad forms, and the shortages for 8 additional active ingredients included two broad forms.

least 80 percent of their volume dispensed via retail pharmacies. We applied this threshold so that results related to changes in patient counts for a drug were broadly generalizable across the drug as a whole, and not just to the share dispensed via retail pharmacies. A limitation of this dataset for our study is that it may undercount patients who experience delays or missed fills because of drug shortages if they ultimately receive a fill. Conversely, it may overcount the number of patients who face a shortage, as it only identifies drugs at the active ingredient level, rather than disaggregating by NDC. Finally, TPT unique patient counts across drug products are likely biased upward because a single patient can have fills for multiple products in the same month.

## Case Study Selection

We examined a set of case studies in order to better understand the variation of changes in price and volume among shortage drugs and their substitutes. From the 117 unique shortage drugs available in the NSP data, we selected 26 illustrative case studies that (a) met certain selection criteria, and (b) to the extent feasible, covered different types of drugs and shortages. We identified substitute drugs for these 26 illustrative case studies through input from two physicians and a pharmacist. Appendix A includes a detailed description of our selection approach and Appendix C includes a list of the case study shortage drugs and their substitutes. We describe the context around shortages and illustrate monthly trends in volume and prices for a narrower set of five illustrative case study shortage drugs and their substitutes. The five narrower case studies are as follows:

1.) asparaginase (a pediatric oncology drug with few substitutes)
2.) belatacept (a shortage driven by increasing demand)
3.) carbidopa/levodopa (a drug used to treat Parkinson's disease primarily dispensed via retail and mail-order pharmacy)
4.) heparin (a shortage drug with substantial hospital utilization)
5.) valsartan (a long-term shortage of a common cardiovascular drug due to quality concerns).

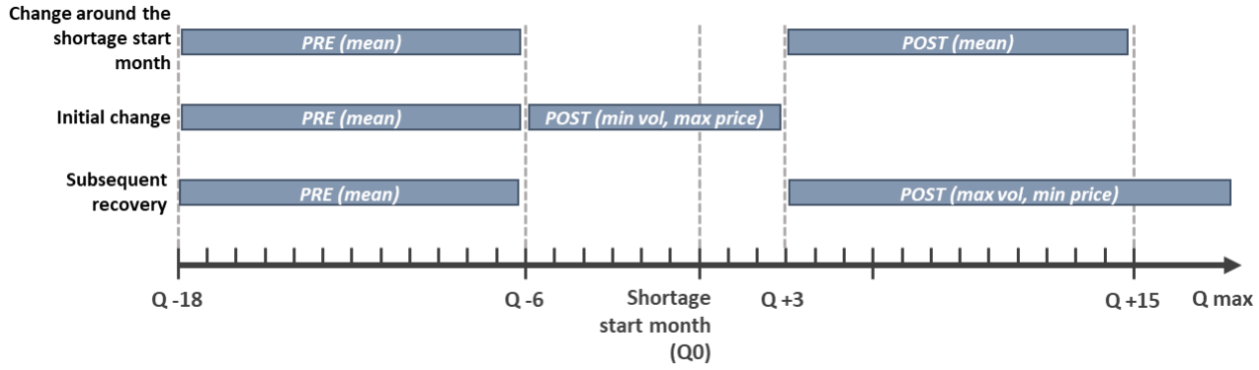
Neither the set of 26 nor the narrower set of five illustrative case studies are meant to be representative of our broader sample of drugs shortages. We rely on the case studies to illustrate potential, but not necessary average or typical, changes in volume, prices, and other outcomes through drug shortages.

## Market-Level Volume and Price Measures

We calculated changes in volume and prices using three main measures that differed in their definition of pre-shortage (PRE) and a follow-up measurement period (POST) relative to the month in which a shortage began. See Figure 3.1 for a summary. The timing of each measure is anchored on the month in which the shortage was first reported to the FDA by manufacturers.

While we refer to this month as the "shortage start month," the effects of a shortage on volume and prices may first occur in prior or later months as described above. As a result, for some measures we exclude months immediately before and after the shortage start month, and we exclude relatively more months prior to the shortage start month under the assumption that delays in manufacturer reporting to FDA are relatively more common than early reports. Because many drug shortages in our sample were ongoing through the last month of NSP data in our extract, the "post" periods described below do not necessarily align with the period after the shortage is resolved.

**Figure 3.1. Outcome Measure Time Frames**




Source: Author illustration.

We used the following three measures, the first of which we considered our main approach while the other two are used for some appendix results:

- Change around the shortage start month. This measure uses 12-month pre and post periods. The pre and post periods exclude a ten-month washout period centered on the month in which the shortage began. The washout period allows for some uncertainty in the precise shortage start month. The measures are the volume-weighted percent changes in volume and price between the pre and post periods. Note that "post" does not signify that the shortage itself is resolved. In many cases, shortages persist 15 months or longer.
- Initial change. The pre period for this measure is the same as the pre period described for the prior measure. The post period is the nine months centered on the shortage start month. The measures are the volume-weighted percent changes from pre period volume and price to the minimum volume and maximum price in the post period. These measures are therefore upper bounds of the reduction in volume and increase in price relative to pre-shortage levels.
- Subsequent recovery. The pre period is the same as above, but the post period includes all available months from the fourth month after the start of the shortage. The measure is the percentage of change from the minimum volume and price in the

pre period to the maximum volume and minimum price in the post period. These measures are therefore upper bounds of the reduction in volume and increase in price relative to pre-shortage levels.

We used volume measured in IQVIA's standard units to calculate changes in volume. Standard units are equal to one for most oral solid forms (e.g., capsules and tablets), 5 milliliter (mL) increments for most oral liquids, and a count of syringes, vials, or other "eaches" for most infused, injected, and other formulations. We calculated prices by dividing manufacturer sales in NSP by this standard unit-based volume measure. We report results for changes around the shortage start month measure in Chapter Four and results from the initial change and subsequent recovery measures in Appendix B.

## Unique Patient Measure

We calculated three measures of changes in unique patients that used the same terms and timing of the PRE and POST measurement periods relative to the month in which a shortage began that we used for volume, as shown in Figure 3.1. For each shortage drug, we then calculated the mean, minimum and/or maximum of the unique patients per month across each PRE and/or POST period. We then calculated the three measures for each shortage drug using the methods above, reporting the median and mean percent changes in our summary statistics.

# 4. Empirical Results

This chapter reports results from our analysis of IQVIA NSP and TPT data.

## Shortage Drug Characteristics

Of the 117 total study shortage drugs, over half (n=63; 54 percent) were infused or injected while 32 percent (n=37) were oral solid forms like tablets and capsules and 14 percent (n=17) were other forms. A few shortage drugs had much larger volume measured in standard units than others, leading to a mean (268.5 million standard units annually) much higher than the median (16.7 million standard units annually) volume (see Table 4.1). As described above, most active ingredient-formulation-level shortage drugs have some specific NDCs in shortage while other specific NDCs are not in shortage. We found 105 of 117 shortage drugs had at least one NDC within the same form that was not in shortage. On average, the specific NDCs in shortage accounted for roughly half of the pre-shortage volume. Prices for shortage NDCs and all NDCs within shortage drugs were broadly comparable (also in Table 4.1; difference in mean price between specific NDCs in shortage and not in shortage not statistically significant). Pharmacy-dispensed shortage drugs on average had 652,000 monthly patients with fills in the year prior to the shortage.

**Table 4.1. Pre-Shortage Characteristics of Shortage Drugs**

| | Median | Mean | 95% C.I. |
|---|---|---|---|
| **Volume (12 months, millions of standard units)** | 16.7 | 268.5 | (116.1, 420.9) |
| Shortage drugs, shortage NDCs | 8.8 | 124.2 | (42.9, 205.6) |
| Shortage drugs, non-shortage NDCs | 2.3 | 160.8 | (52.4, 269.2) |
| **Manufacturer Price (12 months, $/standard unit)** | 1.3 | 90.9 | (-2.3, 184.0) |
| Shortage drugs, shortage NDCs | 1.5 | 53.4 | (-3.6, 110.3) |
| Shortage drugs, non-shortage NDCs | 0.9 | 62.2 | (-32.0, 156.5) |
| **Monthly unique patients (avg. over 12 months, retail shortage drug NDCs, nearest thousand)** | 214,000 | 652,100 | (165,400, 1,138,800) |

Source: Authors' analysis of IQVIA NSP and TPT data for study FDA shortages.
Note: Differences in mean volume and prices between shortage and non-shortage NDCs were not statistically significant. Analysis for all outcomes except unique patients reflect specific shortage NDCs for 117 shortage drugs. Results for specific NDCs not in shortage limited to 105 shortage drugs with such NDCs. The unique patients measure reflects the average over 12 pre-shortage months for 30 primarily retail pharmacy-dispensed shortage drugs.

## Changes in Volume, Price, and Unique Patient Measures

Table 4.2 reports descriptive results for changes in volume, price, and unique patient counts for all shortage drugs examined in the sample--a drug form may have both shortage and non-shortage NDCs--around a shortage start month. Volume declined by 27.8 percent, price increased 16.6 percent, and unique patients declined by 10.8 percent on average, across shortage drugs. Volume reductions, price increases, and unique patient reductions were larger through the initial change period. Volume rebounded and prices declined through the subsequent recovery period, while unique patients experienced a modest, non-significant increase (see Table B.1 for initial change and subsequent recovery results). Overall, these results align with our earlier findings that, on average, shortages are associated with declines in volume and modest increases in price (Mulcahy, et al. 2021). Interestingly, some shortages were associated with i*ncreases* in volume and *decreases* in price (see Figure B.1).

**Table 4.2. Changes in Volume, Price, and Unique Patient Measures Around Shortage Start Month**

| | Median | Mean | 95% C.I. |
|---|---|---|---|
| **Absolute change** | | | |
| Volume (SUs, mils.) | -0.5 | -25.7 | (-53.3, 2.0) |
| Manufacturer price (per SU) | 0.0 | 1.3 | (-0.9, 3.5) |
| Unique patients (monthly) | -1,500 | -17,000 | (-67,000, 33,000) |
| **Relative change** | | | |
| Volume (%) | -35.4 | -27.8 | (-37.7, -17.8) |
| Manufacturer price (%) | 7.2 | 16.6 | (9.7, 23.4) |
| Unique patients (%) | -6.7 | 10.8 | (-25.4, 3.8) |

Source: Authors' analysis of IQVIA NSP and TPT data for study FDA shortages. Note: Analysis includes specific shortage NDCs for 117 shortage drugs for volume and price results and 30 primarily retail pharmacy-dispensed shortage drugs for mean unique patient results. Increases winsorized at 1 to preserve scale.

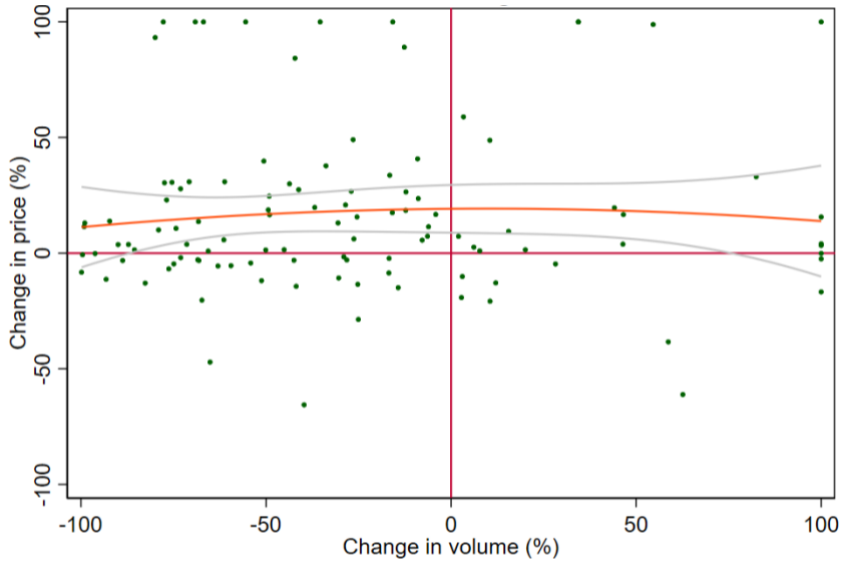
Across all study drugs, annual spending *decreased* by $1.2 billion (from $4.1 billion) because decreases in volume were proportionally larger than increases in prices.[10] Importantly, there remains a slight price increase for the available supply of shortage drugs, and the net implications for patients in terms of direct costs hinge on the prices for available substitutes as we discuss below.

Figure 4.1 compares changes in volume and price for each of the 117 shortage drugs in our analytic sample. Price increases did not systematically vary with the percentage of change in

[10] The decrease was $1.2 billion when measured around the shortage start month. Annual spending across all shortage drugs was $4.1 billion prior to shortage start and $2.9 billion after the start of the shortage.

volume. As described in Appendix B, we did find evidence that shortage drugs with larger initial declines in volume had larger initial increases in price.

**Figure 4.1. Change in Volume Versus Price Measured Around Shortage Start Month**




Source: Authors' analysis of IQVIA NSP data for study shortages. Notes: Orange line plots quadratic best fit line while grey lines mark the 95 percent confidence interval for the prediction. Analysis includes specific shortage NDCs for 117 shortage drugs. Increases winsorized at 1 to preserve scale.

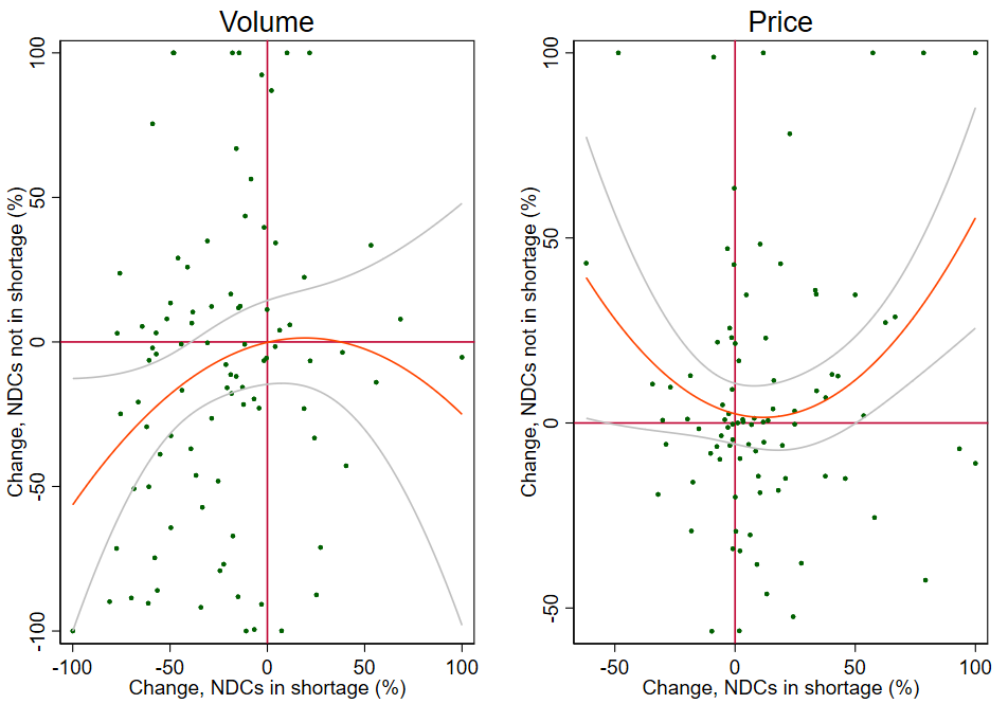
Within each shortage drug, we separately analyzed changes in volume and price for the specific NDCs in shortage versus other NDCs not in shortage (Table 4.3). To the extent patients, prescribers, and pharmacists substitute an available non-shortage NDC for a shortage NDC, a higher or lower price for the available substitute NDC may affect direct patient costs. On average, non-shortage substitute NDCs had smaller decreases in volume and increases in price through the start of shortages. Figure 4.2 compares changes in volume and price centered on the shortage start months for shortage versus non-shortage NDCs. We did not find a clear association between volume changes, suggesting non-shortage NDCs are not or are only sometimes substitutes for NDCs in shortage. We also did not find a clear association between the two changes in prices.

**Table 4.3. Volume and Price Summary Statistics**

| | Median | Mean | 95% C.I. |
|---|---|---|---|
| **Change in volume (millions of standard units)** | | | |
| *Shortage drugs, all NDCs* | -1.8 | -49.0 | (-95.8, -2.3) |
| Shortage drugs, shortage NDCs *(from Table 4.2)* | -0.5 | -25.7 | (-53.3, 2.0) |
| Shortage drugs, non-shortage NDCs | 0.0 | -27.1 | (-73.2, 19.1) |
| **Change in volume (% of pre-shortage level)** | | | |
| *Shortage drugs, all NDCs* | -28.5 | -22.9 | (-32.2, -13.5) |
| Shortage drugs, shortage NDCs *(from Table 4.2)* | -35.4 | -27.8 | (-37.7, -17.8) |
| Shortage drugs, non-shortage NDCs | -22.1 | -17.1 | (-30.0, -4.4) |
| **Change in price (dollars per standard unit)** | | | |
| *Shortage drugs, all NDCs* | 0.0 | 3.3 | (-0.2, 6.7) |
| Shortage drugs, shortage NDCs *(from Table 4.2)* | 0.0 | 2.2 | (-0.3, 4.7) |
| Shortage drugs, non-shortage NDCs | 0.0 | 0.6 | (0.5, 0.7) |
| **Change in price (% of pre-shortage level)** | | | |
| *Shortage drugs, all NDCs* | 7.3 | 15.1 | (7.8, 22.5) |
| Shortage drugs, shortage NDCs *(from Table 4.2)* | 7.2 | 16.6 | (9.7, 23.4) |
| Shortage drugs, non-shortage NDCs | 3.7 | 11.7 | (10.9, 12.4) |

Source: Authors' analysis of IQVIA NSP data for study shortages. Notes: Results cover 117 shortage drugs except for specific NDCs not in shortage limited to 105 shortage drugs with such NDCs. Results not presented for unique patients because the TPT data is at the product rather than NDC level (therefore the specific NDCs in shortage cannot be identified). Increases winsorized at 1 to preserve scale.

**Figure 4.2. Price and Volume Changes for Shortage Drugs, Specific NDCs in Shortage and Not in Shortage**




Source: Authors' analysis of IQVIA NSP data for study shortages. Notes: Orange line plots quadratic best fit line while grey lines mark the 95 percent confidence interval for the prediction. Analysis includes shortage NDCs for 117 shortage drugs. Increases winsorized at 1 to preserve scale.

## Number of Americans Affected by Shortages

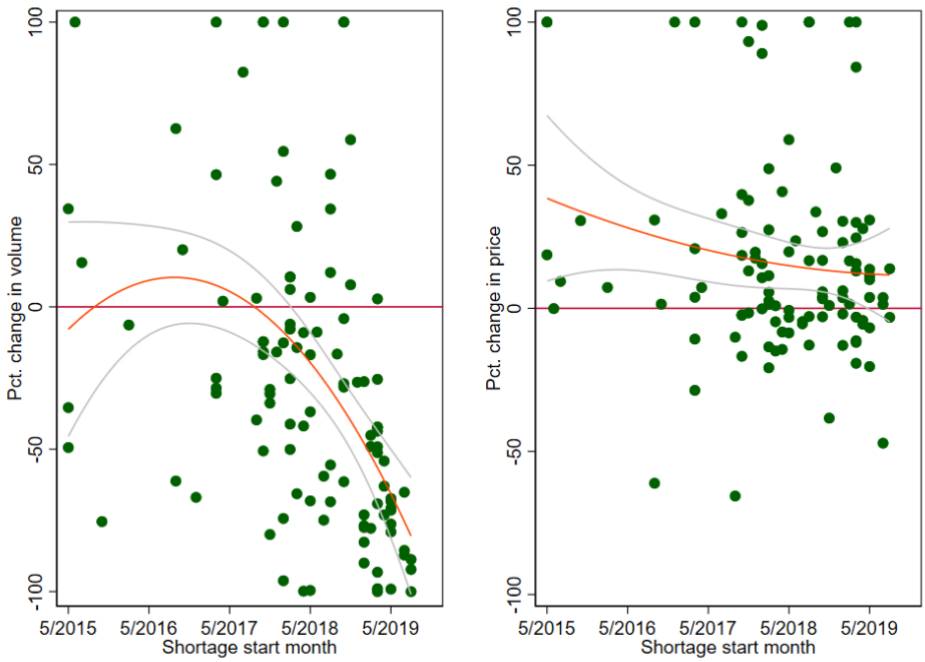
We did not have sufficient data to address this question. The 30 study shortage drugs that were primarily dispensed through retail channels had an average of about 20 million unique patients with fills monthly in the pre-shortage period, counting patients multiple times if they had prescriptions for multiple shortage drugs. The number of unique patients declined by 10.8 percent, or by about 510,000 patients monthly, around the shortage start month. It is not clear how many consumers were "affected" by the shortage in that they accrued higher or lower direct and indirect costs than normal even if they ultimately obtained the shortage drug or a substitute.

## Differences Over Time and By Drug Category

### *Over time*

Figure 4.3 plots the percentage of change in volume and price changes around the shortage start month against the start month for each shortage.

**Figure 4.3. Volume and price changes for shortage drugs versus shortage start month**




Source: Authors' analysis of IQVIA NSP data for study shortages. Notes: Reported changes are measured around the shortage start month. Orange line plots quadratic best fit line while grey lines mark the 95 percent confidence interval for the prediction. Analysis includes shortage NDCs for 117 shortage drugs. Increases winsorized at 1 to preserve scale.

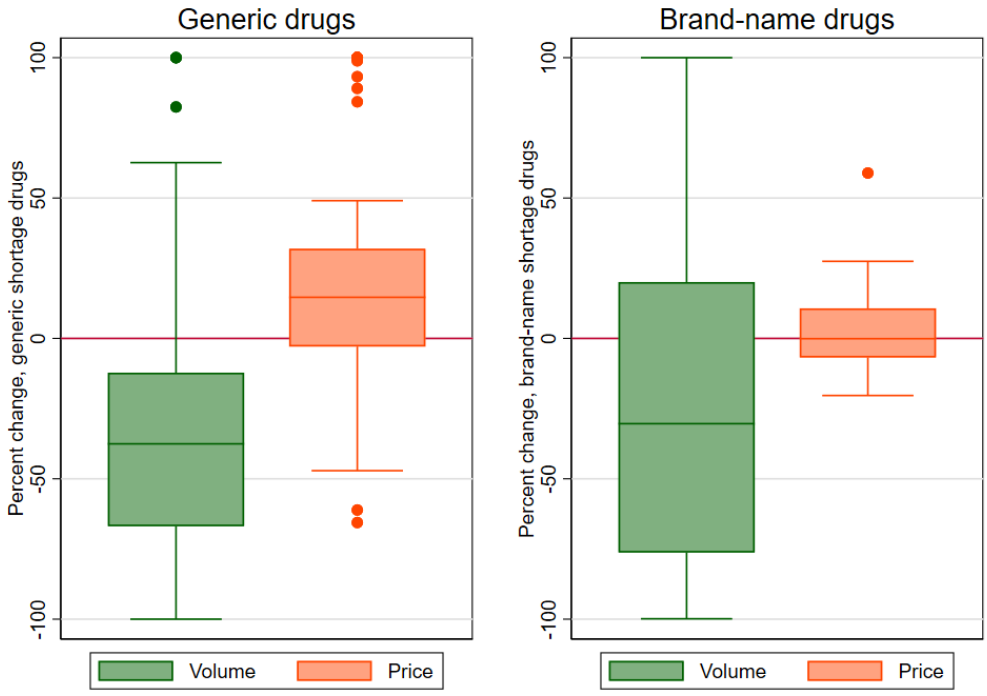
Due to the nature of our FDA extract, it is important to note that the composition of shortages changes over time, and that as a result the trends shown in Figure 4.3 should be interpreted with caution. More specifically, the FDA database extract includes active shortages and shortages resolved within the past six months as of March 2020. Analysis of the full FDA database, including historical shortages, would likely include additional earlier shortages with relatively larger reductions in volume. With that limitation in mind, Figure 4.3 shows larger average declines in volume for shortages starting more recently and relatively stable average changes in prices.

### *By brand vs. generic status*

We found shortage drugs that were primarily generic vs. primarily brand-name had relatively similar median percentage reductions in volume (with medians of 37.6 percent and 30.4 percent, respectively; Figure 4.4). However, the distribution for volume changes for brand-name drugs was wider, with relatively more brand-name drugs rebounding quickly after the start of shortages. This might be the result of stronger financial incentives (specifically, larger margins) to recover from shortages for brand-name versus generic drugs. We found price increases were

more common for generic drugs than for brand-name drugs. The median price increase for generic drugs was 14.6 percent compared to 0 percent for brand-name drugs.

**Figure 4.4. Volume and Price Changes for Generic Versus Brand-name Drugs**




Source: Authors' analysis of IQVIA NSP data for study shortages. Note: Increases winsorized at 1 to preserve scale. Analysis includes shortage NDCs for 117 shortage drugs.

### *By distribution channel*

On average, 38 percent of shortage drug volume measured in standard units reached patients through retail pharmacies, compared to 33 percent from hospitals and 29 percent from "other" including other facility-based settings. However, the median retail volume share was much lower at 5 percent, suggesting a small number of primarily retail-dispensed shortage drugs had very large volume in standard units.

Shortage drugs with more than 80 percent of volume dispensed through the retail channel had relatively larger reductions in volume using the change around the shortage start month timeframe (66 percent) compared with shortage drugs with more than 80 percent of volume dispensed primarily through the hospital channel (55 percent) or primarily through another channel (29 percent). Shortage drugs primarily dispensed via the retail channel had the largest relative increases in manufacturer prices (14 percent) compared with smaller increases for primarily hospital-dispensed drugs (1 percent) and all other drugs (5 percent).

## Differences By Patient Age and Gender

Table 4.4 compares changes in the number and percentage of patients filling shortage drugs by age. On average, younger adults were the smallest proportion of consumers with pre-shortage pharmacy fills, followed by children, with adults over 45 being the largest proportion. After shortage began, adults ages 45–54 faced the largest average decline in unique patients with fills (14.0%).[11] The decrease in unique patients was smaller, 9.3%, for adults aged 65 and older.

Table 4.5 compares changes in the proportion of patients filling shortage drugs by gender. On average, female and male patients experienced similar declines in fills; neither mean decrease was statistically distinguishable from zero.

**Table 4.4. Changes in Mean Number of Patients by Age**

| | Mean patients/change | 95% C.I. |
|---|---|---|
| **Pre-shortage number of monthly patients by age group (thousands)** | | |
| Age 0 to 17 | 43.3 | (3.7, 83.0) |
| Age 18 to 24 | 20.2 | (1.0, 39.4) |
| Age 25 to 34 | 51.0 | (3.0, 98.9) |
| Age 35 to 44 | 71.9 | (18.2, 125.5) |
| Age 45 to 54 | 112.0 | (18.2, 205.7) |
| Age 55 to 64 | 154.3 | (16.4, 292.2) |
| Age 65 to 85 | 206.2 | (40.6, 371.8) |
| Unknown age | 1.3 | (0.5, 2.1) |
| Total | 652.1 | (165.4, 1,138.8) |
| **Percent change by age group (%)** | | |
| Age 0 to 17 | 0.5 | (-24.0, 24.9) |
| Age 18 to 24 | -5.4 | (-22.4, 11.6) |
| Age 25 to 34 | -9.8 | (-24.7, 5.0) |
| Age 35 to 44 | -10.6 | (-25.0, 3.7) |
| Age 45 to 54 | -14.0 | (-27.1, -1.0) |
| Age 55 to 64 | -11.8 | (-24.1, 0.5) |
| Age 65 to 85 | -9.3 | (-21.3, 2.8) |

[11] While that one decrease was statistically distinguishable from zero, none of the changes for other age groups in Table 4.4 were.

| | Mean patients/change | 95% C.I. |
|---|---|---|
| Unknown age | -15.0 | (-73.6, 43.5) |
| **Total** | 10.8 | (-25.4, 3.8) |

Source: Authors' analysis of IQVIA TPT data for study FDA shortages. Note: Analysis reflects 30 primarily retail pharmacy-dispensed shortage drugs for mean unique patient results. Changes are measured around the shortage start month. C.I. is confidence interval. Only the change for adults aged 45 to 43 was statistically significant at p=0.035.

**Table 4.5. Changes in Mean Number of Patients by Gender**

| | Mean Number of Patients per Month | 95% C.I. |
|---|---|---|
| **Pre-shortage number of monthly patients by gender (thousands)** | | |
| Male | 307.3 | (491.3, 565.5) |
| Female | 352.8 | (119.9, 585.7) |
| Total | 652.1 | (165.4, 1,138.8) |
| **Percent change by gender** | | |
| Male | -10.2% | (-24.4, 4.0) |
| Female | -10.3% | (-25.1, 4.5) |
| Total | -10.8% | (-25.4, 3.8) |

Source: Authors' analysis of IQVIA TPT data for study FDA shortages. Note: Analysis reflects 30 primarily retail pharmacy-dispensed shortage drugs for mean unique patient results. Changes are measured around the shortage start month. None of the changes were statistically significant.

## Summary of NSP Analysis

Our results suggest shortage drugs typically experience declines in volume, modest increases in price, and some disruptions in reaching unique patients. In general, quantifying these changes over the longer term washed out some effects centered right around the onset of the shortage. Furthermore, these general findings do not apply to every shortage: volume increased and prices decreased for some shortages.

We found some differences in results depending on drug and patient characteristics. Generic shortage drugs had larger increases in prices than brand-name drugs. We also found that older consumers (ages 65-85) represented 31 percent of unique patients filling prescriptions for retail-dispensed drugs that went into shortage which was the largest share across age groups. However, only adults aged 45 to 54 had a statistically significant decrease in the share of monthly patients with fills (14 percent). We were not able to comprehensively assess trends in utilization using the data available for this study.

Most patients have prescription and medical insurance to cover drug costs, other than coinsurance and out-of-pocket costs during deductible phases. However, conceptually, a 17 percent higher manufacturer price could translate into some effects on consumer costs, either through higher out-of-pocket costs on the margin or through higher overall drug spending and therefore potentially higher premiums in the future. The magnitudes of these changes in response to a single drug shortage is likely negligible on average.

As noted in the Chapter One, the NSP data have limited relevance to amounts actually paid by patients. The 17 percent average increase in manufacturer price is relatively modest, particularly when considering broader inflation in drug prices over the study period. For comparison, the growth in the pharmaceutical preparation producer price index from January 2016 to December 2020, the span of our IQVIA NSP data extract for this study, was also 17 percent, suggesting that manufacturer prices for shortage drugs may not have increased much (or at all) in real terms (i.e., after accounting for inflation). Furthermore, for brand-name drugs, rebates and other discounts increased over this period, leading to potentially lower net prices (IQVIA, 2021).

## Summary of Illustrative Case Studies

One key driver of the overall changes in patient costs is the availability and characteristics of substitutes. The NSP results described in this chapter cover all 117 shortage drugs and, in some analyses, changes for the specific shortage NDCs versus non-shortage NDCs. However, other forms of shortage drugs and substitutes for shortage drugs were not included. Appendix C contains detailed results from our set of illustrative case studies where we compare changes in volume and prices for both shortage drugs and for their substitutes. We found the volume of substitute drugs increased over most intervals, most notably by 13 percent during the recovery period. This suggests patients are switching to substitute drugs in at least some cases. The larger increase during the recovery period could indicate a ramp-up period needed by the manufacturers of substitute drugs to increase their supply. We found manufacturer prices for substitutes typically remained about the same as those prior to the shortage, except for a decrease during the recovery period (median and mean of 6 percent and 15 percent, respectively). These delayed increases may again indicate a lag in pricing responses by the manufacturers of substitutes.

Our 5 illustrative case studies help further describe the wide range of potential shortage impacts. The shortage for belatacept (brand-name Nulojix, an immunosuppressant used to prevent rejection in patients receiving kidney transplants) stemmed from increasing demand and issues around a manufacturing change. We found volume increased over time through the onset of the shortage and over the long-term, which is consistent with increasing demand, while manufacturer prices remained flat. For carbidopa/levodopa (a generic drug used to treat Parkinson’s disease), prices for both shortage and substitute drugs were flat or decreasing over time. We observed substantial increases in manufacturer price (by roughly two-thirds) for

heparin NDCs in shortage and large changes in in manufacturer prices for non-shortage heparin NDCs. However, most heparin is used in the inpatient setting where consumers are typically shielded from immediate cost increases.

# 5. Discussion and Conclusion

## Summary of Key Findings

While there are many conceptual links between drug shortages and patient costs, we expect the likelihood and magnitude of these effects are modest for most shortages. The most direct effect of drug shortages on costs to the overall health care system is higher prices for shortage drugs. We found manufacturer prices increased only slightly, on average, for shortage drugs, and we expect that complex and interrelated drug supply chain, payment, and coverage factors will shield most patients from these increases, at least in the short term. We also found declines in the overall number of patients with fills for shortage drugs that were primarily retail-dispensed. Compared with other ages in the U.S. population, older adults experienced the smallest declines in the number of patients with fills, suggesting either that they have a more inelastic (i.e., less price-sensitive) demand for these drugs or that prescribers are possibly rationing based on patients' health needs.

Other potential links between drug shortages and patient costs are context-specific and difficult to assess holistically. Whether switching to substitutes increases or decreases patient direct costs for drugs depends on the price of appropriate substitutes relative to the shortage drug. The important health implications of delaying prescription fills or switching to substitute drugs likely vary depending on disease, the effectiveness and safety of shortage versus non-shortage drugs, and the characteristics of individual patients.

However, in some cases prices for shortage drugs increased substantially, and in others, the price of substitute forms or active ingredients might be much higher than the pre-shortage price for the shortage drug. There are narrower, specific scenarios in which these large changes could have more-direct impacts on patient costs, and we recommend policymakers focus on addressing these scenarios. First, patients without drug and/or medical coverage, with relatively less generous drug and/or medical coverage (e.g., plans with high deductibles), or who are responsible for a fixed share of prices charged by pharmacies (e.g., through coinsurance) will likely be more exposed to increases in prices for shortage and substitute drugs than those with coverage. Second, shortage drugs with few close substitutes that are used to treat serious conditions will likely have more direct and more severe implications on patient health, with likely implications for downstream spending on medical care, declines in health, and potentially on patient mortality.

## Policy Implications and Mitigation Strategies

We found some evidence that patients, prescribers, and pharmacists pivot to available versions of shortage drugs and to broader substitutes (when available) in response to shortages.

Furthermore, we found that the volume of substitutes sold after the start of a shortage increases, likely due to strategic responses by manufacturers and intervention by policymakers. In general, substitutes were about the same price on average as shortage drugs. These findings highlight various mechanisms within our manufacturing and health care delivery systems that can be used to mitigate the effects of drug shortages.

The feasibility of relying on substitutes and industry response to mitigate the effects of shortages after they have already occurred hinges on a robust manufacturing base and access to timely information on trends in supply and demand. The FDA has an important role in collecting information on shortages from manufacturers and communicating information to industry and the public. As discussed in our earlier report (Mulcahy, et al., 2021), the FDA does not always have complete information about the context around drug supply chains or shortages. The FDA is limited by statute to the information that it can collect from manufacturers,[12] and voluntary reporting beyond required information might not be comprehensive. Furthermore, while prescription drug distributors, pharmacies, and providers might have insight into their own supply and demand for drugs, this information is not collected or analyzed by FDA in a comprehensive way. As a sign of the incomplete information available to the federal government, two recent Executive orders require the U.S. Department of Health and Human Services to collect and report new information related to prescription drug supply chains, both in general and specifically in response to the COVID-19 pandemic (Biden, 2021a; Biden, 2021b).

Both industry and policymakers will benefit from more-complete and more-detailed information about drug shortage causes. As an example, FDA may be able to intervene earlier to coordinate increases in manufacturing for shortage drugs or substitutes if it received earlier notification and more context around the nature of the shortage and expected duration. Congress and/or FDA could weigh the advantages and disadvantages of further public reporting requirements related to shortages, including more-detailed information on shortage causes.

There are several other potential strategies and policy tools available to the FDA to prevent and mitigate drug shortages. These include exercising regulatory discretion to waive manufacturing, safety, or quality requirements, or to extend expiration dates; importing drugs into the United States that are otherwise not approved for sale; and coordinating manufacturer responses. By preventing or mitigating, these tools also have the potential to limit the implications of shortages on costs for consumers.

## Limitations and Next Steps

As discussed in Chapter One, our empirical analysis used market-level data from IQVIA's NSP and TPT data, which were the only data available at the time of this analysis. The NSP and

[12] Currently, the specific categories of shortage causes reported publicly in FDA's shortage database are specifically defined in the Food and Drug Administration Safety and Innovation Act (Pub. L. 112–144, 2012).

TPT data describe overall U.S. changes in manufacturer spending, volume, and unique patients for specific drugs. While NSP and TPT data are useful for tracking national trends in drug utilization, they have relatively limited utility in quantifying the impact of drug shortages on patient costs. More specifically, these data cannot be used to directly assess patient-level responses to shortages, such as delayed prescription fills, reductions in adherence, or switches to alternative drugs. Furthermore, these data do not disaggregate amounts paid for drugs specifically by consumers, which is crucial to understand when estimating the direct cost of shortages to consumers. Finally, these data cannot be used to estimate costs associated with downstream changes in health care utilization associated with shortages.

We did not use a comparison group of non-shortage drugs for these analyses. As we describe in Chapter Four, our estimated average increase in prices for shortage drugs was less than the increase in inflation over the study period, suggesting that the change in real terms may be closer to zero, or even a decrease. Future analyses could use a comparison group of matched non-shortage drugs for reference.

We recommend further claims-based analysis to estimate associations between drug shortages and patient costs. An ideal study would use a combination of medical and prescription claims to assess the relationship between shortages and each outcome that we list in Table 5.1. There are several important considerations related to the selection of claims data for this analysis. Analyses would ideally use adjudicated claims where final patient out-of-pocket amounts are recorded. There would also ideally be a clear linkage between medical and prescription claims; comprehensive coverage across service types, providers, and even payers for the health care services; and prescriptions received by individual payers. While state all-payer claims databases could be one appealing source of data to support future analyses, these databases are limited in geographic scope and have their own limitations. Other commercially available products, Medicare claims, or data from multi-payer claims aggregators such as IQVIA and Symphony Health might also be appropriate.

**Table 5.1. Outcomes of Interest for Potential Future Analyses**

| Outcome | Approach |
|---|---|
| Number of patients with fills dispensed the shortage drug or alternative medications. | • Descriptive analysis comparing dispenses of shortage drugs and alternatives among those with relevant diagnoses from before to after shortage occurrence. For medical claims-based studies, can limit population to those with specific condition. |
| Proportion Days Covered (PDC) of a shortage drug | • Interrupted time series analysis comparing monthly PDCs of shortage drugs meant for chronic use from before to after shortage occurrence<br>• Difference-in-differences estimation comparing monthly changes in PDCs for shortage drugs compared to matched non-shortage drugs. |

| Outcome | Approach |
|---|---|
| Rate of patients who switched from shortage drug to alternative medications | • Descriptive analysis comparing dispenses of shortage drugs and alternative medications from before to after shortage occurrence among the patients initially using the shortage drug. |
| Average out-of-pocket (OOP) costs per patient for shortage drugs | • Interrupted time series analysis comparing monthly OOP costs per patient for shortage drugs from before to after shortage occurrence.<br>• Difference-in-differences estimation comparing monthly changes in patient OOP costs for shortage drugs compared to matched non-shortage drugs.<br>• Note all medical claims-based analyses will have to use charges. While there is only a tangential relationship between charges and amounts paid by patients, there may be a way to impute a patient cost amount. |
| Average out-of-pocket (OOP) costs per patient for shortage drugs or alternative medications | • Descriptive analysis comparing monthly OOP costs per patient for shortage drugs and alternative medications from before to after shortage occurrence.<br>• Note some medical claims-based analyses will have to use charges. While there is a only a tangential relationship between charges and amounts paid by patients, there may be a way to impute a patient cost amount. |

## Conclusion

In conclusion, while drug shortages have many conceptual links to patient costs, we found inconclusive evidence to suggest that the effects are typically large in magnitude. We found drug shortages were associated with a median 35 percent reduction in volume and a median 9 percent reduction in unique patients with fills measured around the start of the shortage. However, we also found that utilization rebounds in the longer term and that prescribers, patients, and/or pharmacists shift to substitutes in response to shortages (when available). We found manufacturer drug prices increased by a median of 7 percent. However, manufacturer prices are neither the net prices paid by insurers, nor the out-of-pocket amounts paid immediately by patients. Important features of insurance benefit design and the mechanics of payment drugs and payment for broader health care services likely shield patients from increases in manufacturer prices resulting in immediate or any changes in out-of-pocket costs except in specific scenarios (e.g., those without coverage, those responsible for coinsurance, or those in the deductible phase). We did not empirically assess several shortages effects with potentially important implications for consumer costs, including adverse health outcomes. We recommend further study, including analyses using claims data, to better describe the full effects of drug shortages on consumer costs and patient outcomes.

# Appendix A: Empirical Analysis Data and Methods Details

## Additional FDA Drug Shortage Database and Sample Details

### *Handling of discontinuations*

We excluded shortages marked as discontinuations in the FDA database that had the same "Initial Posting Date" and "Discontinuation Date." These entries appeared to report specific NDC-level discontinuations reported by manufacturers rather than broader drug shortages. Discontinued products can in some cases have important implications for prescribers, health systems, and patients. However, manufacturers often discontinue specific package-level NDCs (e.g., 1000 tablet bottles of a drug) while supplying related package-level NDCs (e.g., 100 tablet bottles of the same drug). As a result, we opted to exclude these discontinuations from our analysis (n=631). We retained shortages flagged as discontinuations where the duration of the shortage was greater than one day. In these cases, we assumed the discontinuation followed a shortage period (n=48).

### *Separating and correcting unique NDCs*

Some FDA database records listed multiple NDCs. We separated these NDCs into separate observations so that we could link the FDA database to the NDC-level IQVIA NSP data described below. Except for the NDC field, the separate NDC-level records retained all of the information associated with the original shortage-level record. We made a small number of corrections to the FDA data, including replacing incorrect NDCs after cross-referencing to reference files, such as the Wolter Kluwer's Medi-Span file (n=3), removing duplicate records (n=4), and removing shortages that appear to occur entirely within the time frame of another shortage (n=3). The final FDA analytic data set included 1,650 NDC-level records.

## Case Study Selection

From the 117 unique shortage drugs available in the NSP data, we identified potential illustrative case studies as those meeting the following criteria:

- a shortage duration of longer than 30 days to increase the odds of finding a measurable change in volume and price in our extracted monthly NSP and TPT data
- at least some sales in the year prior to the shortage start date (otherwise there would be no pre-shortage data to analyze)
- primarily dispensed through the retail pharmacy channel or administered by practitioners to facilitate potential future links to claims data; this involved several related criteria:

- primarily pharmacy-dispensed during the year prior to shortage start date with less than 10% of total volume dispensed through each of the other three channels;
- or, for drugs not primarily pharmacy-dispensed both of the following:
  - no more than 25 percent of combined office/clinic and hospital volume dispensed via the hospital channel. A share of greater than 25 percent may indicate drugs primarily used in the inpatient setting, which cannot be easily analyzed using claims.
  - no more than 20% of volume dispensed via the combined "other" category (i.e., not dispensed in the pharmacy, office, or hospital).

A total of 82 shortage drugs met these criteria. We convened a group of two RAND physicians and one pharmacist to identify the therapeutic alternatives for the 82 shortage drugs using their clinical expertise. Following identification of alternatives, we further limited the sample shortage drugs to the following characteristics: (1) shortage drugs with therapeutic alternatives that are predominantly also prescription drugs; (2) shortage drugs and substitutes that have relatively narrow and overlapping therapeutic indications; (3) shortage drugs and substitutes primarily dispensed via the same channel(s). This limited the sample to shortage cases and treatment alternatives that were either all pharmacy-dispensed or all physician-dispensed rather than a mixture of pharmacy- and physician-dispensed.

Following the identification of shortage drugs with the above characteristics, we then selected illustrative case studies that differed in terms of the following characteristics:

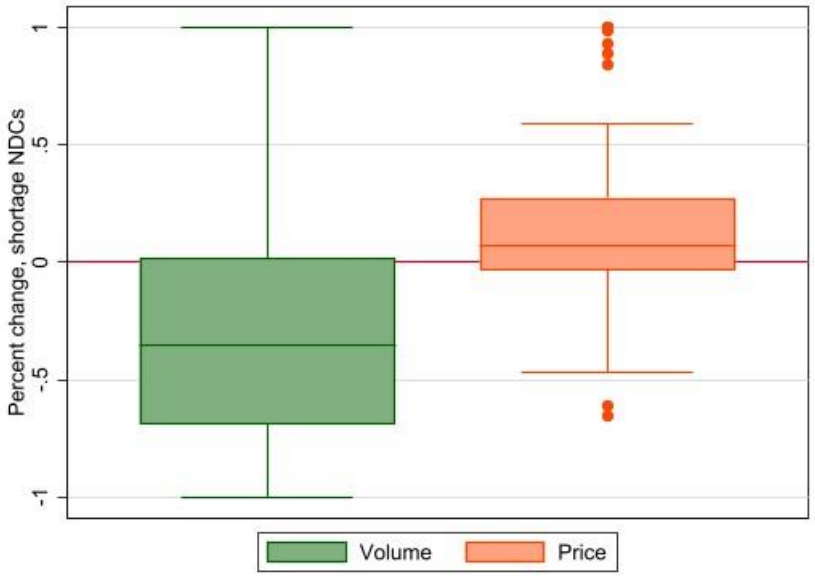
- shortage duration
- shortage cause (when known)
- scope of manufacturers and NDCs involved relative to the total count of manufacturers and NDCs for the drug
- therapeutic area
- designation as an FDA-listed "Essential Medicine"[13]
- main use (i.e., indication)
- measured change in volume from the year prior to the shortage to the year after the shortage (using the change around the shortage start month approach)
- measured change in price from the year prior to the shortage to the year after the shortage (using the change around the shortage start month approach).

[13] For a complete list, see the "Drug and Biologic Essential Medicines, Medical Countermeasures, and Critical Inputs for the List Described in Section 3(c) of the Executive Order 13944 (FDA, 2020).

# Appendix B: Supplemental Results Exhibits

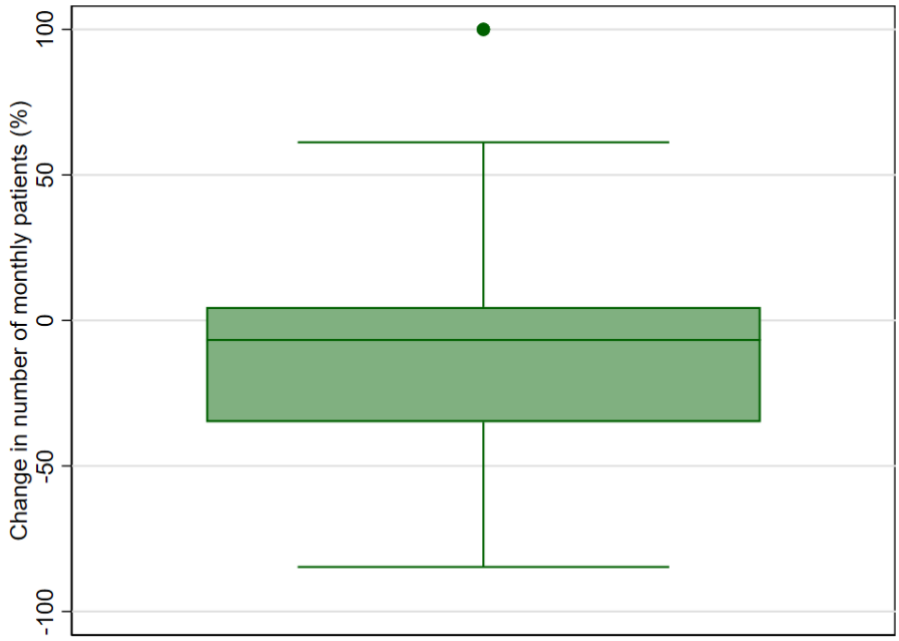
This appendix includes supplemental tables and figures. Figure B.1a illustrates the distribution of changes in volume and prices for shortage NDCs around the shortage start month. As described in our prior report, we observe counterintuitive *increases* in volume and *decreases* in price through the start of some shortages (Mulcahy, et al., 2021). These surprising changes could reflect measurement error in shortage start dates, responses from manufacturers and/or policymakers, and other factors. Declines in volume were greatest when measured over the initial decline period (see Figure B.2). Volume typically recovered subsequently. Figure B.1b illustrates changes in average number of unique patients per month around the shortage start month for drug shortages that were primarily dispensed through the retail channel. The number of unique patients declined by approximately 11 percent.

**Figure B.1a: Percentage of Change in Volume and Price Measured Around Shortage Start Month, Specific NDCs in Shortage Only**




Source: Authors' analysis of IQVIA NSP data for study shortages. Note: Increases winsorized at 1 to preserve scale. Analysis includes 117 shortage drugs. Axis values -1 and 1 represent -100 and 100%, respectively.

**Figure B.1b. Percent Change in Average Monthly Unique Patients Measured Around Shortage Start Month**




Source: Authors' analysis of IQVIA TPT data for study shortages. Analysis includes 30 primarily retail pharmacy-dispensed shortage drugs. Note: Increases and decreases winsorized at 100 percent to preserve scale.

Table B.1 reports mean and median changes in volume, price, and unique patients measured over three different intervals.

**Table B.1. Change in Volume, Price, and Unique Patient Measure Summary Statistics**

| | Median (%) | Mean (%) | 95% C.I. |
|---|---|---|---|
| **Volume** | | | |
| Around shortage start | -35.4 | -27.8 | (-37.7, -17.8) |
| Initial change | -50.1 | -51.6 | (-57.2, -43.5) |
| Subsequent recovery | 29.4 | 28.0 | (17.4, 38.5) |
| **Price** | | | |
| Around shortage start | 7.2 | 16.6 | (9.7, 23.4) |
| Initial change | 27.7 | 38.2 | (32.7, 46.6) |
| Subsequent recovery | -6.7 | -2.1 | (-9.1, 4.9) |
| **Average monthly unique patients** | | | |
| Around shortage start | -6.7 | 10.8 | (-25.4, 3.8) |

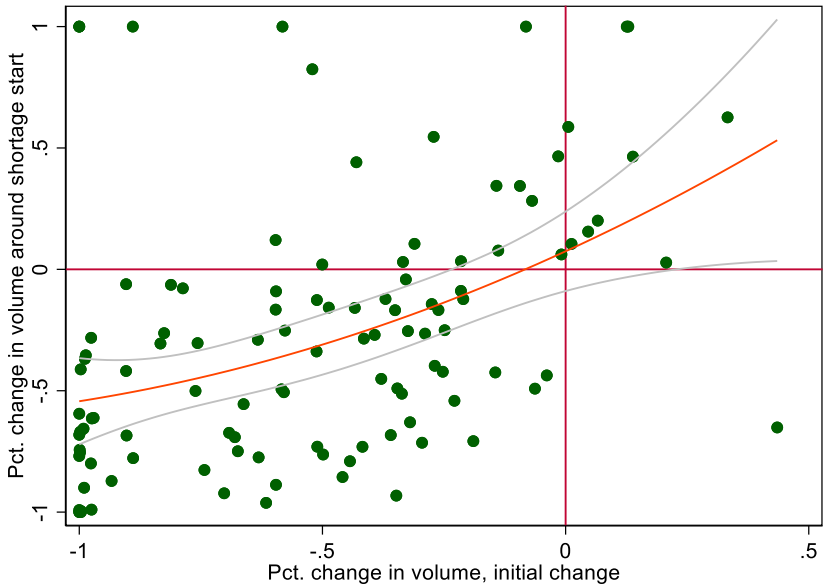
| | Median (%) | Mean (%) | 95% C.I. |
|---|---|---|---|
| Initial change | -4.4 | -7.0 | (-14.1, 0.0) |
| Subsequent recovery | -6.8 | -11.1 | (-25.7, 3.5) |

Source: Authors' analysis of IQVIA NSP and TPT data for study FDA shortages. Note: Analysis reflects 117 shortage drugs for volume and price results and 30 primarily retail pharmacy-dispensed shortage drugs for unique patient results.

We compared relative changes in volume, price, and unique patient measures against one another in a series of scatter plots to assess whether changes in outcomes varied systematically when measured over different intervals. Figures B.2, B.3, and B.4 compare volume, price, and unique patient measures, respectively, between the initial change versus subsequent recovery periods. Each plot includes a quadratic best fit line and 95 percent confidence interval. There is a clear but noisy relationship between the two volume measures (Figure B.2). Interestingly, volume changes around the shortage start month appear to often mask larger initial changes. Longer-term impacts of shortage might wash out when changes in volume and prices are measured over longer intervals.

The price measures are positively correlated when measured over different intervals and particularly between the initial change interval and around the shortage start month (Figure B.3). Changes in unique patient count, like changes in volume, appear more muted when measured around the shortage start month compared to over the initial change timeframe. Similarly, Figures B.5, B.6, and B.7 compare initial change versus subsequent recovery measures and illustrate similar relationships.

**Figure B.2: Change in Volume, Initial Change Versus Around Shortage Start Intervals**



Source for Appendix Figures B.1 through B.6: Authors' analysis of IQVIA NSP data for study shortages. Notes for Appendix Figures B.1 through B.6: Orange line plots quadratic best fit line while grey lines mark the 95 percent confidence interval for the prediction. Axis values -1 and 1 represent -100 and 100%, respectively.

**Figure B.3: Change in Price, Initial Change Versus Around Shortage Start Intervals**

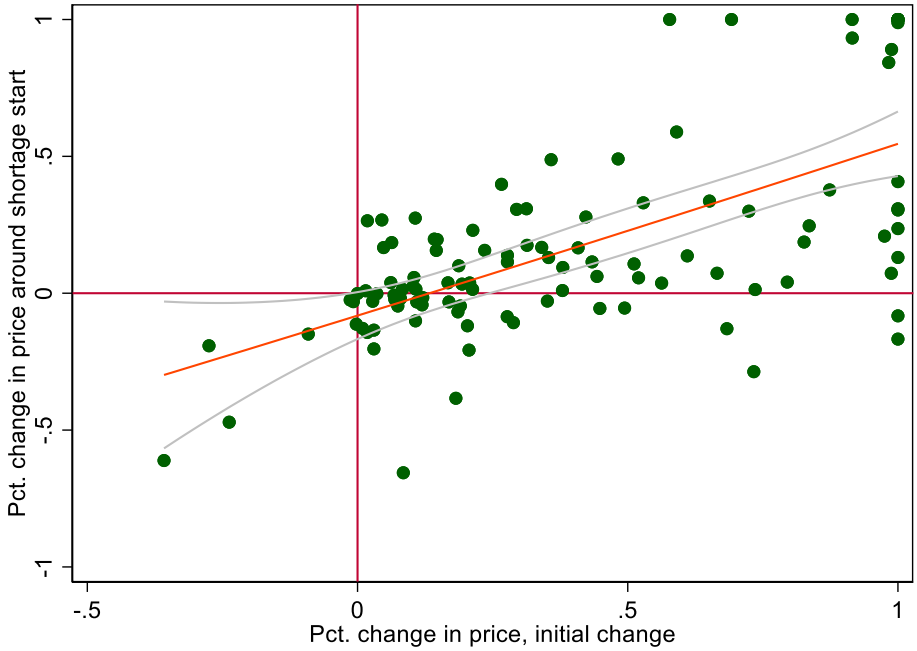



**Figure B.4: Change in Average Monthly Patients, Initial Change Versus Around Shortage Start Intervals**

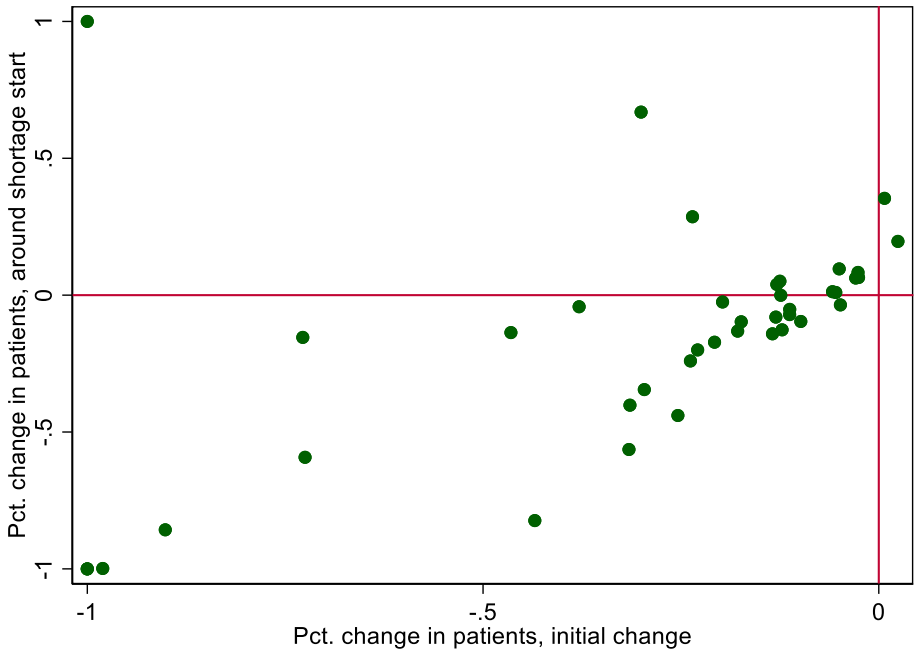


**Figure B.5: Change in Volume, Initial Change Versus Recovery Intervals**

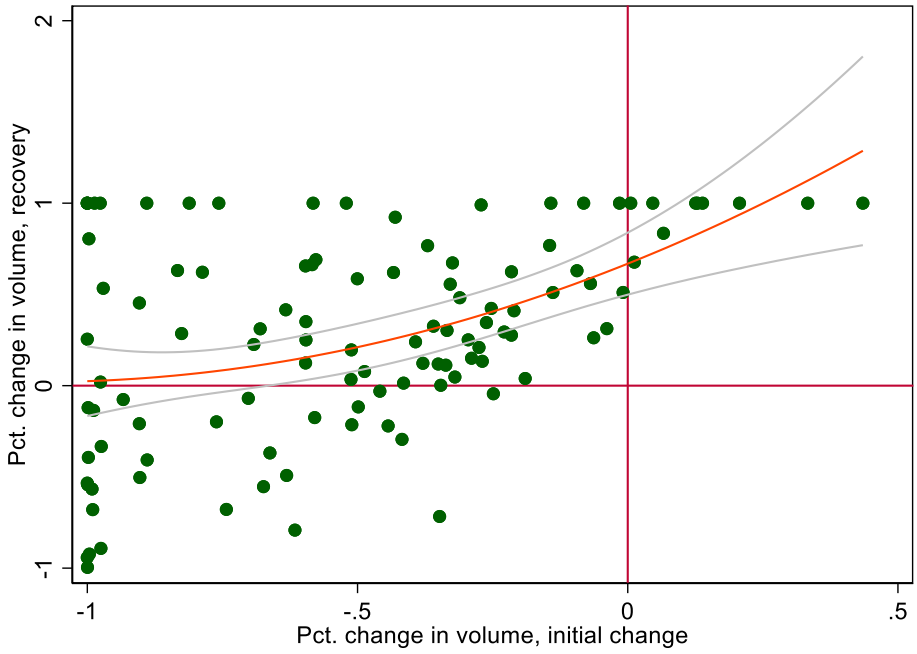



**Figure B.6: Change in Price, Initial Change Versus Recovery Intervals**

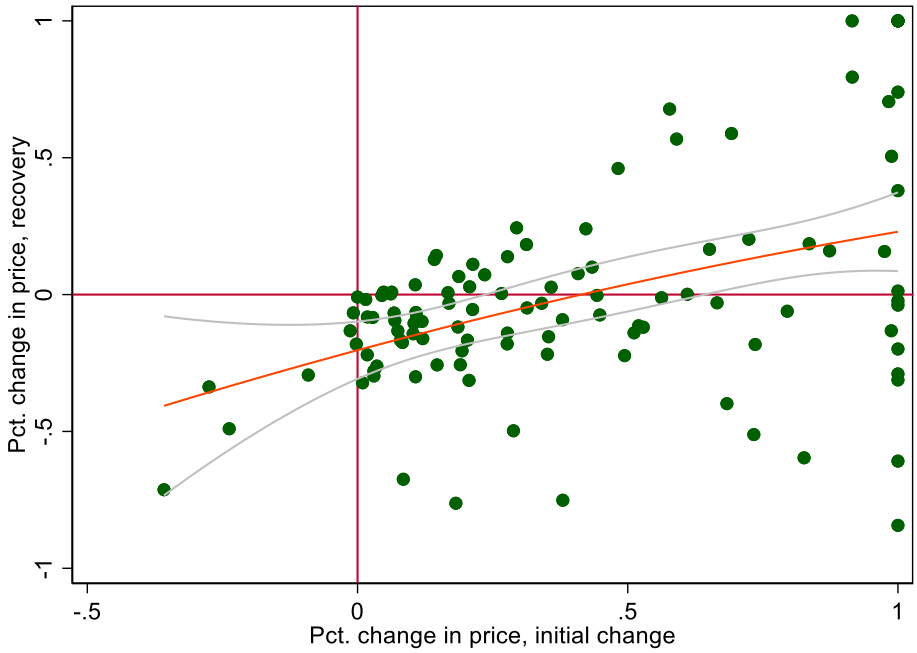


**Figure B.7: Change in Average Monthly Patients, Initial Decline Versus Recovery Intervals**

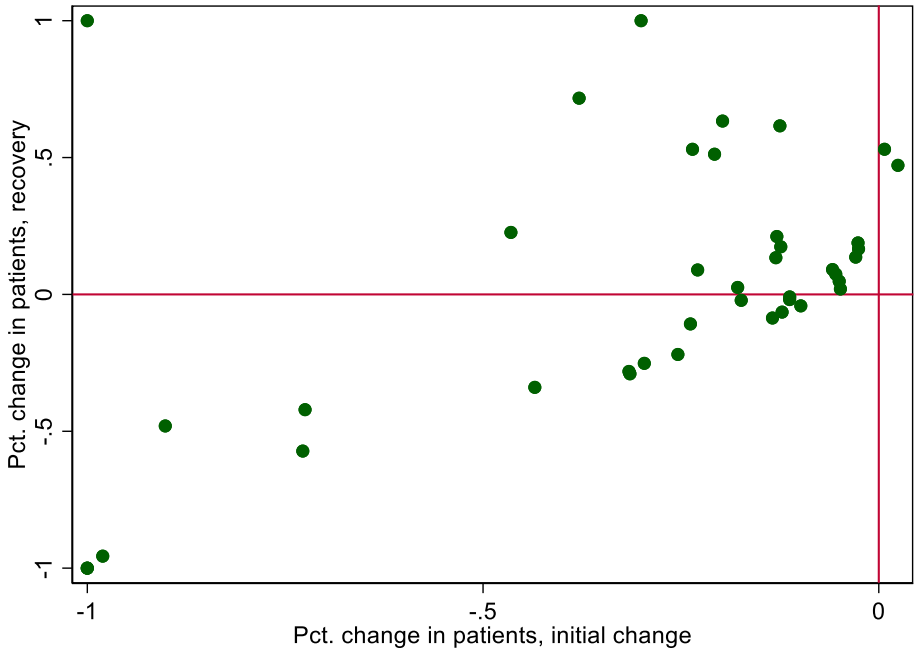
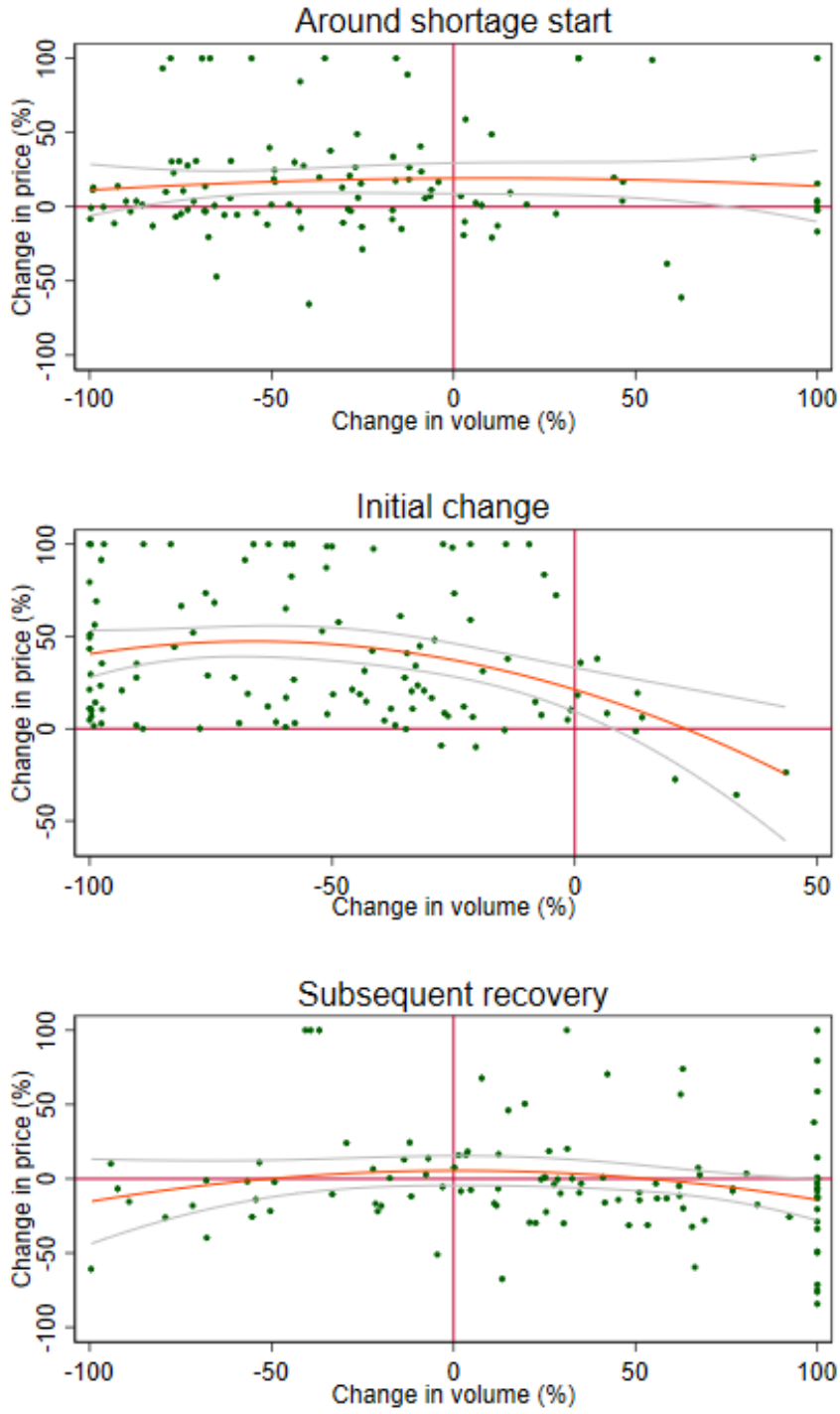



Figure B.8 compares changes in volume and price over three periods. Price increases do not scale with the change in volume when measured around the shortage start month or over the subsequent recovery time frame. However, there are larger increases in prices for shortages with larger initial reductions in volume.

Relationships between each volume and price measure are weak at best, with larger average price increases for shortages with larger relative declines in volume measured around the shortage start month and over the initial change interval. Changes in non-shortage NDC volume and price were not consistently associated with changes in shortage NDC volume and price, suggesting that responses to shortages vary across manufacturers, are influenced by policymakers, depend on market conditions, or other factors.

**Figure B.8: Relationships Between Pairs of Volume and Price Measures**




Source: Authors' analysis of IQVIA NSP data for study shortages. Notes: Orange line plots quadratic best fit line while grey lines mark the 95 percent confidence interval for the prediction.

# Appendix C: Illustrative Case Study Shortages

This appendix presents our results for analyses of shortage case studies in NSP and TPT data.

## Characteristics of Case Studies

We identified 26 active ingredients as case studies, listed in Table C.1. Twelve of these cases were oral solids, one was oral liquid, and nine were parenteral form. Most of the shortages extended across multiple manufacturers and NDCs. The reasons for shortages varied between issues with demand, manufacturing, delivery, active pharmaceutical ingredients. They covered a wide range of therapeutic classes, including ophthalmology, diabetes, hematology, cardiovascular, and psychiatry. The cases also varied by shortage duration, ranging from 143 to 1,253 days in shortage, with a median of 432 days.

**Table C.1: Case Study Characteristics**

| Active ingredient | Form | Class/use | Reason | Extent | Start date | Duration (days) |
|---|---|---|---|---|---|---|
| Alogliptin | AB | Diabetes | Demand | All manufs/NDCs | 8/14/2019 | 219 |
| Amphetamine-dextroamphetamine | AB | Psychiatry | API/demand | Some manufs/NDCs | 9/12/2019 | 190 |
| Asparaginase | FG | Hematology-oncology/pediatrics | NR | Single manuf/NDC | 10/14/2016 | 1253 |
| Belatacept | FG | Transplant | Demand | Single manuf/NDC | 3/6/2017 | 1110 |
| Buspirone | AB | Psychiatry | NR | Some manufs/NDCs | 11/21/2018 | 421 |
| Carbidopa-levodopa | AB | Neurology/Parkinson's | Manuf./discon. | Few manufs/NDCs | 9/27/2017 | 653 |
| Dorzolamide-timolol | N | Ophthalmology | NR | Some manufs/NDCs | 1/24/2018 | 786 |
| Epinephrine | FG | Pulmonary/Allergy | Delivery | Some manufs/NDCs | 5/9/2018 | 681 |
| Fludrocortisone | AB | Endocrinology/Metabolism | Manuf. | Some manufs/NDCs | 12/12/2018 | 238 |
| Fluvoxamine | AB | Psychiatry | API | Few manufs/NDCs | 2/5/2019 | 409 |
| Glimepiride | AB | Diabetes | API | Single manuf/NDC | 8/30/2018 | 471 |
| Heparin | FG | Hematology | NR | Few manufs/NDCs | 11/14/2017 | 858 |
| Hydroxyprogesterone | FB | Reproductive | NR | Some manufs/NDCs | 1/25/2019 | 190 |
| Ketamine | FG | Anesthesia | Demand | Some manufs/NDCs | 2/16/2018 | 764 |
| Ketorolac | FG | Analgesia/Addiction | Manufacturing | Some manufs/NDCs | 3/23/2018 | 721 |
| Latanoprost | N | Ophthalmology | NR | Few manufs/NDCs | 3/19/2019 | 367 |
| Leucovorin | FG | Oncology/peds. | Manuf. | Few manufs/NDCs | 10/19/2018 | 249 |
| Levetiracetam | AB | Neurology (seizures) | API | Some manufs/NDCs | 4/1/2019 | 354 |
| Methocarbamol | AB | Analgesia/Addiction | NR | Some manufs/NDCs | 8/17/2018 | 484 |
| Nelarabine | FG | Hematology | NR | Single manuf/NDC | 10/30/2018 | 434 |
| Nystatin | DE | Anti-infective | Manuf. | Some manufs/NDCs | 1/8/2019 | 430 |
| Olmesartan medoxomil | AB | Cardiovascular | API | Some manufs/NDCs | 3/12/2019 | 360 |
| Remifentanil | FG | Analgesia/Addiction; Pediatric | NR | Some manufs/NDCs | 2/6/2018 | 756 |
| Tacrolimus | AB | Transplant | NR | Some manufs/NDCs | 5/17/2019 | 309 |
| Trifluridine | N | Ophthalmology | API | Some manufs/NDCs | 10/29/2019 | 143 |
| Valsartan | AB | Antihypertensive ARB | Quality/manuf. | Some manufs/NDCs | 8/3/2018 | 579 |

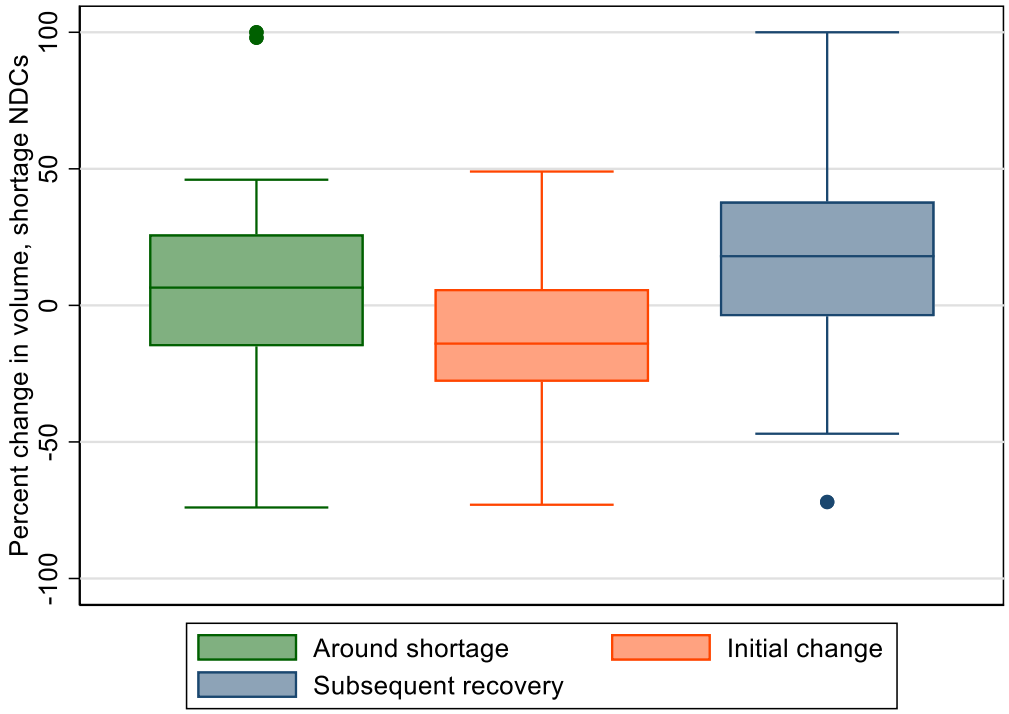
Notes: “Form” is form category as described in the methods section. “API” is active pharmaceutical ingredient. “Manuf” is manufacturer. “Discon” is discontinued. “NDCs” is national drug codes. “NR” is not reported.

Source: RAND analysis of FDA data.

## Changes in Volume and Price of Case Studies

The results of our NSP analysis of shortage case studies are consistent with the NSP analysis across all FDA-listed shortages. Figure C.1 is a box plot displaying the range of changes in volume by the following metrics: around shortage, initial change, and subsequent recovery. The around shortage and subsequent recovery plots were centered above zero, while the initial change plot was centered below zero. All plots had similar levels of wide variation. In terms of average changes, we also found declines in the initial change measure and increases in the around shortage and the subsequent recovery measures (Table C.1).

**Figure C.1 Distribution of Changes in Volume for Case Study Shortage Drugs**




Source: RAND analysis of FDA data linked to IQVIA NSP data. Note: Analysis limited to the 26 case study drugs for which we assigned substitutes.

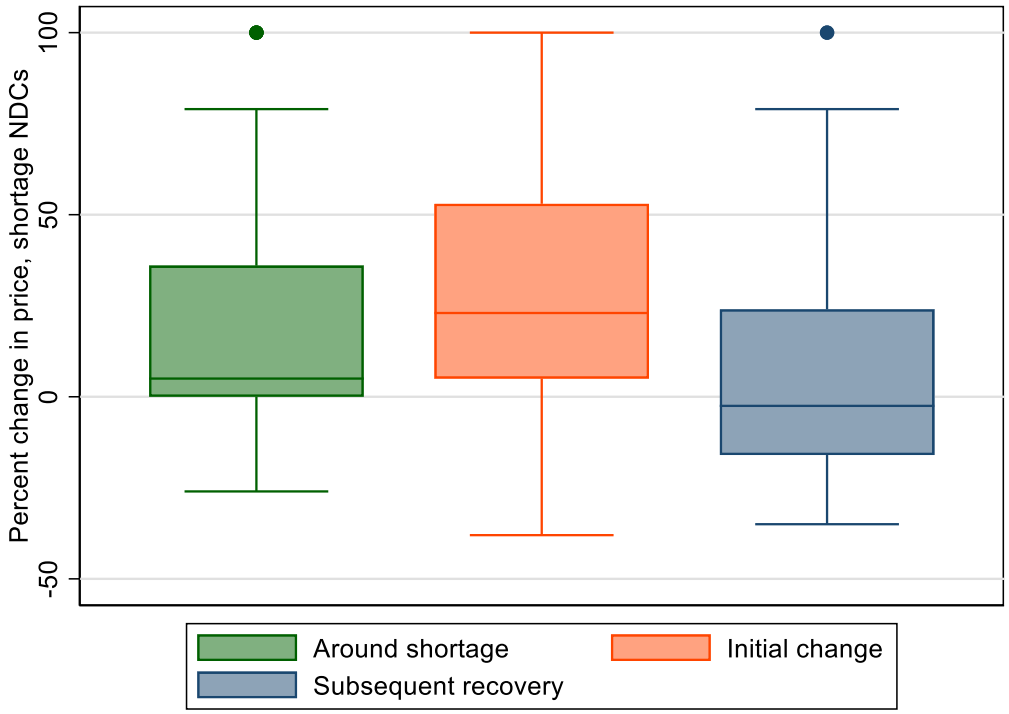
**Table C.2: Summary Statistics for Volume Changes, Case Study Shortage Drugs (%)**

| | Around shortage | Initial change | Subsequent recovery |
|---|---|---|---|
| Mean | 8.0 | -13.5 | 21.0 |
| Std. dev. | 41.2 | 28.4 | 44.1 |
| Median | 6.5 | -14.0 | 18.0 |

Source: RAND analysis of FDA data linked to IQVIA NSP data. Note: Std. dev is standard deviation. Note: Analysis limited to the 26 case study drugs for which we assigned substitutes.

Figure C.2 is a box plot displaying the range of changes in price by around shortage, initial change, and subsequent recovery. Around shortage and initial change plots were centered above zero, while subsequent recovery was centered below zero. All plots had wide variation. In terms of average changes, we found increases in all three measures (Table C.3).

**Figure C.2 Distribution of Changes in Price for Case Study Shortage Drugs**




Source: RAND analysis of FDA data linked to IQVIA NSP data. Note: Analysis limited to the 26 case study drugs for which we assigned substitutes.

**Table C.3: Summary Statistics for Price Changes, Case Study Shortage Drugs (%)**

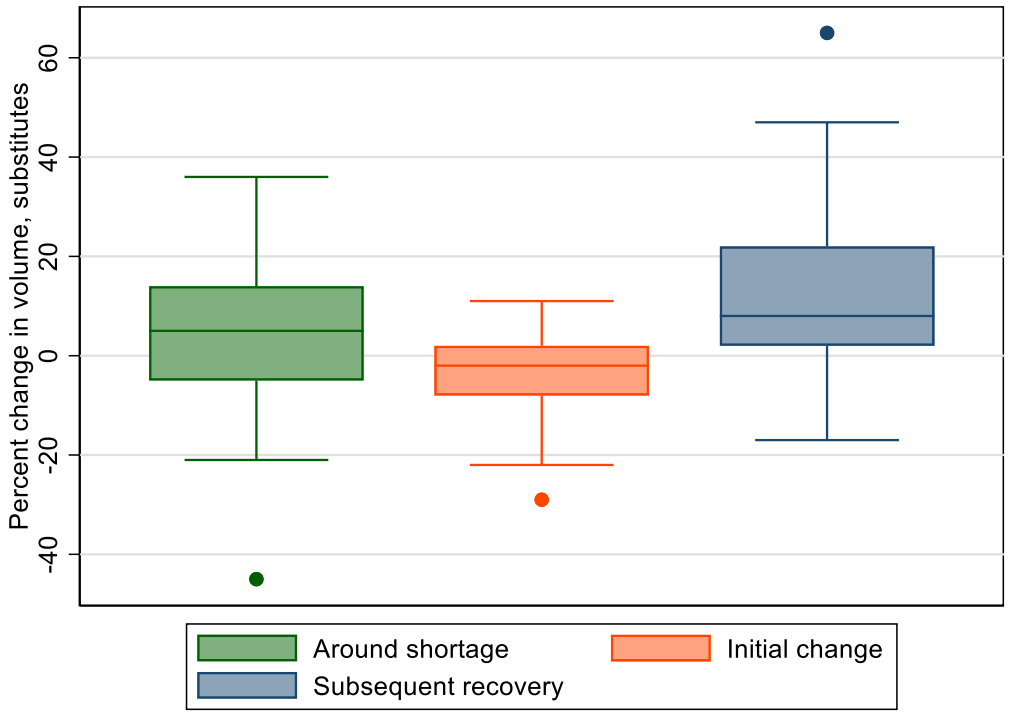
| | Around shortage | Initial change | Subsequent recovery |
|---|---|---|---|
| Mean | 21.3 | 28.8 | 8.0 |
| Std. dev. | 36.6 | 36.1 | 34.7 |
| Median | 5.0 | 23 | -2.5 |

Source: RAND analysis of FDA data linked to IQVIA NSP data. Note: Std. dev is standard deviation. Note: Analysis limited to the 26 case study drugs for which we assigned substitutes.

## Changes in Volume and Price of Substitutes

Figure C.3 is a box plot displaying the range of changes in substitute volume by around shortage, initial change, and subsequent recovery. The around shortage and initial change measures were centered close to zero, while subsequent recovery had a median increase in volume of 8.0%. In terms of average changes, we also found increases in the around shortage and subsequent recovery measures and a decrease in the initial change measure (Table C.4).

**Figure C.3 Distribution of Changes in Volume for Case Study Substitute Drugs**




Source: RAND analysis of FDA data linked to IQVIA NSP data. Note: Analysis limited to the 26 case study drugs for which we assigned substitutes.

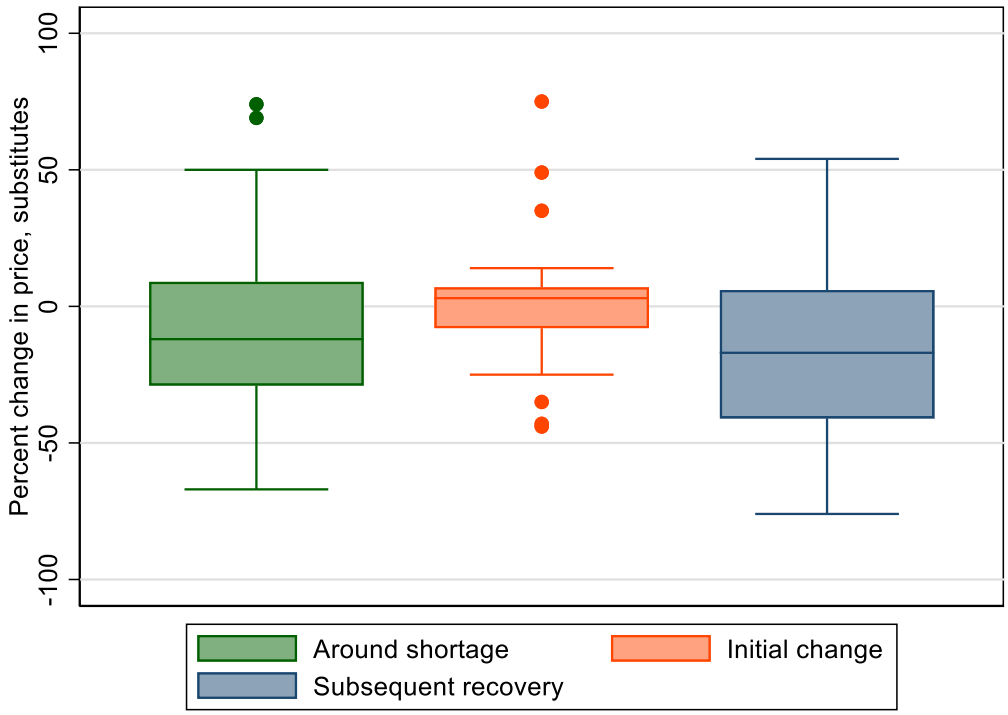
**Table C.4: Summary Statistics for Volume Changes, Case Study Substitute Drugs (%)**

| | Around shortage | Initial change | Subsequent recovery |
|---|---|---|---|
| Mean | 3.3 | -3.8 | 13.5 |
| Std. dev. | 17.0 | 8.4 | 18.3 |
| p50 | 5.0 | -2.0 | 8.0 |

Source: RAND analysis of FDA data linked to IQVIA NSP data. Note: Std. dev is standard deviation. Note: Analysis limited to the 26 case study drugs for which we assigned substitutes.

Figure C.4 is a box plot displaying the range of changes in substitute price by around shortage, initial change, and subsequent recovery. Both the medians and means of initial change were close to zero, while around shortage and subsequent recovery experienced modest median and mean price decreases (Table C.5).

**Figure C.4 Distribution of Changes in Price for Case Study Substitute Drugs**




Source: RAND analysis of FDA data linked to IQVIA NSP data. Note: Analysis limited to the 26 case study drugs for which we assigned substitutes.

**Table C.5: Summary Statistics for Price Changes, Case Study Substitute Drugs (%)**

| | Around shortage | Initial change | Subsequent recovery |
|---|---|---|---|
| Mean | -6.7 | 2.2 | -14.7 |
| Std. dev. | 37.1 | 25.7 | 34.6 |
| p50 | -12.0 | 3.0 | -17.0 |

Source: RAND analysis of FDA data linked to IQVIA NSP data. Note: Std. dev is standard deviation. Note: Analysis limited to the 26 case study drugs for which we assigned substitutes.

## Comparison of Shortage Cases to Substitutes

Table C.6 compares changes in prices for shortage NDCs, other forms of the shortage active ingredient, and active ingredients that are substitutes. To the extent patients, prescribers, and pharmacists use another form of the active ingredient in shortage or a substitute for a shortage NDC, a higher or lower price for these alternative treatments may affect direct patient costs. On average, other forms of the active ingredient in shortage and substitutes both had lower pre-shortage prices and decreases in price through the start of shortages, while shortages experienced increases in price. Except for the increase in price among shortage NDCs, none of the other metrics were statistically significant.

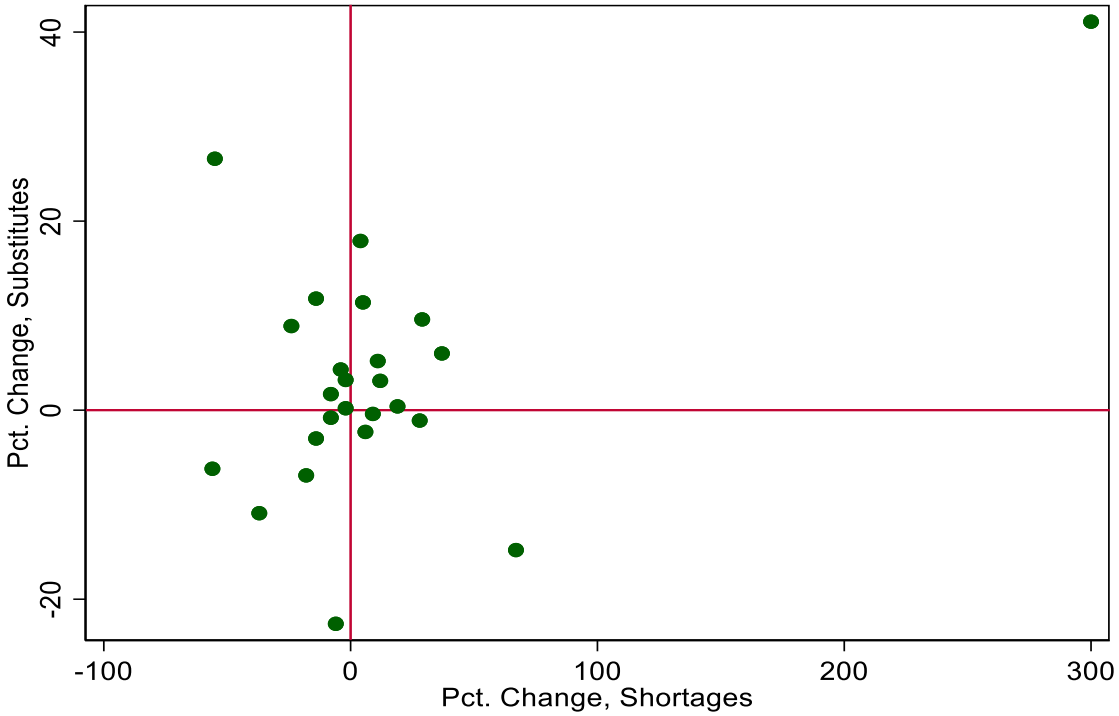
**Table C.6. Comparisons of Price Changes Between Shortage and Substitute Drugs**

| | Mean | 95% C.I. |
|---|---|---|
| **Pre-shortage price per standard unit** | | |
| Shortage NDCs | 189.78 | (-71.7, 451.3) |
| Shortage drug, other forms | 53.31 | (-36.2, 142.8) |
| Substitutes | 100.84 | (-16.4, 218.1) |
| **Change in price (around shortage)** | | |
| Shortage NDCs | 21.3% | (5.0%, 37.5%) |
| Shortage drug, other forms | -2.0% | (-23.7%, 19.7%) |
| Substitutes | -6.7% | (-23.1%, 9.8%) |

Source: RAND analysis of FDA data linked to IQVIA NSP data. Note: Analysis limited to the 26 case study drugs for which we assigned substitutes.

Figure C.5 is a scatter plot displaying the percent change in substitute versus shortage drug volume, both measured around the shortage start month. The majority of cases are clustered around zero for both axes, meaning cases that experienced minimal changes in shortage volume also experienced minimal changes in substitute volume. There does not appear to be an overall substitution pattern of decreases in shortages corresponding to increases in substitutes, though there are several examples that demonstrate this.

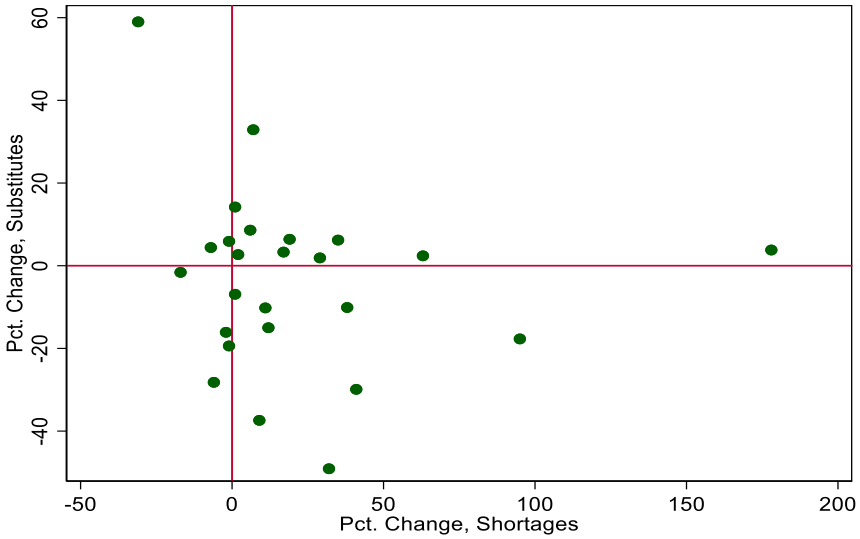
**Figure C.5. Changes in Volume of Substitutes by Changes in Volume of Shortages**




Source: RAND analysis of FDA data linked to IQVIA NSP data. Note: Analysis limited to the 26 case study drugs for which we assigned substitutes.

Figure C.6 is a scatter plot displaying the percent change in substitute versus shortage drug prices, both measured around the shortage start month. While the vast majority of shortages experienced price increases, substitutes were about equally likely to experience decreases as they were to experience increases. Shortages that experienced greater increases in price had substitutes that experienced greater declines in price.

**Figure C.6. Changes in Price of Substitutes by Changes in Price of Shortages**




Source: RAND analysis of FDA data linked to IQVIA NSP data. Note: Analysis limited to the 26 case study drugs for which we assigned substitutes.

## Illustrative Examples of Specific U.S. Drug Shortages

This section introduces five illustrative examples through the lens of the shortage framework. The charts in this section are based on our analysis of IQVIA NSP data which is described in the main report. These cases represent the wide variation of volume and price changes that occur when a drug enters a shortage: some experience substantial declines in volume without any recovery (e.g., asparaginase), others experience substantial volume declines and subsequent volume increases (e.g., heparin), and others experience modest to no declines in volume (belatacept, carbidopa-levodopa, valsartan). With the exception of carbidopa-levodopa, all other case studies experienced price increases following the shortage.

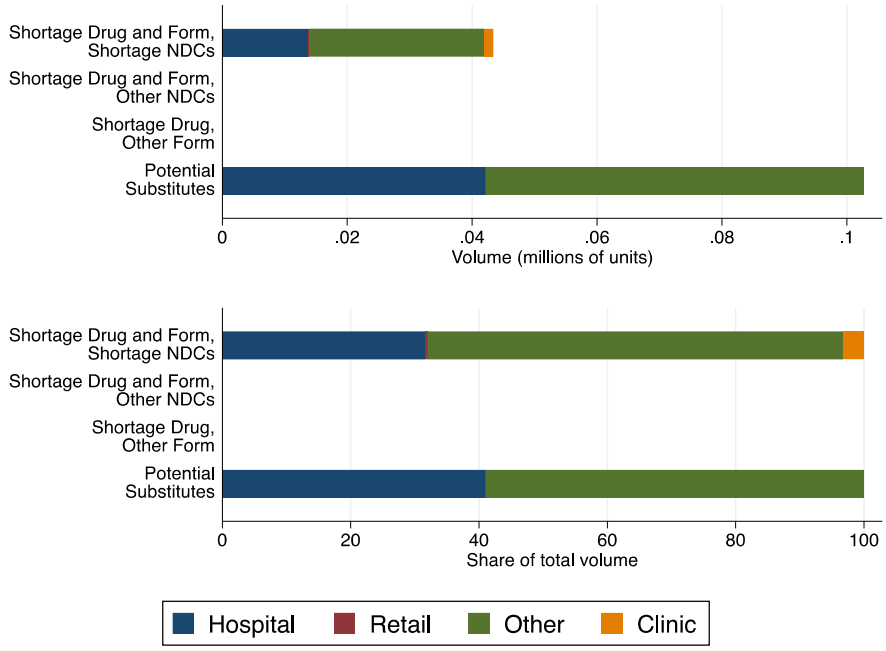
### *Asparaginase (brand names Elspar, Kidrolase, Spectrila, Rylaze)*

Asparaginase is a brand-name enzyme used to treat acute lymphoblastic leukemia (ALL). It is sold as a dry (lyophilized) powder that is reconstituted and administered via intravenous infusion. Asparaginase is produced by several manufacturers, including OSO Biopharmaceutical Manufacturing, Merck, Jazz Pharmaceuticals, and medac GmbH. The FDA did not list a reason for this shortage, though the ASHP described the shortage for one of the formulations as a result of "ongoing manufacturing issues and capacity constraints." The FDA recorded asparaginase as a shortage starting in October 2016, with volume initially fluctuating, followed by a decrease to almost zero by 2018. The main substitute for this drug is pegaspargase, a pegylated version of asparaginase. Pegasparagase experienced a similar decline in volume to asparaginase in mid-to-late 2017, though it eventually recovered before declining again in late 2019.

## Asparaginase

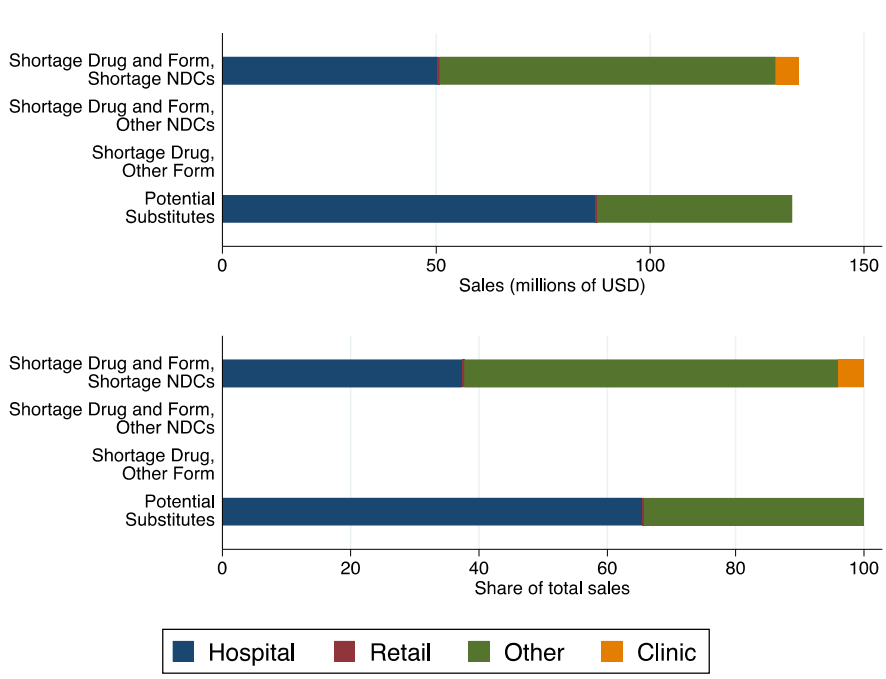
| | | | | | |
|---|---|---|---|---|---|
| **Shortage presentation:** | Asparaginase (dry vial for injection, 10MU) | | | | |
| **Shortage active ingredient other forms:** | | | | | |
| **Substitutes:** | pegaspargase | | | | |
| **Shortage start date:** | 10/14/2016 | **Shortage end date:** | 3/20/2020 | **Disposition:** | Current |
| **Other changes:** | | | | | |
| **Presentation manuf. in shortage:** | 1 of 1 | | **Presentation NDCs. in shortage:** | | 2 of 2 |
| **Active ingred. manuf. in shortage:** | 1 of 1 | | **Active ingred. NDCs in shortage:** | | 2 of 2 |
| **Typical uses:** | Hematology, Oncology, Pediatric | | | | |

**Pre-shortage volume[14]**




[14] Over a 12-month period excluding the 6 months prior to the shortage start date month.

**Pre-shortage sales[15]**



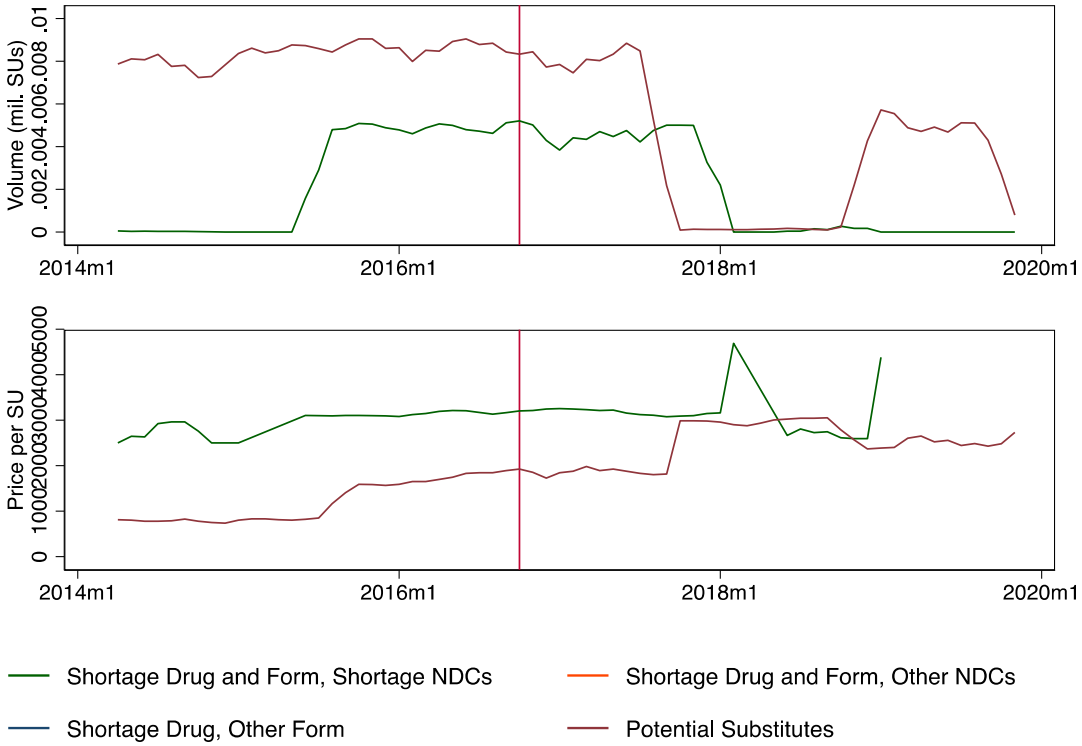

**Metrics, Volume and Price (% Change)**

| | Change around the shortage start month | | Initial change | | Subsequent recovery | |
|---|---|---|---|---|---|---|
| Category | Vol | Price | Vol | Price | Vol | Price |
| Shortage Drug and Form, Shortage Manuf. | 20.1 | 1.6 | 6.3 | 4.8 | 38.4 | -16.4 |
| Shortage Drug and Form, Other Manuf. | N/A | N/A | N/A | N/A | N/A | N/A |
| Shortage Drug, Other Form | N/A | N/A | N/A | N/A | N/A | N/A |
| Potential Substitutes | -44.9 | 73.7 | -10.5 | 48.9 | 2.4 | 39.6 |

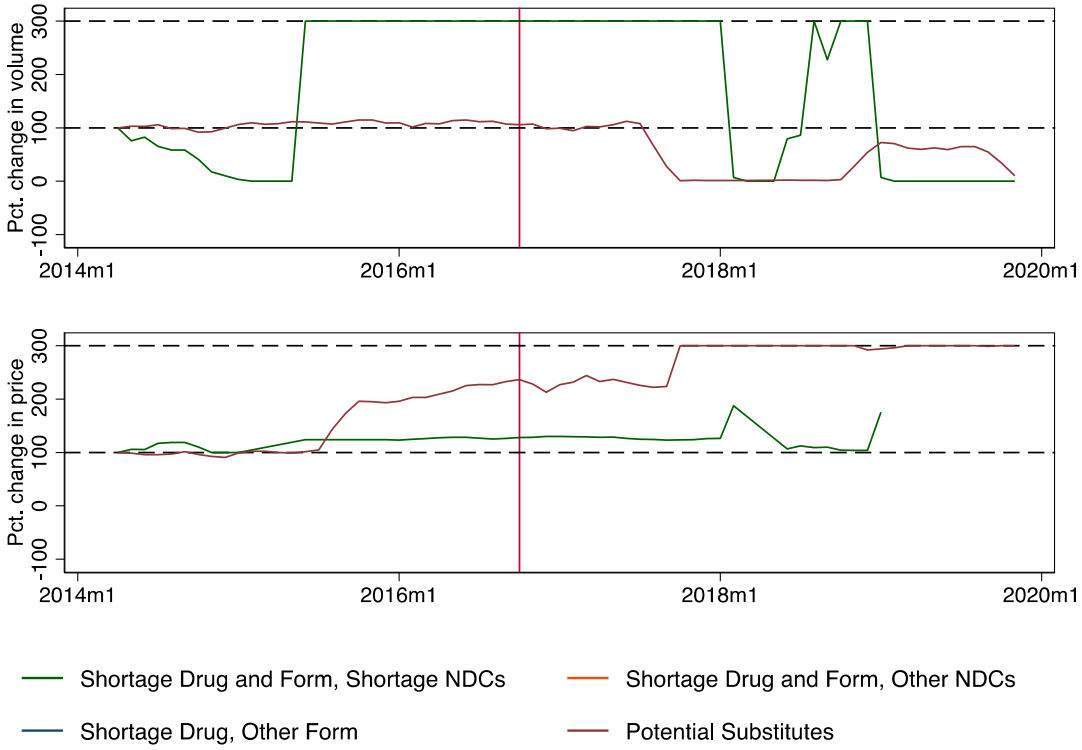
Note: N/A: No data for this specific shortage.

[15] Over a 12-month period excluding the 6 months prior to the shortage start date month.

**Three-Month Moving Average Volume and Prices (Levels)**



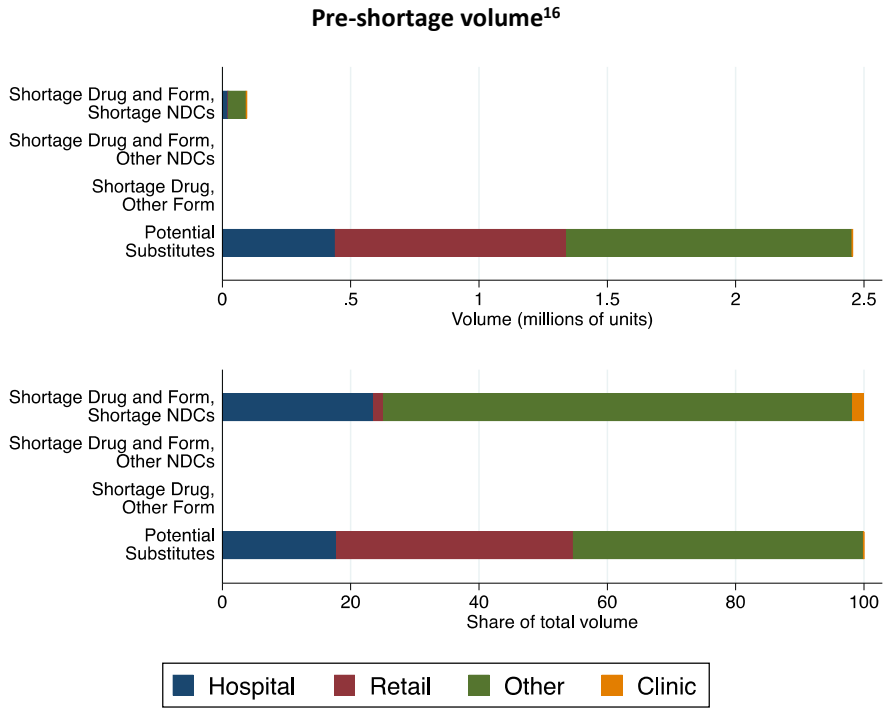

**Three-Month Moving Average Volume and Prices vs. First Non-Zero Volume and Price (300% Ceiling)**



*Belatacept (brand name Nulojix)*

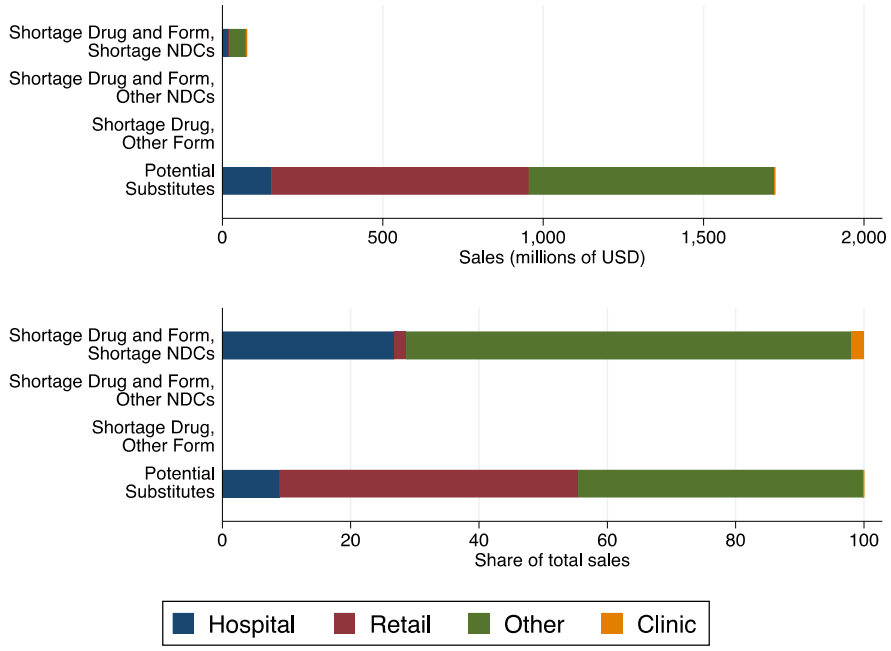
Belatacept is a brand-name biologic immunosuppressant used to prevent rejection in patients receiving kidney transplants. It is sold as a dry (lyophilized) powder that is reconstituted and administered via intravenous infusion. Belatacept is currently marketed only by Bristol-Myers Squibb and is protected from direct competition by regulatory exclusivity granted by the U.S. FDA through 2023. The FDA recorded a belatacept shortage starting in early 2017, even though Bristol-Myers Squibb had been working to increase U.S. volume to meet growing demand for the drug up to that point. While increasing demand was the primary cause of the shortage, a failed transition to a new manufacturing process in early 2017 marked the formal start of the shortage period. The main substitutes are abatacept, tacrolimus, and cyclosporine. Neither belatacept nor its substitutes appeared to experience changes in volumes around the shortage occurrence.

| | | | | | |
|---|---|---|---|---|---|
| **Shortage presentation:** | Belatacept (dry vial for infusion, 250MG) | | | | |
| **Shortage active ingredient other forms:** | None | | | | |
| **Substitutes:** | abatacept, tacrolimus, cyclosporine | | | | |
| **Shortage start date:** | 3/16/2017 | **Shortage end date:** | 12/16/2019 | **Disposition:** | Current |
| **Other changes:** | | | | | |
| **Presentation manuf. in shortage:** | 1 of 1 | | **Presentation NDCs. in shortage:** | | 1 of 1 |
| **Active ingred. manuf. in shortage:** | 1 of 1 | | **Active ingred. NDCs in shortage:** | | 1 of 1 |
| **Typical uses:** | Transplant | | | | |




[16] Over a 12-month period excluding the 6 months prior to the shortage start date month.

**Pre-shortage sales[17]**



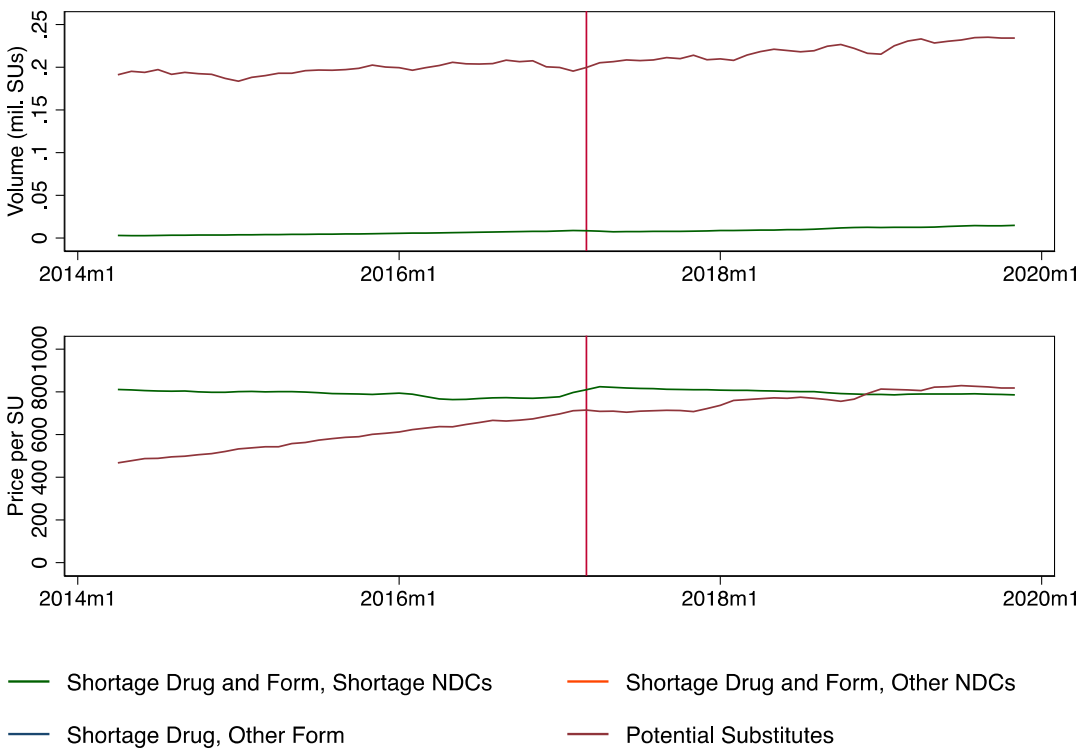

**Metrics, Volume and Price (% Change)**

| | Change around the shortage start month | | Initial change | | Subsequent recovery | |
|---|---|---|---|---|---|---|
| Category | Vol | Price | Vol | Price | Vol | Price |
| Shortage Drug and Form, Shortage Manuf. | 46.4 | 3.8 | 23.3 | 5.6 | 153.5 | 0.8 |
| Shortage Drug and Form, Other Manuf. | N/A | N/A | N/A | N/A | N/A | N/A |
| Shortage Drug, Other Form | N/A | N/A | N/A | N/A | N/A | N/A |
| Potential Substitutes | 5.7 | 18.1 | -2.8 | 14.4 | 16.9 | 13.2 |

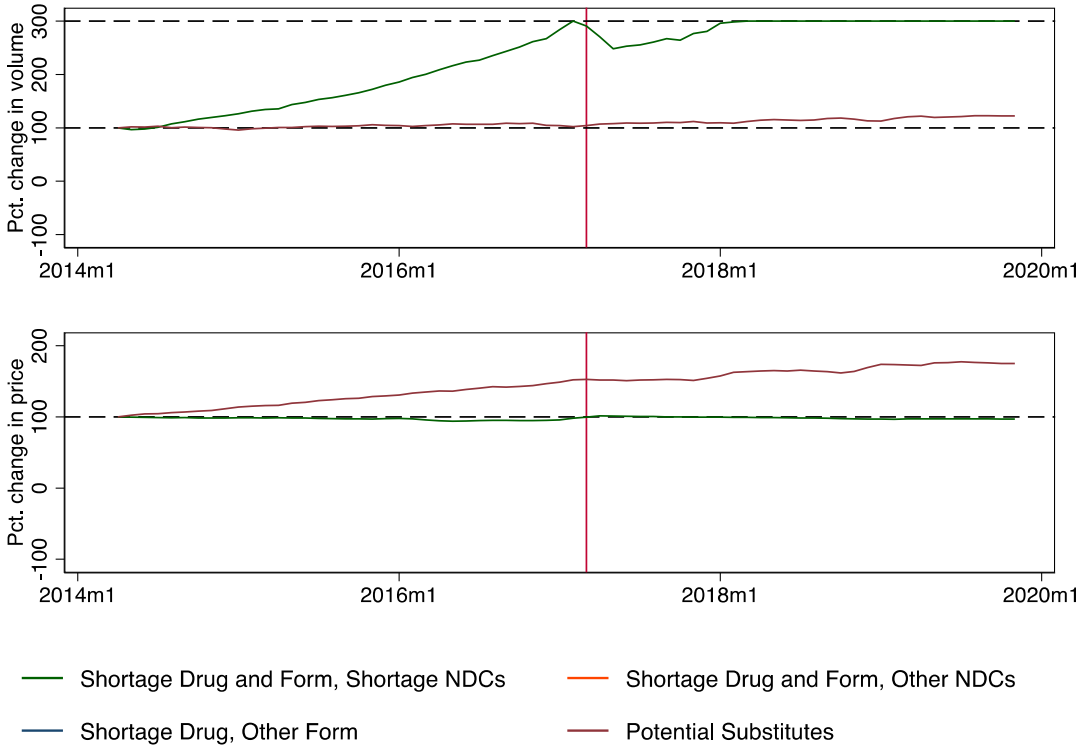
Note: N/A: No data for this specific shortage.

[17] Over a 12-month period excluding the 6 months prior to the shortage start date month.

**Three-Month Moving Average Volume and Prices (Levels)**



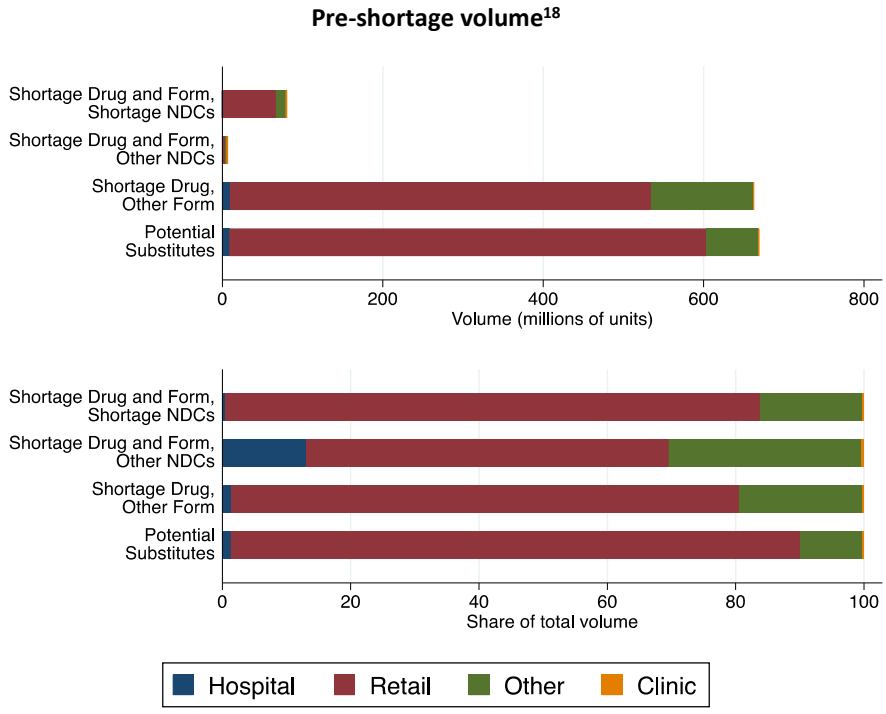

**Three-Month Moving Average Volume and Prices vs. First Non-Zero Volume and Price (300% Ceiling)**



*Carbidopa-Levodopa (brand names Rytary, Duopa, Sinemet, Atamet)*

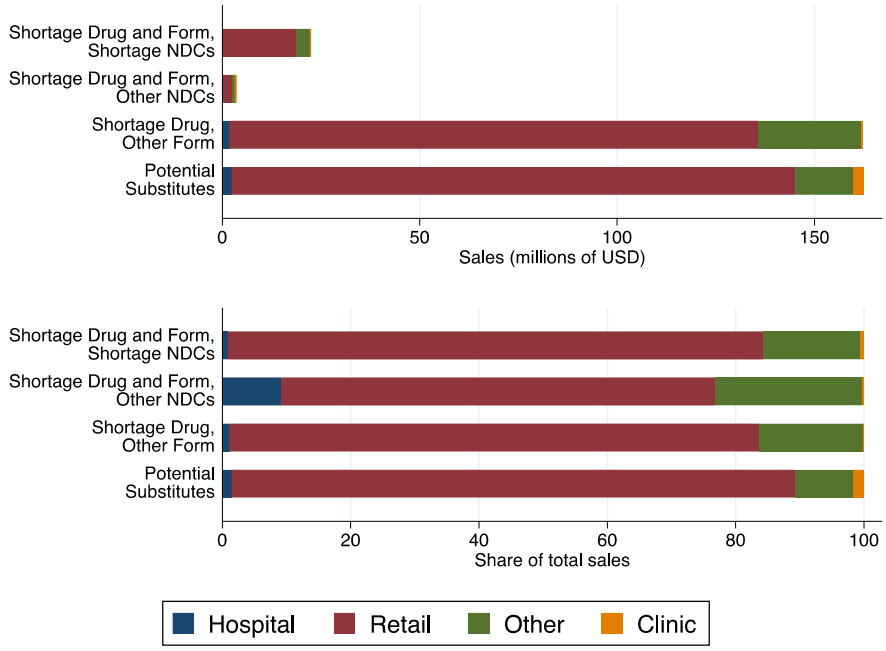
Carbidopa-Levodopa is a dopamine promoter used to treat Parkinson's disease. It is sold as a tablet or capsule and administered orally. Carbidopa-Levodopa is manufactured in different forms by Impax Pharmaceuticals, AbbVie, Merck, and others, and with some available as generics. Though Carbidopa-Levodopa has gone into shortage prior to our study period, the shortage of interest in our study was from September 2017 through July 2019. This shortage was due to a combination of manufacturing issues and discontinuations. Volume declined in the months immediately prior to the shortage, which then experienced an immediate recovery. Volume for its substitutes, which included ropinirole, pramipexole, and cabergoline, gradually increased throughout the study period.

| | | | | | |
|---|---|---|---|---|---|
| **Shortage presentation:** | Carbidopa/Levodopa coated tablets (uncoated long-acting tablets, 25-100mg and 50-200mg) | | | | |
| **Shortage active ingredient other forms:** | Extended release non-coated tablets, immediate release tablets, oral liquid (excluded from analysis) | | | | |
| **Substitutes:** | Oral solid ropinirole, pramipexole, and cabergoline | | | | |
| **Shortage start date:** | 9/27/2017 | **Shortage end date:** | 7/12/2019 | **Disposition:** | Resolved |
| **Other changes:** | 1 NDC discontinued 7/2019 | | | | |
| **Presentation manuf. in shortage:** | 3 of 8 | | **Presentation NDCs. in shortage:** | | 8 of 18 |
| **Active ingred. manuf. in shortage:** | 3 of 19 | | **Active ingred. NDCs in shortage:** | | 8 of 90 |
| **Typical uses:** | Neurology (Parkinson's disease) | | | | |




[18] Over a 12-month period excluding the 6 months prior to the shortage start date month.

**Pre-shortage sales**[19]

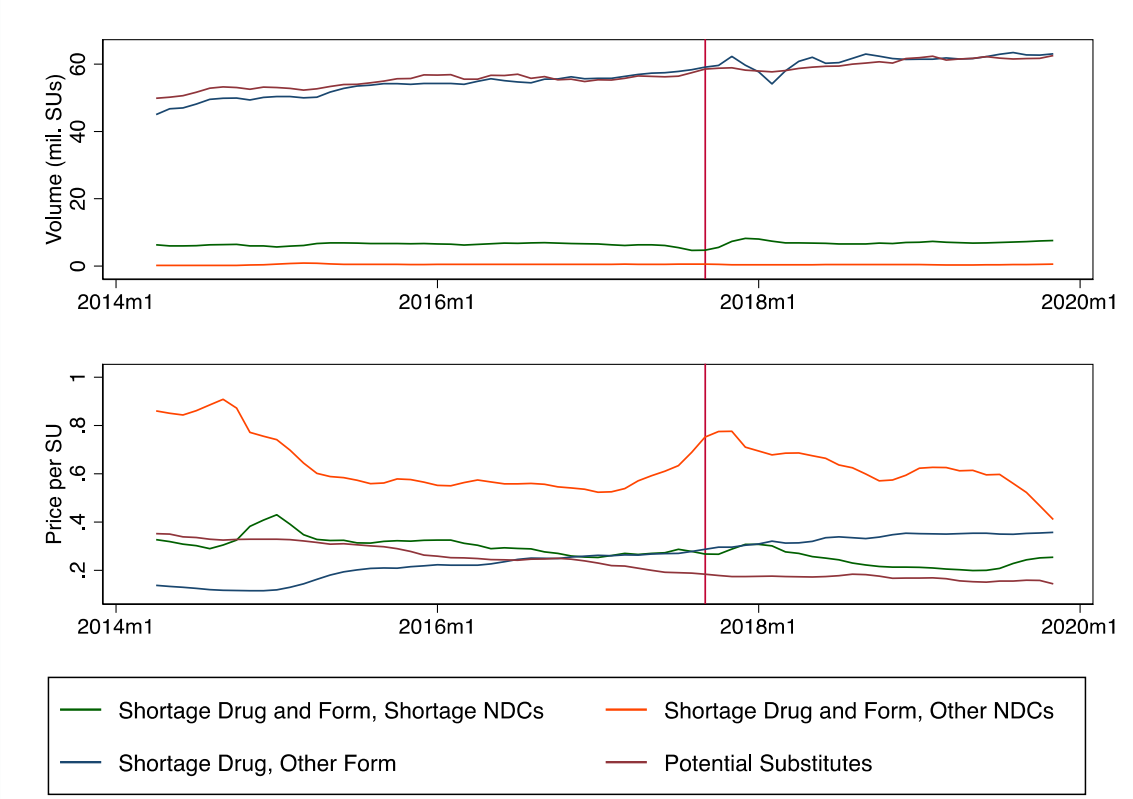



**Metrics, Volume and Price (% Change)**

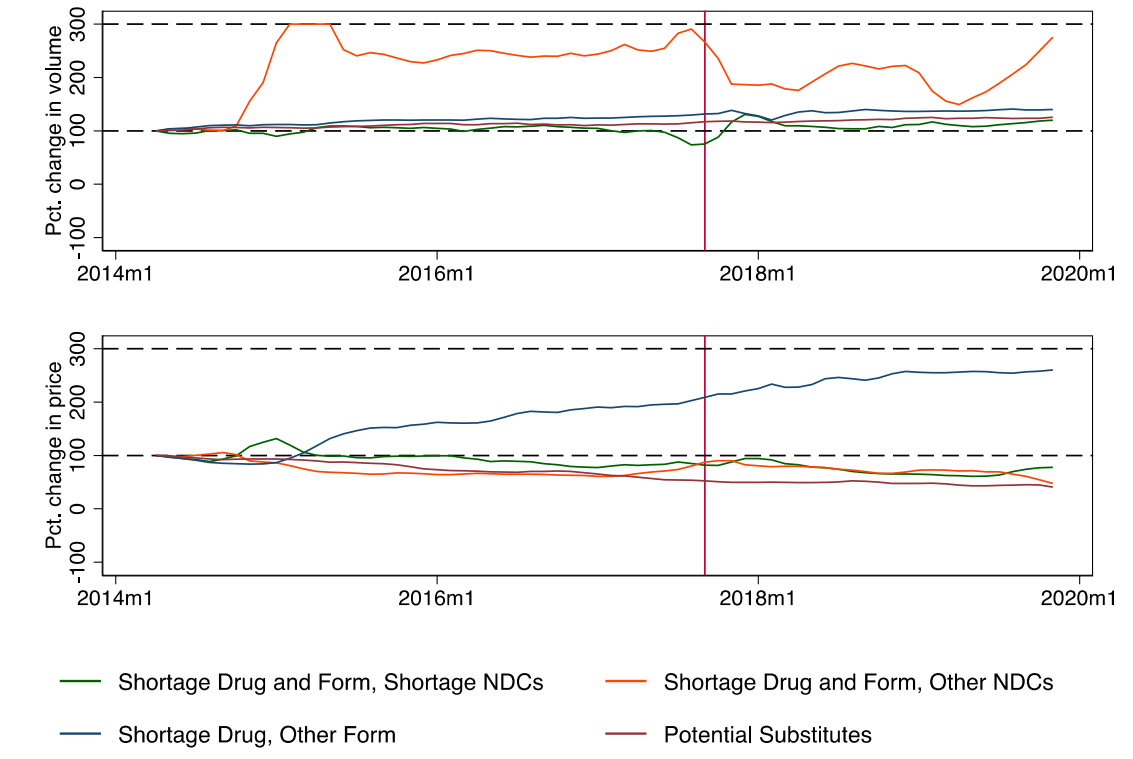
| | Change around the shortage start month | | Initial change | | Subsequent recovery | |
|---|---|---|---|---|---|---|
| Category | Vol | Price | Vol | Price | Vol | Price |
| Shortage Drug and Form, Shortage Manuf. | 4.1 | -10.6 | -30.3 | 10.1 | 20.8 | -28.7 |
| Shortage Drug and Form, Other Manuf. | -16.3 | 16.3 | -23.6 | 40.9 | 12.7 | -25.3 |
| Shortage Drug, Other Form | 9.1 | 34.8 | 1.9 | 24.1 | 14.7 | 26.6 |
| Potential Substitutes | 6.5 | -27.7 | -0.1 | -10.3 | 12.1 | -40.7 |

[19] Over a 12-month period excluding the 6 months prior to the shortage start date month.

**Three-Month Moving Average Volume and Prices (Levels)**




**Three-Month Moving Average Volume and Prices vs. First Non-Zero Volume and Price (300% Ceiling)**



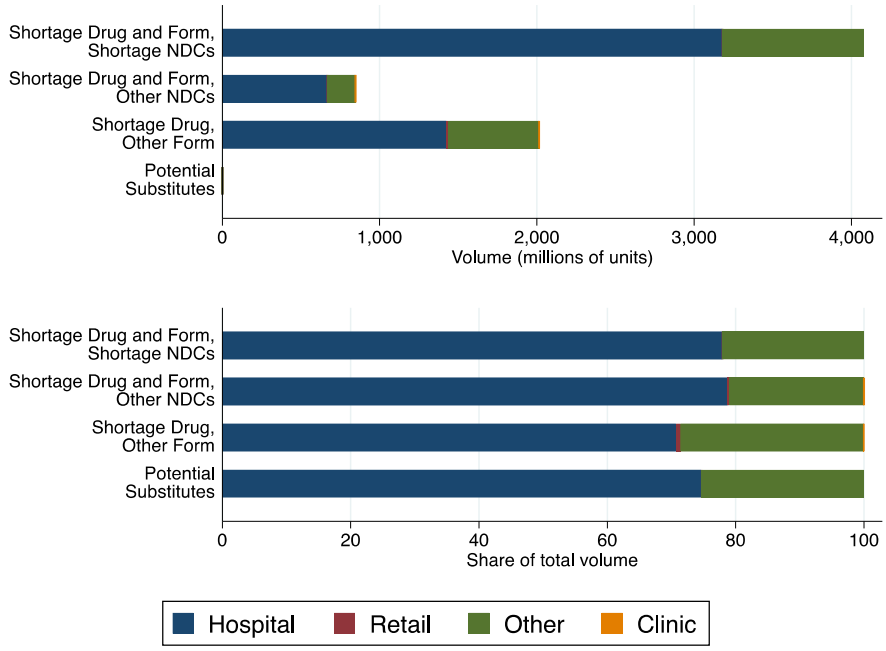
### *Heparin*

Heparin is an anticoagulant administered by intravenous or subcutaneous injection and is sold by several manufacturers. One type of heparin, unfractionated heparin, is the primary anticoagulant used for open-heart surgery and in dialysis. Hurricane Maria damaged facilities of one heparin manufacturer, Baxter, in September 2017.[20] Several Baxter heparin products manufactured at its Puerto Rico plant remain in shortage, and the FDA granted Baxter authorization to temporarily import premixed heparin bags from the United Kingdom starting in 2019 (Baxter, 2019). Other heparin products are in shortage, and several of the more recent shortages appear to be due to anticipated or actual shortages of API. Much of the pharmaceutical-grade heparin manufactured globally is derived from porcine intestine mucosa in China (Vilanova, Tovar and Mourão, 2018). By 2019, there was mounting concern that the outbreak of African Swine Fever in China starting mid-2018 could disrupt the supply of heparin API to drug manufacturers (Pallone et al., 2019). At least one manufacturer – Fresenius Kabi – began strategically allocating (i.e., rationing) its supply of heparin in anticipation of supply disruptions (Preusker, 2019). Despite a substantial decrease in heparin volume following the shortage, there was minimal volume changes in its substitutes, which were desirudin, lepirudin, and bivalirudin.

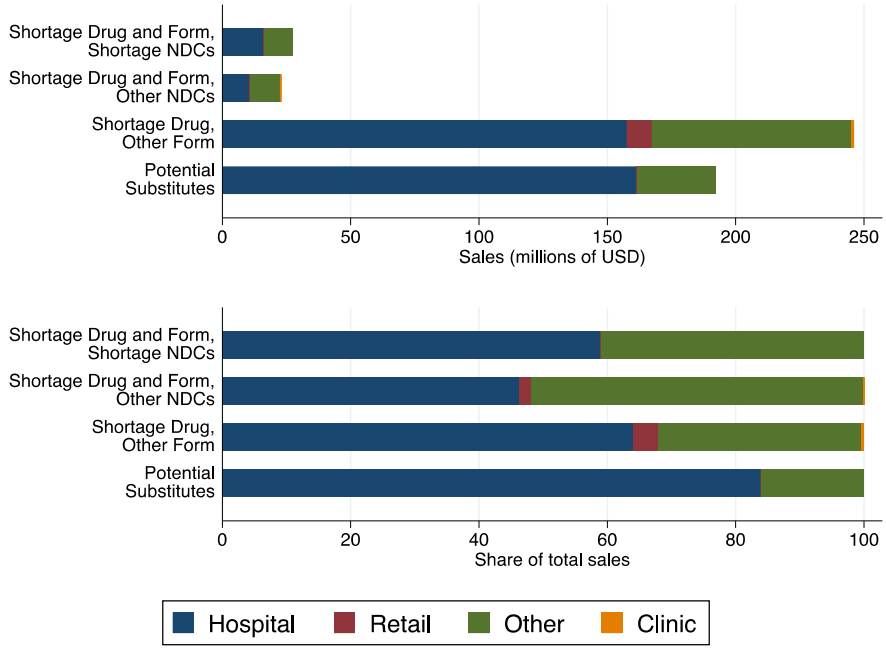
| | | | | | |
|---|---|---|---|---|---|
| **Shortage presentation:** | Heparin (vials and bottles, 1MU/1ML, 1MU/500ML, 1000U/500ML, 2000U/1000ML | | | | |
| **Shortage active ingredient other forms:** | Syringes, some vials and bottles | | | | |
| **Substitutes:** | desirudin, lepirudin, bivalirudin | | | | |
| **Shortage start date:** | 11/14/2017 | **Shortage end date:** | 3/20/2020 | **Disposition:** | Current |
| **Other changes:** | One FFZ presentation shortage ends on 12/11/2019 | | | | |
| **Presentation manuf. in shortage:** | 3 of 9 | | **Presentation NDCs. in shortage:** | | 5 of 130 |
| **Active ingred. manuf. in shortage:** | 3 of 15 | | **Active ingred. NDCs in shortage:** | | 5 of 207 |
| **Typical uses:** | Hematology | | | | |

20 Baxter faced disruptions of other intravenous drugs manufactured in Puerto Rico. See https://www.ashp.org/-/media/assets/drug-shortages/docs/drug-shortages-baxter-supply-update-09292017.ashx. Other drug manufactures in Puerto Rico were also affected. See https://www.nytimes.com/2017/10/23/health/puerto-rico-hurricane-maria-drug-shortage.html.

**Pre-shortage volume**[21]




**Pre-shortage sales**[22]



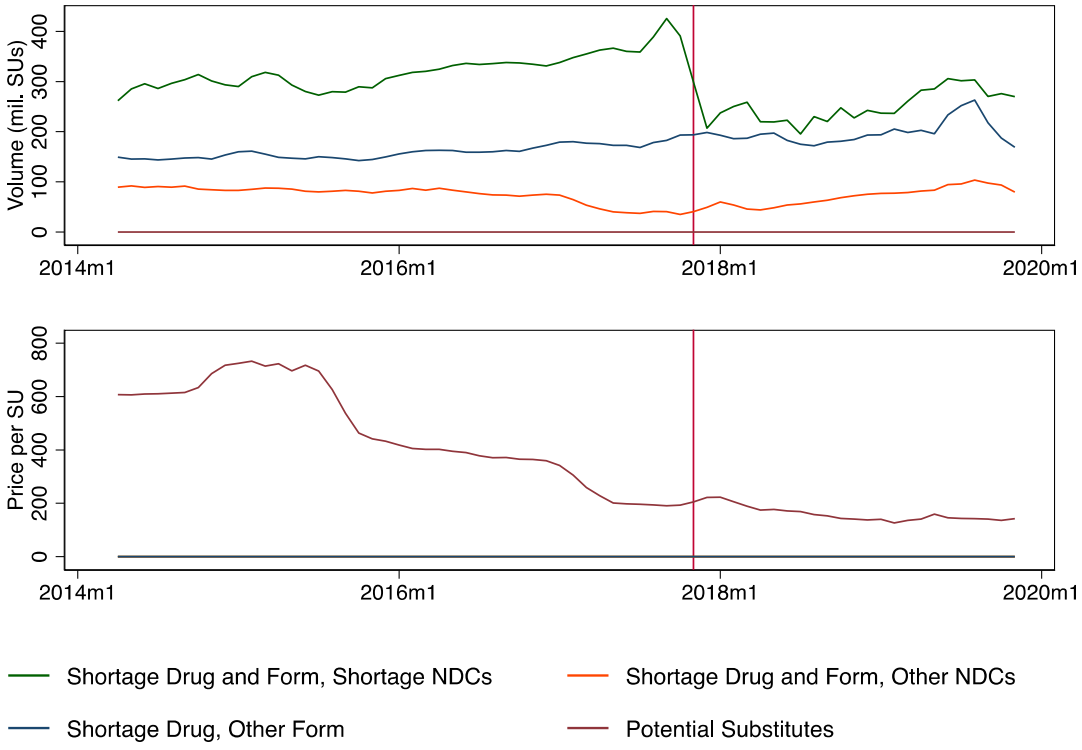

[21] Over a 12-month period excluding the 6 months prior to the shortage start date month.

[22] Over a 12-month period excluding the 6 months prior to the shortage start date month.

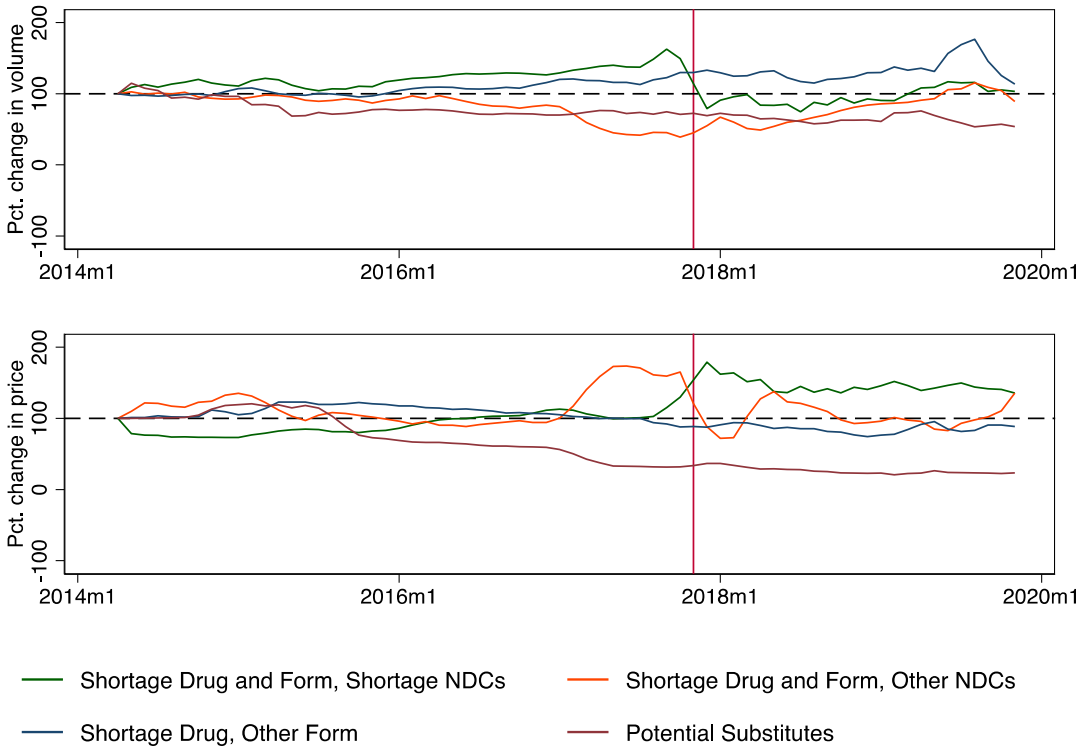
**Metrics, Volume and Price (% Change)**

| | Change around the shortage start month | | Initial change | | Subsequent recovery | |
|---|---|---|---|---|---|---|
| Category | Vol | Price | Vol | Price | Vol | Price |
| Shortage Drug and Form, Shortage Manuf. | -32.4 | 36.2 | -39.1 | 69.8 | -10.1 | 28.8 |
| Shortage Drug and Form, Other Manuf. | -12.2 | 4.8 | -50.2 | 65.5 | 46.7 | -21.0 |
| Shortage Drug, Other Form | 11.3 | -22.6 | 0.2 | -6.5 | 56.6 | -30.5 |
| Potential Substitutes | -12.2 | -54.5 | -4.3 | -35.2 | 4.6 | -63.3 |

**Three-Month Moving Average Volume and Prices (Levels)**



**Three-Month Moving Average Volume and Prices vs. First Non-Zero Volume and Price (300% Ceiling)**

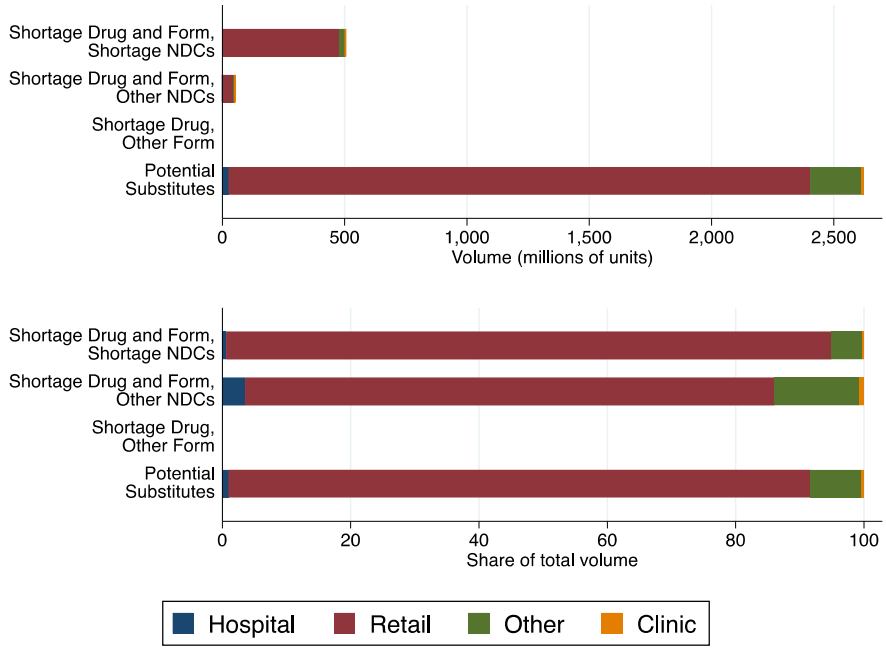


*Valsartan (brand name Diovan)*

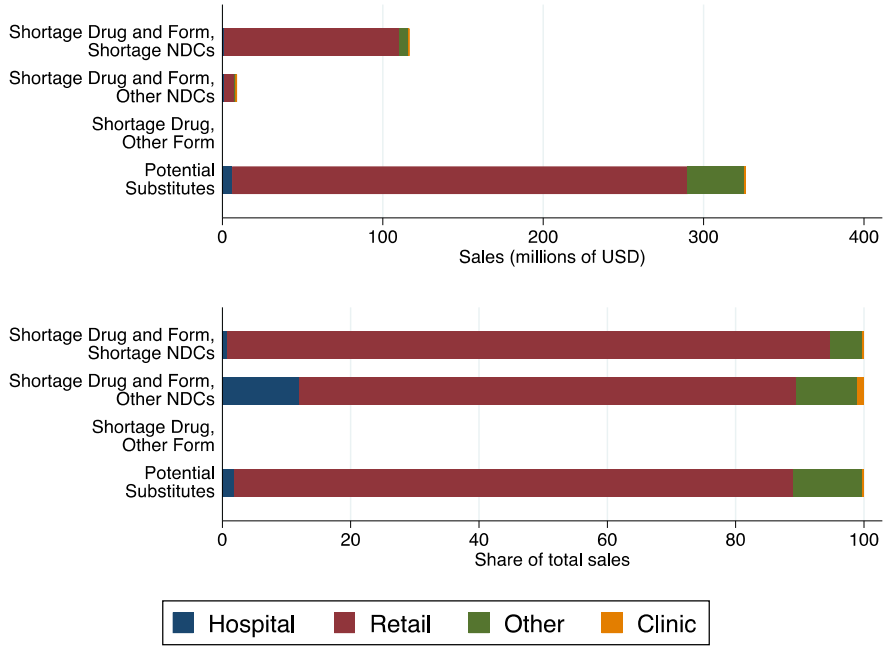
Valsartan is an oral angiotensin II receptor blocker (ARB) antihypertensive that is used to treat patients who have high blood pressure, heart failure, or have experienced a heart attack (Novartis, 2017). Originally manufactured by Novartis in 1996, the patent for valsartan expired in September 2012, which allowed for generic entry into the market. In July 2018, the FDA announced a voluntary recall of numerous generic forms of valsartan after discovering the product was contaminated with a carcinogen (N-nitrosodimethylamine (NDMA)). Other ARB antihypertensives, including losartan (Cozaar) were also affected. Shortly after the initial recalls, the FDA listed valsartan as being in shortage. These shortages were due to safety concerns based on the production of the medications. Following the shortage, valsartan experienced a large decline in volume and an increase in its substitutes, which were losartan, Olmesartan, telmisartan, irbesartan, and candesartan.

| | | | | | |
|---|---|---|---|---|---|
| **Shortage presentation:** | Valsartan coated tablets (40MG, 80MG, 160MG, 320MG) and capsules (40MG, 80MG, 160MG, 320MG) | | | | |
| **Shortage active ingredient other forms:** | None | | | | |
| **Substitutes:** | losartan, olmesartan medoxomil, telmisartan, irbesartan, eprosartan, candesartan cilexetil | | | | |
| **Shortage start date:** | 8/3/2018 | **Shortage end date:** | 3/4/2020 | **Disposition:** | Resolved |
| **Other changes:** | Capsules (NFC code ACA) discontinued 1/16/2020 | | | | |
| **Presentation manuf. in shortage:** | 12 of 22 | **Presentation NDCs. in shortage:** | 51 of 116 | | |
| **Active ingred. manuf. in shortage:** | 12 of 22 | **Active ingred. NDCs in shortage:** | 51 of 116 | | |
| **Typical uses:** | Cardiovascular | | | | |
| **Notes:** | Antihypertensive | | | | |

**Pre-shortage volume[23]**




**Pre-shortage sales[24]**




[23] Over a 12-month period excluding the 6 months prior to the shortage start date month.

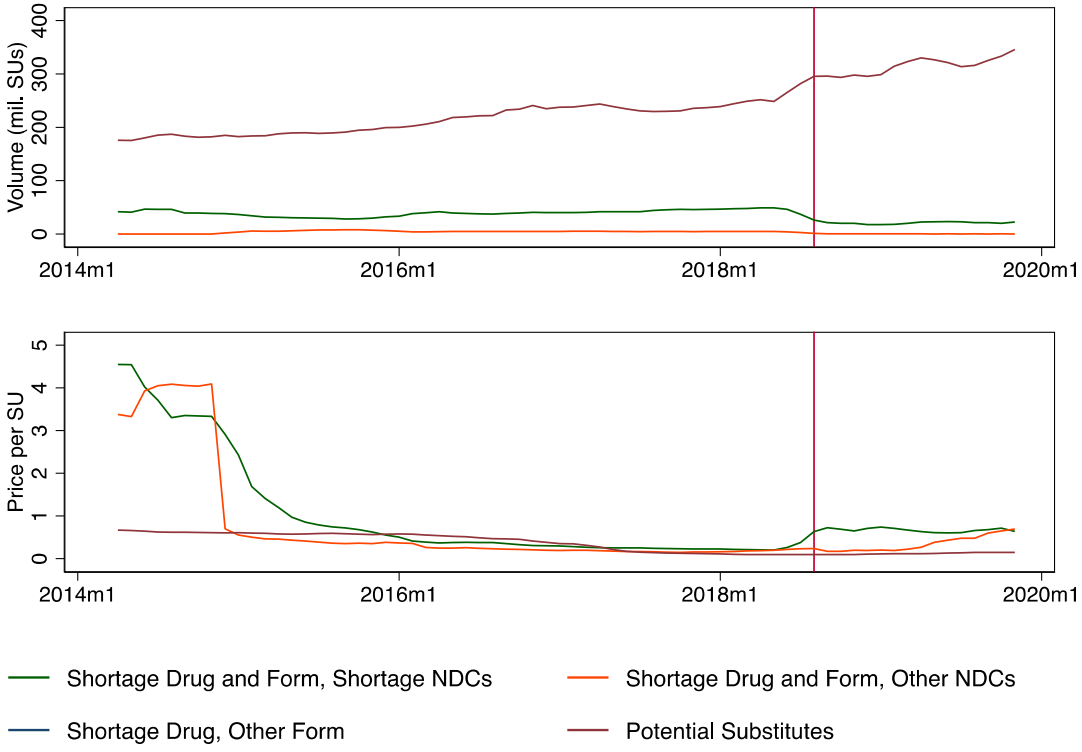
[24] Over a 12-month period excluding the 6 months prior to the shortage start date month.

**Metrics, Volume and Price (% Change)**

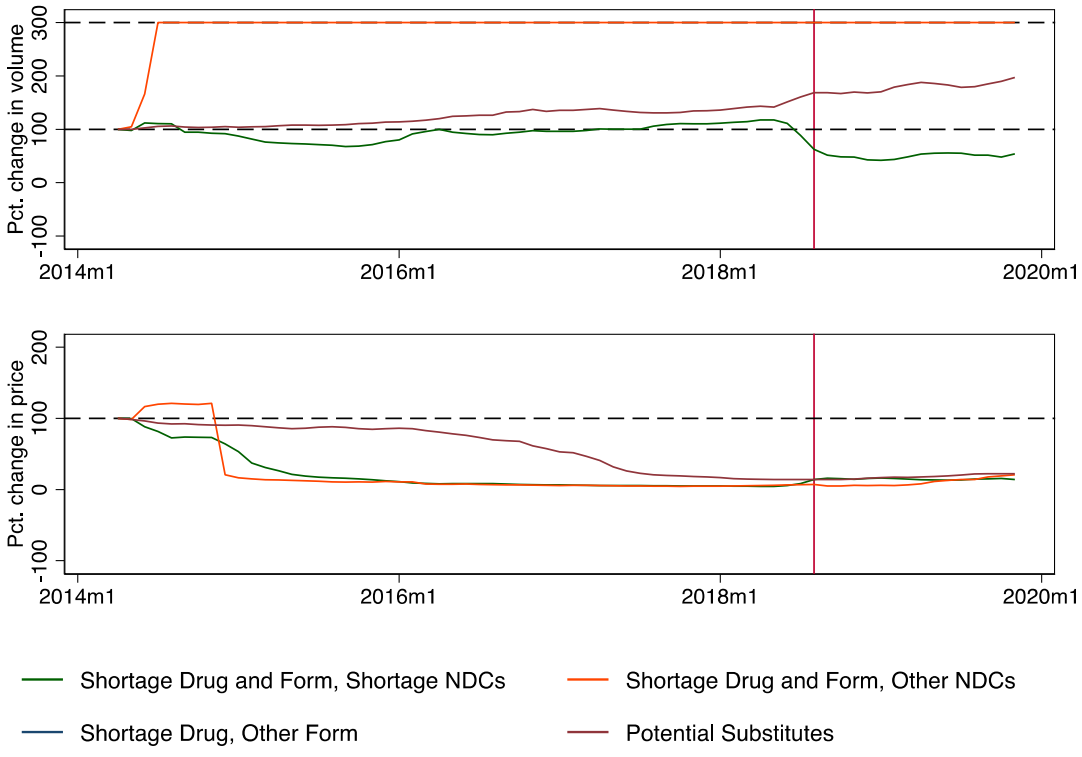
| | Change around the shortage start month | | Initial change | | Subsequent recovery | |
|---|---|---|---|---|---|---|
| Category | Vol | Price | Vol | Price | Vol | Price |
| Shortage Drug and Form, Shortage Manuf. | -52.0 | 169.2 | -53.9 | 192.7 | -46.6 | 145.0 |
| Shortage Drug and Form, Other Manuf. | -92.5 | 136.2 | -90.1 | 41.4 | -88.3 | 13.7 |
| Shortage Drug, Other Form | N/A | N/A | N/A | N/A | N/A | N/A |
| Potential Substitutes | 35.9 | -30.6 | 3.6 | -44.5 | 46.7 | -42.6 |

Note: N/A: No data for this specific shortage.

**Three-Month Moving Average Volume and Prices (Levels)**



**Three-Month Moving Average Volume and Prices vs. First Non-Zero Volume and Price (300% Ceiling)**



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