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Linking Medication Errors to Drug Shortages: Evidence from Heparin Supply Chain Disruptions Caused by Hurricane Maria

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Abstract. ***Problem definition*:** Scant empirical research studies the impact of drug shortages on the quality of medical care in hospitals. We study the causal relationship between drug shortages and medication errors using a natural experiment: hurricane damage to factories that produce heparin, an essential medication used frequently in hospitals. ***Methodology/results*:** We collect data on medication errors from the U.S. Food and Drug Administration's Adverse Event Reporting System and drug sales from IQVIA's National Sales Perspective. Applying the synthetic control method, we find that hurricane-related heparin supply disruptions increased medication error rates by 152%. In addition, we find significant spillover effects. The disruption increased medication error rates of a substitute drug, enoxaparin, by about 114%. ***Managerial implications*:** Our study uses an exogenous event to show that medication supply chain disruptions may negatively impact hospitals' quality of care. We contribute to the literature by empirically linking the effects of supply chain disruptions to downstream service quality. Our results show that commonly used measures to mitigate the impact of drug shortages, such as substituting medications, may be unsafe. We discuss several measures that hospital managers may consider implementing to mitigate the potentially harmful effects of drug shortages.

Supplemental Material: The online appendix is available at https://doi.org/10.1287/msom.2023.0297.

Keywords: supply chain disruption • drug shortage • medication error • service quality • synthetic control method

1. Introduction

There is increasing concern about the risk of supply chain disruptions (Council of Economic Advisers 2022). Disruptions arise from disease outbreaks, geopolitical events (Council of Economic Advisers 2022, National Academies of Sciences et al. 2022), and multitier global supply chain structures where multiple organizations rely on the same small number of upstream suppliers (Bimpikis et al. 2019) that may underinvest in resilience (Capponi et al. 2024). In addition, in a White House report, the Council of Economic Advisers (2022) warns that an increasing frequency of natural disasters, such as floods, severe storms, wildfires, and tropical cyclones, will cause an uptick in supply chain disruptions. Yet, scant empirical research studies the effects of supply chain disruptions created by natural disasters (Hendricks et al. 2020). We fill this gap by studying a shortage of essential medicine caused by a natural disaster and testing its impact on one important indicator of quality of care: medication errors.

We use the U.S. Food and Drug Administration (FDA) definition of a medication shortage, which is an event in which the total supply of all interchangeable versions of a drug is insufficient to meet patient demand (Food and Drug Administration 2011). Reports document drug shortages in the United States, drawing attention to the issue; 163 drugs fell short of demand from 2013 to 2017 (Food and Drug Administration 2019b), and in 2023, there were 55 new drug shortages (Food and Drug Administration 2023). Drug shortages are persistent, lasting an average of 181 days before full recovery (Lee et al. 2021). Many factors interact to make pharmaceutical supply chains vulnerable to shortages

(National Academies of Sciences et al. 2022); relatively few suppliers (Conti and Berndt 2020), just-in-time inventory policies (Fox et al. 2014, Food and Drug Administration 2019b), complex production technology (Woodcock and Wosińska 2013), and heavy reliance on overseas suppliers (Food and Drug Administration 2019b) make drug supply chains vulnerable (The White House 2021, Wosińska et al. 2023). A national study of U.S. hospitals reports that 100% of the 365 facilities surveyed experienced drug shortages from July 2018 to December 2018 (Vizient 2019).

Medication shortages may negatively impact hospital operations, but their impact on the quality of care has not been thoroughly examined (Fox et al. 2014, Vail et al. 2017, Food and Drug Administration 2019b, Lee et al. 2021). There is some evidence that pharmaceutical supply chain disruptions may lead to medication errors, adverse drug events, and patient deaths (McBride et al. 2013, McLaughlin et al. 2013, Caulder et al. 2015, Kehl et al. 2015). However, these reports use practitioner surveys to link drug shortages with low-quality care. A notable exception is Vail et al. (2017), which uses patient-level data to show that U.S. hospital patients with septic shock during times of norepinephrine shortage had higher in-hospital mortality.

It is difficult to estimate the causal effects of product supply disruptions on quality because supply disruptions may be anticipated, and consequently, their potential impacts may be averted or mitigated by practitioners (Abadie 2021). In the U.S. pharmaceutical market, the FDA requires manufacturers to forewarn their customers about anticipated shortages from a known production problem (Food and Drug Administration 2023). In addition, quality can be hard to measure (Bates et al. 1995, Donaldson et al. 2000).

We study the impact of a pharmaceutical supply chain disruption caused by an exogenous shock, a hurricane, on medication errors, which is an important metric of quality of care. In September 2017, Hurricane Maria hit Puerto Rico, where over 50 U.S. drug manufacturers are located, causing severe damage to manufacturing facilities that produce several medications (Baxter Healthcare Corporation 2017a, b; Food and Drug Administration 2017b; Spinler 2019), including heparin, an anticoagulant drug considered an essential medicine for patients in U.S. acute care medical facilities (Food and Drug Administration 2020a). After the hurricane, there were shortages of heparin because of manufacturing disruptions (Food and Drug Administration 2017a).

To test our hypotheses that drug shortages will cause an increase in medication errors, we extract heparin-related medication error events from the Food and Drug Administration Adverse Event Reporting System (FAERS) and analyze changes in medication errors before and after the supply disruption. The FAERS is a database containing reports on adverse events and medication errors that were submitted to the FDA (Food and Drug Administration 2018). A medication error is defined as an error of commission or omission of any step in drug prescribing through administration (Patient Safety Network 2019). We focus specifically on medication errors because they are an important indicator of quality of care (Bates et al. 1995, Donaldson et al. 2000). We employ the synthetic control method to estimate the causal impact of the hurricane on medication errors. We control the volume of drugs being used, which is necessary to measure medication error rates, by leveraging national prescription drug sales data from IQVIA National Sales Perspective (NSP) (IQVIA 2024). We also examine the impact of the supply chain disruption of heparin on medication errors of a different medicine, enoxaparin, whose supply was not affected by the hurricane. Enoxaparin may be used as a therapeutic substitute for heparin based on clinical guidelines (Garcia et al. 2012, Rosovsky et al. 2020).

We find that the supply chain disruption significantly increased heparin medication error rates by 152% on average compared with before the supply disruption. The number of heparin medication errors increased as the shortage worsened. This result supports our first hypothesis that errors occur when clinicians are forced by supply shortages to use different products of the supply-affected drug. We also find a significant spillover effect. Medication error rates of an alternative drug for heparin, enoxaparin, increased by 114% on average compared with before the heparin supply disruption. This supports our second hypothesis that a supply chain disruption of one drug (e.g., heparin) can lead to increased errors of an alternative drug (e.g., enoxaparin) not affected by the supply chain disruption. Our overall findings suggest that common responses to drug shortages, substituting within and across drugs, lead to increased medication errors. Our results are robust to alternative estimators, such as the recently developed synthetic difference in differences (SDID) (Arkhangelsky et al. 2021) and several robustness checks. Finally, we discuss strategies that clinicians may consider using to mitigate decrements in the quality of medical care when supply chain disruptions emerge.

Our paper is related to multiple streams of literature. First, we extend the supply chain management literature that studies the effects of supply chain disruptions. Previous papers in this area focus on the economic impacts of supply chain disruptions on firms' financial performance (e.g., Hendricks and Singhal 2003, 2005a, b). Using medication error as a measure of quality, we show that disruption of an essential service supply, an anticoagulant, harms service quality. Next, we contribute to the medical literature on the impact of drug shortages on the quality of

care (McBride et al. 2013, McLaughlin et al. 2013, Caulder et al. 2015, Kehl et al. 2015, Vail et al. 2017) by linking medication errors to drug shortages. We believe that our paper is the first to provide a causal estimate of the effect of supply chain disruptions on medication errors and the spillover effect on substitute drugs. Lastly, our research is related to the operations management and economics literature studying ways to reduce drug shortages (Jia and Zhao 2017, Yurukoglu et al. 2017, Lee et al. 2021, Galdin 2024, Swinney et al. 2024, Noh et al. 2025).

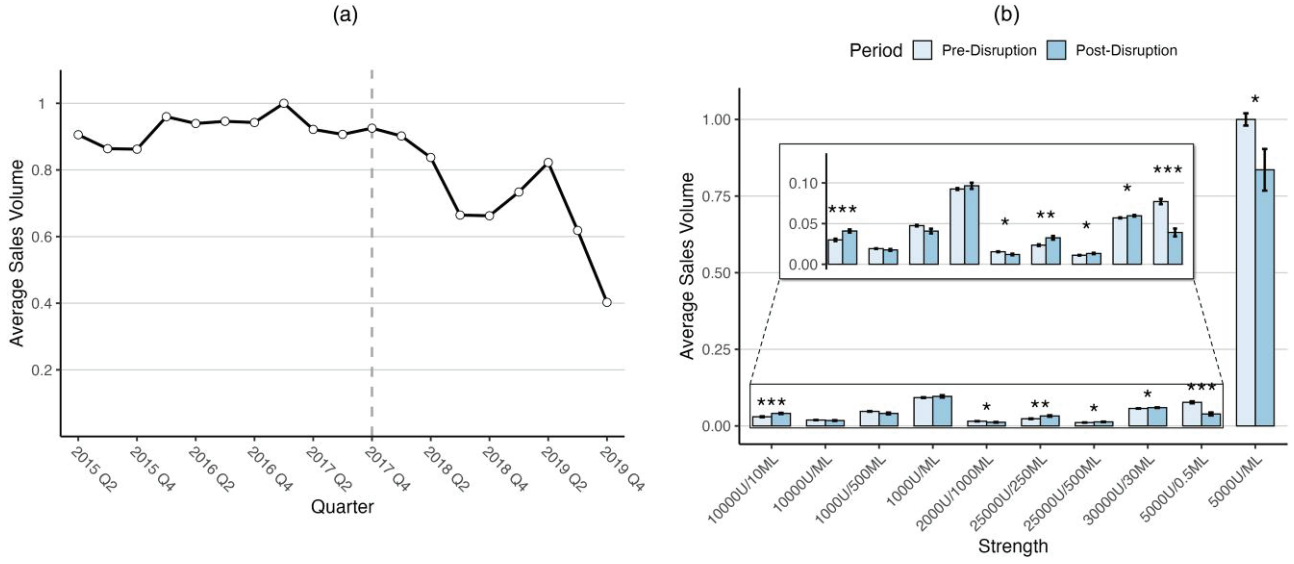
2. Context and Hypotheses

2.1. Context

To study the impact of supply chain disruptions on medication errors, we analyze a disruption in the supply of heparin caused by Hurricane Maria in September 2017 and test its impact on national-level medication errors collected from the FAERS data set. Hurricane Maria damaged many pharmaceutical facilities, resulting in firms operating below 50% capacity (Food and Drug Administration 2017b). Manufacturing plants of two heparin producers, Pfizer and Baxter, suffered substantial damage, disrupting the supply of heparin for years (Baxter Healthcare Corporation 2017a, b; Spinler 2019). For example, immediately after the hurricane, Baxter notified its customers which products had limited inventory (e.g., heparin sodium and 0.9% sodium chloride injection) and consequently, would be distributed based on customers' average monthly purchase history (Baxter Healthcare Corporation 2017b). In late October 2017, Baxter responded to the shortage by temporarily importing heparin products from the United Kingdom under the coordination of the FDA (Baxter Healthcare Corporation 2017a, b). Nonetheless, in November 2017, the FDA announced that heparin was in shortage in the United States (Food and Drug Administration 2017a). As of December 2020, heparin remained in shortage in the United States (Food and Drug Administration 2020b).

Figure 1(a) plots the quarterly average sales volumes of all heparin products in the United States. A pharmaceutical product is identified by a unique national drug code (NDC), which has three components: (1) the company code (labeler), (2) the product code (determined by the strength of the drug, its dosage form (i.e., capsule, tablet, or liquid), and the ingredients (formulation)), and (3) the package code. After the supply chain disruption, depicted by the vertical dashed line in Figure 1(a), the sales volume of heparin decreased significantly. The sales volume decreased continuously and reached its lowest point in 2019 quarter 4 (Q4), suggesting that the extent of shortages worsened over time, except for a brief recovery in Q1 and Q2 of 2019. This low sales level did not stem from the 2019 outbreak of African swine fever in China (the active ingredient in heparin is derived from pig intestines) (Food and Drug Administration 2019a).

Figure 1. (Color online) Sales Volume Changes



Data Source. Created using proprietary data obtained from IQVIA NSP, used with permission.

Notes. In panel (a), each point represents the average quarterly sales volume of all heparin products with a distinct national drug code. The vertical dashed line represents the heparin supply chain disruption. In panel (b), each bar represents the average quarterly sales volume of heparin products by strength (x axis) and period (color of the bar). The error bar indicates the standard error of the mean. The predisruption period is from 2014 quarter 4 (Q4) to 2017 Q4, and the postdisruption period is from 2018 Q1 to 2019 Q4 as in our analysis. Per the nondisclosure agreement with IQVIA, we disguise actual sales volumes by normalizing the values to the maximum value in the panels. (a) Sales volume of heparin. (b) Sales volume of heparin by strength and period. Asterisks indicate the t-test significance.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

The heparin supply chain disruption presents a unique opportunity to empirically study how supply chain disruptions alter the quality of medical services for three reasons. First, the supply disruption is caused by a natural disaster, an exogenous event that enables us to design a natural experiment estimating the unbiased effect of supply disruptions on medication errors. Second, medication administration is a complex, multistep process consisting of prescription, preparation, distribution, and administration; it involves multiple clinicians, including physicians, pharmacists, and nurses. This complexity can lead to medication errors (Bates et al. 1995). Pertinent to our study, the supply disruption in heparin may cause clinicians to purchase and use alternative prescription drugs unaffected by the primary disruption, which may result in medication errors. The first type of substitution that we consider is a "within-drug" substitution, which we define as using a drug with the same active pharmaceutical ingredient as the drug that is out of stock but from a different producer, in a different concentration, or in a different volume. For example, heparin comes in numerous dose strengths, and substituting a different dose strength of heparin can lead to dose-calculation errors. The second type of substitution that we study is "across-drug" substitution, which uses a different drug (i.e., a different active pharmaceutical ingredient). This substitution is relevant because there are nonheparin prescription drug substitutes, including guidelines, that enable clinicians to substitute these drugs for heparin. We focus on enoxaparin, an anticoagulant used to prevent deep vein thrombosis, which medical experts suggest can substitute for heparin (Garcia et al. 2012, Rosovsky et al. 2020). Third, heparin is an essential drug widely used in U.S. hospitals for inpatient medical care (U.S. Department of Health and Human Services 2014). Approximately 12 million patients are treated with heparin annually in the United States (Nilius et al. 2021). The high usage makes it feasible to detect the effects of a nationwide heparin supply disruption on medical errors using national-level medication error data.

2.2. Hypotheses

When faced with a supply disruption of a routinely used medication, clinicians may use a substitute drug if available (Fox et al. 2014). Substitutions can be within drug or across drug. We first discuss within-drug substitutions. Figure 1(b) shows the sales volume of heparin products by unique concentration (or strength). We observe a significant decrease in sales volumes of the most popular strength (5,000 units (U)/milliliter (mL)) after the disruption. In contrast, several strengths (e.g., 10,000 U/10 mL and 25,000 U/250 mL) showed significant increases in sales volumes after the supply disruption, suggesting that there were within-drug substitutions across different strengths.

During the heparin supply disruption, if clinicians purchased other heparin products with different concentrations (e.g., within-drug substitutions), heparin-related medication errors could increase for the following reasons. The risk of administration errors related to substitutions is shown in the laboratory experiments of Tucker (2016), where nearly 20% of nurses who made a dose conversion did so incorrectly and administered a 10 times overdose of insulin. In actual practice settings, clinicians try to avoid look-alike or sound-alike errors by purchasing the same brand repeatedly (Fox et al. 2014). If the hurricane forced healthcare organizations to switch to a different brand of heparin, errors might ensue because of a lack of familiarity with products from a different manufacturer. Furthermore, many sterile injectable drugs come in ready-to-use packaging or as a compound of multiple drugs. When the supply of these products is disrupted, the in-hospital pharmacy may prepare the medication by compounding the same product using a different strength, which could lead to preparation errors (Fox et al. 2014, Mazer-Amirshahi et al. 2014, Caulder et al. 2015).

There is some anecdotal evidence in the medical literature that medication errors increase because of drug shortages (McBride et al. 2013, McLaughlin et al. 2013, Caulder et al. 2015). However, Hughes et al. (2015) and Storey et al. (2016) do not find connections between medication errors and shortages of fentanyl and benzodiazepines or between medication errors and shortages of parenteral nutrition, respectively. It may be that the lack of connection arises from study design. For example, Hughes et al. (2015) look at only prescribing errors using retrospective chart review, and Storey et al. (2016) do not account for the amount of medication used. It may be that different methods would have uncovered an impact on medication errors. In summary, prior literature suggests that substitutions within drugs caused by supply disruptions can increase medication errors because of variations from prior routines in how medications are prescribed, prepared, and administered, which can lead to human error. Thus, we hypothesize the following.

Hypothesis 1. *Pharmaceutical supply chain disruptions will increase medication errors of the supply-disrupted drug because of within-drug substitutions.*

Across-drug substitution is a common practice during shortages (McBride et al. 2013). Previous authors have suggested that across-drug substitutions increase the risk of medication errors because of a lack of familiarity with proper dosing, administration procedures, and contraindications of the related medications (Fox et al. 2014, Mazer-Amirshahi et al. 2014, Kehl et al. 2015). As an example case, methohexital

was used as a substitute during a propofol shortage, which resulted in dilution errors and a patient receiving a fatal overdose (Schmidt 2012). For these reasons, we hypothesize that pharmaceutical supply chain disruptions increase medication errors of therapeutic substitutes because of across-drug substitutions, even though the therapeutic substitutes do not experience any supply disruptions. In other words, supply disruptions may have spillover effects and result in errors related to therapeutic substitutes.

Hypothesis 2. *Pharmaceutical supply chain disruptions will increase medication errors of therapeutic substitutes because of across-drug substitutions.*

3. Data, Variables, and Methodology

In this section, we describe data sources and define outcome and predictor variables. After that, we explain our analysis method, which is the synthetic control method.

3.1. Data

We collect our data on medication errors from the FAERS and calculate medication error rates by accounting for the volume of drugs being used, which is obtained from IQVIA NSP.

For medication errors, we use FAERS Quarterly Data Extract Files containing reports of adverse drug events and medication errors. Each year, the database receives more than 1 million reports submitted by healthcare professionals, consumers, and drug manufacturers (Food and Drug Administration 2018). The FDA uses the FAERS to monitor the safety of products and to make decisions about regulatory actions, such as restricting the use of a drug, communicating new safety information to the public, and even removing a product from the market (Food and Drug Administration 2018). Medical research uses the FAERS to evaluate the risks of certain drugs or treatments (e.g., Raschi et al. 2014, Kimura et al. 2015, Tkachenko et al. 2019). Because the data are submitted voluntarily, the database does not include the entire incidence and prevalence of medication errors in the United States and underreports adverse drug events (Alatawi and Hansen 2017, Sonawane et al. 2018). Despite these limitations, our causal estimates will not be biased unless the reporting rate changes over time (e.g., the reporting rate could change because of stimulated reporting by the FDA alerts of heparin shortages; Hoffman et al. (2014) show that FAERS reporting is not significantly affected by public alerts by analyzing 10 years of FAERS data).

In the FAERS, medication errors are labeled with the Medical Dictionary for Regulatory Activities (MedDRA) error terms, including "dose calculation error," "drug administered in wrong device," "drug dispensing error," "accidental overdose," "drug label confusion," and others. Our primary outcome measure is the number of medication errors, $error_{it}$, for drug i at quarter-year t from 2014 Q4 to 2019 Q4 (21 periods). We purposely limit our study period to 2019 to exclude the coronavirus disease 2019 pandemic period. We use the country of report in the data to include only errors that occur in the United States. To avoid double counting, we exclude follow-up reports.

We collect the sales volume of drugs before and after the hurricane from IQVIA NSP. Then, we merge this with data on medication errors to measure medication error rates. We obtain quarterly data on prescription drug sales volume and other predictor variables using IQVIA NSP. NSP contains national sales of prescription drugs to pharmacies, clinics, and hospitals among other distribution channels. Each observation includes the name of the molecule (active pharmaceutical ingredient) and branded name, sales amount in drug unit volume, sales amount in U.S. dollars, supplier of the product, distribution channel (e.g., pharmacies, clinics, hospitals, or food stores), product form (e.g., oral or injectable), strength, and other information (including therapeutic category, product launch date, and others) (Conti and Berndt 2020, IQVIA 2024, Park et al. 2024). From this data set, we extract the sales volume of drugs and other predictor variables (in Section 3.3) from 2014 Q4 to 2019 Q4.

As described in Section 3.4, we use the Merative Micromedex RED BOOK, which provides information on all U.S. drug products, to identify the subset of drugs that we use as our control group based on having similar characteristics to heparin. Finally, we utilize the FDA Drug Shortages Database (Food and Drug Administration 2020a) to identify drug shortages. This database records shortages of medically necessary products when the total supply of an FDA-regulated drug is insufficient to meet patient demand (Food and Drug Administration 2011, 2020b). This database specifies the start and end dates of shortages as well as provides a detailed list of all drug products involved.

3.2. Outcome Variables

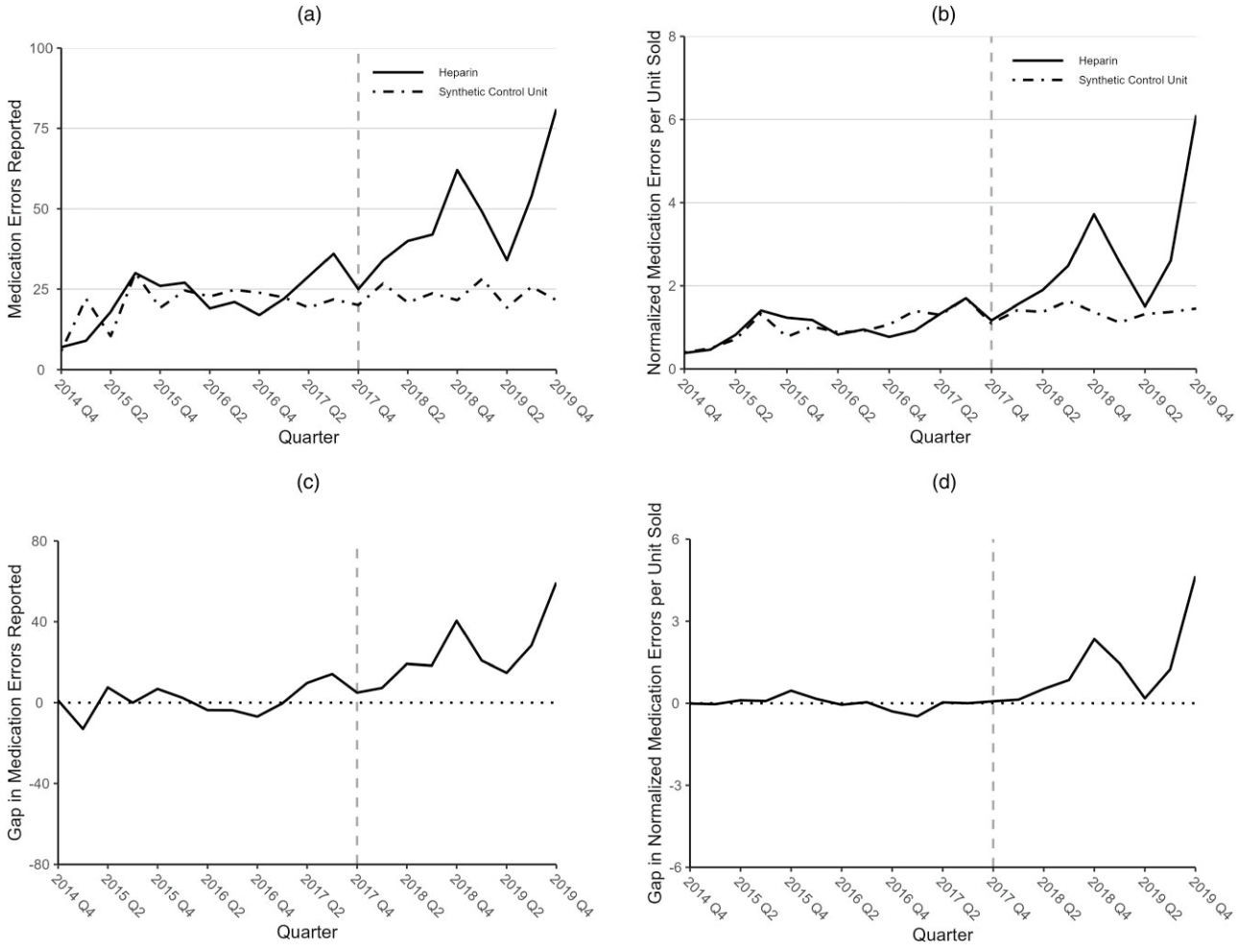
Our main outcome variable is the number of medication errors reported, $error_{it}$, for drug i at quarter-year t. Our unit of observation is drug-quarter level. Drug is defined by the active pharmaceutical ingredient; we consider NDCs that have the same active pharmaceutical ingredient but different dosage as the same drug. To account for the volume of drugs being used, we use a second outcome variable: normalized medication errors per unit sold, $error\ rate_{it}$. For this, we first define medication errors per unit sold for each drug i at quarter-year t, denoted here y_{it}^R, by dividing $error_{it}$ by the total sales volume of drug i at quarter-year t, $units\ sold_{it}$. That is, $y_{it}^R = \frac{error_{it}}{units\ sold_{it}}$. We then normalize the medication errors per unit sold by dividing y_{it}^R by

the pretreatment period ($t \leq T_0$) mean medication errors per unit sold (i.e., $y_{it} = y_{it}^R/(1/T_0)\sum_{t=1}^{T_0} y_{it}^R$). The sales volume of each drug varies greatly, which makes the raw medication error rates differ significantly by drug. Thus, normalizing the error rates allows comparison across drugs. Abadie (2021) suggests transforming the outcome variable when the outcome variable of the treated unit is incomparable with the outcome variables of the control groups. Others using the synthetic control method also use a normalized outcome variable (e.g., Lu et al. 2021). We retain $error_{it}$ as an outcome variable for two reasons. The sales volume of heparin decreases significantly after the supply disruption as shown in Figure 1(a), and therefore, an increase in the medication error rate may be because of the sales decrease rather than an increase in medication errors. Another benefit of using $error_{it}$ rather than $error\ rate_{it}$ is that its estimates are easier to interpret. Figures 2 and 3 plot the outcome variables of heparin and its therapeutic substitute enoxaparin, respectively.

3.3. Predictor Variables

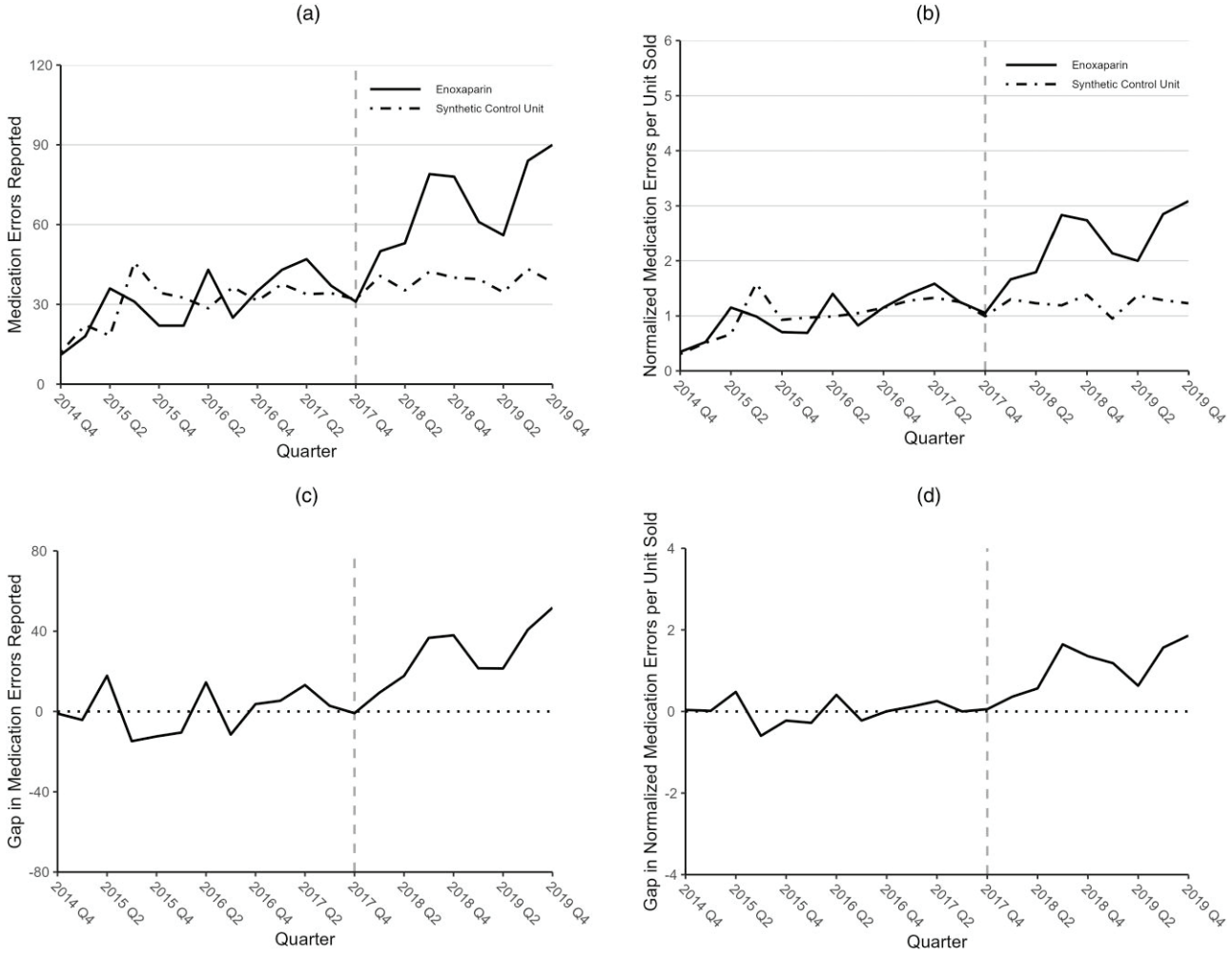
The synthetic control method aims to produce a comparison unit that best resembles the preintervention characteristics of the treated units (Abadie 2021). We include the following drug-quarter-specific characteristics because they are associated with medication errors as we show in Online Appendix B: number of product varieties, number of producers, average price, and age. We count the number of product varieties by counting unique products within a drug, defined

Figure 2. Medication Errors and Medication Error Rates: Heparin vs. Synthetic Control Unit



Notes. Panel (a) plots the quarterly medication errors reported, $error_{it}$, of heparin (solid line) and its corresponding synthetic control unit (dotted-dashed line) constructed for the outcome variable, $error_{it}$. Panel (b) plots the quarterly normalized medication errors per unit sold, $error\ rate_{it}$, of heparin (solid line) and its corresponding synthetic control unit (dotted-dashed line) constructed for the outcome variable, $error\ rate_{it}$. Panels (c) and (d) plot the gaps in outcomes between heparin and its corresponding synthetic control unit. The synthetic control units are constructed using 32 drugs in the control group. The vertical dashed lines represent the heparin supply chain disruption. (a) Outcome: $error_{it}$. (b) Outcome: $error\ rate_{it}$. (c) Gap: $error_{it}$. (d) Gap: $error\ rate_{it}$.

Figure 3. Medication Errors and Medication Error Rates: Enoxaparin vs. Synthetic Control Unit



Notes. Panel (a) plots the quarterly medication errors reported, $error_{it}$, of enoxaparin (solid line) and its corresponding synthetic control unit (dotted-dashed line) constructed for the outcome variable, $error_{it}$. Panel (b) plots the quarterly normalized medication errors per unit sold, *error* $rate_{it}$, of enoxaparin (solid line) and its corresponding synthetic control unit (dotted-dashed line) constructed for the outcome variable, *error* $rate_{it}$. Panels (c) and (d) plot the gaps in outcomes between enoxaparin and its corresponding synthetic control unit. The synthetic control units are constructed using 32 drugs in the control group. The vertical dashed lines represent the heparin supply chain disruption. (a) Outcome: $error_{it}$. (b) Outcome: *error* $rate_{it}$. (c) Gap: $error_{it}$. (d) Gap: *error* $rate_{it}$.

by active pharmaceutical ingredient, based on NSP's product variable. For the number of producers, we count the number of unique labelers (the corporation variable in NSP) of each drug. In addition, the average price is the average across the prices of all products (defined by the national drug code) that belong to the same drug. We define the age of each drug as the time from the earliest product launch year. We create a variable age by subtracting the first year that the drug was available from the current year. Following Abadie et al. (2010, 2015), we also include the pretreatment values of the outcome variables in matching characteristics. In Section 5, our results remain consistent when constructing the synthetic control unit by matching only the pretreatment outcome values.

3.4. Control Group Sampling

The synthetic control method requires a set of potential untreated comparisons (i.e., donor pool) (Abadie 2021). We gather a list of drugs for the donor pool from the list of all available drug products in the United States obtained from the Merative Micromedex RED BOOK. We restrict our donor pool to drugs with currently active NDCs, off-patent generic prescription drugs, and drugs that do not belong to certain therapeutic groups, including opioids and alkalinizing agents such as sodium bicarbonate. It is required that the outcomes of the control units in the donor pool are not affected by the heparin supply disruption. Therefore, we exclude anticoagulant drugs in the donor pool as they could be potential substitutes for heparin. We also exclude all drugs that experienced shortages

between 2017 and 2019 based on the FDA Drug Shortages Database (Food and Drug Administration 2020b) because their own supply disruptions could affect the outcome of these drugs. Lastly, we exclude drugs with few medication errors reported (less than 100) and few units sold (less than 10,000 units) during our study period. After the exclusions, 32 drugs remain in our donor pool. Online Appendix A describes the detailed sampling steps of the control group, and Table OA.3 in Online Appendix C lists the names of all drugs in the control group.

3.5. Methodology: Synthetic Control Method

To test our hypotheses, we employ the synthetic control method developed by Abadie and Gardeazabal (2003) and Abadie et al. (2010) to estimate the effects of aggregate policy interventions affecting only one or a few units on some aggregate outcome of interest using data-driven procedures to choose the comparison control units. The method uses a convex combination of untreated units as a synthetic control that best resembles the characteristics of the treated unit prior to the treatment and approximates the outcome that would have been observed for the treated unit in the absence of treatment (Abadie et al. 2010). We use this method because it has several advantages that are suitable for our study. First, the synthetic control method is appropriate for estimating the effects of aggregate treatment affecting only a few units on aggregate outcomes of interest (Abadie 2021). In our case, the treatment is the national-level supply disruption of a drug, and the outcome of interest is the number of medication errors at an aggregate (national) level. Second, the synthetic control method precludes researchers' discretion and burden in choosing the comparison control unit (Abadie et al. 2010). A synthetic control as a weighted average of the available control units, where the weights can be restricted to be nonnegative and sum to one, enables transparent control unit selection. Third, by allowing time-varying unobservable confounders, the method can address the endogeneity from omitted variable bias (Abadie et al. 2010, Billmeier and Nannicini 2013). Because many time-varying unobserved factors (e.g., clinician skill and hospital mitigation efforts) can affect medication errors, we believe that this feature of the synthetic control method is crucial for our analysis. A limitation of the synthetic control method is that traditional statistical inference is inappropriate because there are only one treated unit and few control units in our settings. For inference, we follow the synthetic control literature by using permutation inference proposed by Abadie et al. (2010, 2015).

We observe data for $i = 1, \ldots, J+1$ drugs over T periods. Without loss of generality, we assume that the first drug ($i = 1$) is the treated unit (heparin) for which the supply is disrupted at time $i = 1, \ldots, J+1$, where T_0 is Q4 2017 in our case. The effect of the supply disruption for the treated unit for $t > T_0$ can be defined as

$$\tau_{1t} = Y_{1t} - Y_{1t}^N, \tag{1}$$

where Y_{1t}, Y_{1t}^N denote the potential outcome with and without the supply disruption, respectively. Observe that Equation (1) allows the treatment effect, τ_{1t}, to change in time. A major challenge is that Y_{1t}^N cannot be observed. The synthetic control method uses a weighted average of the control units in the donor pool with $J \times 1$ vector of weights, $\boldsymbol{W} = (w_2, \ldots, w_{J+1})'$; replaces Y_{1t}^N with $\hat{Y}_{1t}^N$; and estimates τ_{1t} using $\hat{\tau}_{1t}$:

$$\hat{\tau}_{1t} = Y_{1t} - \hat{Y}_{1t}^N, \tag{2}$$

where

$$\hat{Y}_{1t}^N = \sum_{i=2}^{J+1} w_i Y_{it}. \tag{3}$$

Following Abadie et al. (2010) and Billmeier and Nannicini (2013), we specify Y_{it}^N as being generated by a linear factor model, which can be considered a generalization of difference in differences,

$$\hat{Y}_{1t}^N = \boldsymbol{\theta}_t \boldsymbol{Z}_i + \boldsymbol{\lambda}_t \boldsymbol{\mu}_i + \varepsilon_{it}, \tag{4}$$

where $\boldsymbol{Z}_i$ is a vector of observed covariates that are either time varying or time invariant, $\boldsymbol{\theta}_t$ is a vector of time-specific coefficients, $\boldsymbol{\mu}_i$ is a vector of drug-specific unobserved features, $\boldsymbol{\lambda}_t$ is an unobserved common factor across units (e.g., clinicians' skills), and ε_{it} are zero-mean individual transitory shocks. In this model, the coefficients of unobservable drug heterogeneity vary over time, whereas the fixed effects model imposes $\boldsymbol{\lambda}_t$ to be constant over time. Abadie and Gardeazabal (2003) and Abadie et al. (2010) developed the way to choose synthetic control using $\boldsymbol{W}^* = (w_2^*, \ldots, w_{J+1}^*)'$ that minimizes the distance $\|\boldsymbol{X}_1 - \boldsymbol{X}_0\boldsymbol{W}\| = \sqrt{(\boldsymbol{X}_1 - \boldsymbol{X}_0\boldsymbol{W})'\boldsymbol{V}(\boldsymbol{X}_1 - \boldsymbol{X}_0\boldsymbol{W})}$ subject to the restriction that the weights, $w_2, \ldots, w_{J+1}$, are nonnegative and sum to one. Here, $\boldsymbol{X}_1$ is the vector including $\boldsymbol{Z}_1$ and the preintervention outcomes for the treated unit, $\boldsymbol{X}_0$ is the matrix that includes $\boldsymbol{Z}_0$ and the preintervention outcomes of the untreated units in the donor pool, and $\boldsymbol{V}$ is a $k \times k$ diagonal positive semidefinite matrix. We follow Abadie and Gardeazabal (2003) and Abadie et al. (2010) and choose V such that the synthetic control $\boldsymbol{W}(\boldsymbol{V}) = (w_2(\boldsymbol{V}), \ldots, w_{J+1}(\boldsymbol{V}))'$ minimizes the mean squared prediction error (MSPE) with respect to the outcome variable in the pretreatment period. Now, we can estimate the treatment effect for the treated unit at time $t = T_0 + 1, \ldots, T$ as

$$\hat{\tau}_{1t} = Y_{1t} - \sum_{i=2}^{J+1} w_i^* Y_{it}. \tag{5}$$

Table 1. Means of Predisruption Period Characteristics of Heparin, Synthetic Control Units, and the Control Group

Variable	(1) Heparin	(2) Synthetic control (outcome: $error_{it}$)	(3) Synthetic control (outcome: $error\ rate_{it}$)	(4) Average of 32 control drugs
Medication errors ($error_{it}$)	20.45	20.45	—	61.60
Normalized error rate ($error\ rate_{it}$)	0.94	—	0.94	0.98
Producer	8.73	9.13	8.77	9.95
Age	42.64	42.54	23.58	24.55
Variety	13.73	13.79	13.72	12.62
Price	95.21	95.78	102.04	465.30

Notes. Columns (2) and (3) present the means of preperiod characteristics of the synthetic control unit constructed by using outcome variables $error_{it}$ and $error\ rate_{it}$, respectively. The synthetic control units are constructed using 32 drugs in the control group. $N = 693\,(33 \times 21)$.

Abadie et al. (2010) show that under $\boldsymbol{X}_1 = \boldsymbol{X}_0\boldsymbol{W}^*$, $\hat{\tau}_{1t}$ is an unbiased estimator for τ_{1t}, and under $\boldsymbol{X}_1 \approx \boldsymbol{X}_0\boldsymbol{W}^*$, the bias is bounded by the ratio between the scale of individual transitory shocks, ε_{it}, and the number of preintervention periods, T_0.

3.6. Identifying Assumptions

The validity of the synthetic control method requires the following identifying assumptions. First, the characteristics of the treated unit must be sufficiently matched by the synthetic control (Abadie et al. 2010, Abadie 2021); that is, $\boldsymbol{X}_1 \approx \boldsymbol{X}_0\boldsymbol{W}^*$. This requires the synthetic control to fit well both the outcome and the characteristics of the treated unit. For this, we show that characteristics, including outcomes, between the treated unit and the synthetic control unit are alike in Tables 1 and 2.

Second, the variance of the individual-specific transitory shocks, ε_{it}, must be small because the treatment effects will be indistinguishable from other shocks to the outcome if the volatility of the outcome is too large and because the bias of the estimate is bound by ε_{it} (Abadie et al. 2010, Abadie 2021). When $\boldsymbol{X}_1$ and $\boldsymbol{X}_0$ include the preintervention outcomes for the factor model in Equation (4), $\boldsymbol{X}_1 \approx \boldsymbol{X}_0\boldsymbol{W}^*$ typically requires that the variance of the transitory shock is small (Abadie 2021). Hence, we justify this assumption by showing that observed characteristics are similar between the treated unit and the synthetic control unit in Tables 1 and 2.

Third, only the treated unit (heparin) undergoes the treatment (supply chain disruption) and not any control drugs. For this assumption, we exclude drugs that suffered shortages during our sample period from the donor pool as described in Section 3.4. This is important because the synthetic control unit is meant to reproduce the medication errors that would have been observed for the heparin in the absence of supply chain disruption.

Fourth, the treatment should not affect the outcome of the untreated units (Abadie et al. 2010). In other words, the treatment should not have spillover effects (Lu et al. 2021). In our case, the supply disruption of heparin must not affect the medication procedures of other drugs. The spillover effect may exist if there are substitutions between heparin and other drugs. To verify this assumption, we exclude other anticoagulants from our donor pool. Additionally, as we find evidence of substitution between heparin and enoxaparin, we explore the spillover effects of the supply chain disruption by considering enoxaparin as another treated unit in Section 4.2.

4. Results

4.1. Effect on the Supply-Disrupted Drug's Medication Errors

As explained above, we construct the synthetic control for heparin as a convex combination of 32 drugs in the donor pool by matching pretreatment characteristics.

Table 2. Means of Predisruption Period Characteristics of Enoxaparin, Synthetic Control Units, and the Control Group

Variable	(1) Enoxaparin	(2) Synthetic control (outcome: $error_{it}$)	(3) Synthetic control (outcome: $error\ rate_{it}$)	(4) Average of 32 control drugs
Medication errors ($error_{it}$)	30.27	30.27	—	61.60
Normalized error rate ($error\ rate_{it}$)	0.98	—	0.98	0.98
Producer	5.82	5.28	5.82	9.95
Age	22.64	22.64	22.64	24.55
Variety	6.82	6.82	6.82	12.62
Price	129.55	130.45	145.68	465.30

Notes. Columns (2) and (3) present the means of preperiod characteristics of the synthetic control unit constructed by using outcome variables $error_{it}$ and $error\ rate_{it}$, respectively. The synthetic control units are constructed using 32 drugs in the control group. $N = 693$.

We construct synthetic control units separately by using each of the outcome variables, $error_{it}$ and $error\ rate_{it}$. Online Appendix C presents the weights for synthetic control units. Table 1 compares the average predisruption period characteristics of heparin with synthetic control units and 32 drugs in the donor pool. We see that the synthetic control unit constructed for the outcome variable, $error_{it}$, in column (2) in Table 1 produces characteristics similar to heparin in column (1) in Table 1. Likewise, the synthetic control unit constructed for the outcome variable, $error\ rate_{it}$, in column (3) in Table 1 produces similar characteristics of heparin, except for age. Because heparin is the second-oldest drug in our sample, this variable cannot be perfectly fitted using a combination of the comparison drugs. In contrast, the average characteristics of all 32 drugs in column (4) in Table 1 differ significantly from heparin in several variables. Overall, the results in Table 1 suggest that the synthetic control unit provides a much better comparison for heparin than the average of all of the control group drugs.

Panels (a) and (b) of Figure 2 depict the number of medication errors reported, $error_{it}$, and the normalized medication errors per unit sold, $error\ rate_{it}$, respectively, for heparin (solid lines) and its synthetic counterpart (dotted-dashed lines) during the study period. First, the synthetic control units closely fit heparin during the predisruption period in terms of both $error_{it}$ and $error\ rate_{it}$. This supports the first assumption in Section 3.6. Together with the high degree of matching on predictors shown in Table 1, this suggests that the synthetic control unit provides reasonable approximations to both outcome variables that would have occurred from 2018 Q1 to 2019 Q4 (postdisruption period) in the absence of supply chain disruption.

Our estimate of the effect of the supply chain disruption on heparin medication errors is the difference in the outcomes between heparin and its synthetic control unit after the supply chain disruption as in Equation (5), which we plot in Figure 2(c). We estimate that 26.1 more medication errors occur in each quarter on average during the postperiod (104.4 more errors per year). This is a 127% increase relative to the predisruption average medication errors. We find a consistent result using the outcome variable $error\ rate_{it}$, which controls for the volume of drugs sold in each period (Figure 2(d)). We estimate a 1.42 increase in normalized medication error rates in each quarter, which is a 152% increase compared with the predisruption average. The results indicate that the supply chain disruption significantly increased medication errors of heparin. The findings of these two variables complement each other by confirming that the increase in medication errors is not because of an increase in the volume of the drug used and that the increase in the medication error rate is not because of a decrease in the volume of the drug used but rather, an increase in medication errors. Therefore, the results support Hypothesis 1.

An important observation is that the effect of supply disruption on medication errors changes over time. Figure 2 shows that the gaps between heparin and its synthetic control unit are small in the first few quarters after the supply disruption. Recall that Figure 1(a) shows that the heparin sales volumes did not decrease immediately after the supply disruption. However, the effect becomes more pronounced after 2018 Q2 because sales volume fell greatly, suggesting that more clinicians were affected by the shortage. Interestingly, we estimate the smallest effect in Q2 2019 when there was a quick recovery in the sales volumes of heparin. We find the largest effect in Q4 2019 when the extent of the shortage was most severe as illustrated in Figure 1(a). Thus, we find that the less the drug is being used, which is caused by a supply shortage, the more medication errors occur.

4.2. Spillover Effects on the Substitute Drug's Medication Errors

Clinicians can use enoxaparin, a low-molecular-weight heparin, as an alternative to heparin (Garcia et al. 2012, Rosovsky et al. 2020). The authors directly heard from different clinicians who substituted heparin with enoxaparin after Hurricane Maria. For example, a major hospital in the Boston area holds weekly drug shortage committee meetings to address the shortages that they experience. The first author attended the meetings and observed that when they faced difficulty in procuring heparin, their first choice was to use enoxaparin. We further validate this substitution using the IQVIA NSP data. We find that the sales volume of enoxaparin significantly increased after the heparin supply disruption, whereas other injectable anticoagulants did not (Online Appendix D presents the detailed analysis). Importantly for our study, enoxaparin did not experience a shortage during our postheparin supply disruption period. Thus, we can use enoxaparin to test the effect of across-drug substitution.

We test Hypothesis 2 using the synthetic control method and calculate new weights specific to enoxaparin. Table OA.4 in Online Appendix C displays the weights for synthetic control units for enoxaparin. Table 2 compares the average predisruption period characteristics of enoxaparin with synthetic control units and the 32 drugs in the donor pool. In column (2) in Table 2, we confirm that the synthetic control unit constructed for the outcome variable $error_{it}$ produces characteristics similar to enoxaparin in all variables. Additionally, the synthetic control unit constructed for the outcome variable $error\ rate_{it}$ in column (3) in Table 2 matches the characteristics of enoxaparin. The average

characteristics of all 32 control drugs presented in column (4) in Table 2 show substantially different values with enoxaparin. The results in Table 2 corroborate that the synthetic control units provide more suitable comparisons for enoxaparin than the average of the sample drugs.

Panels (a) and (b) of Figure 3 illustrate the trends of the outcome variables $error_{it}$ and $error\ rate_{it}$, respectively, for enoxaparin (solid lines) and its synthetic counterpart (dotted-dashed lines). First, both outcomes of the synthetic control units closely match enoxaparin before the supply chain disruption (vertical lines in Figure 3). Together with the high degree of affinity on all predictors in Table 2, this suggests that the synthetic control unit provides good approximations to both outcome variables that would have occurred from 2018 Q1 to 2019 Q4 (postdisruption period) in the absence of supply chain disruption of heparin. The increasing trends in postperiod outcomes for enoxaparin suggest increases in medication errors caused by the supply chain disruption of another drug: heparin.

We estimate the effects of supply chain disruptions on medication errors and medication error rates for enoxaparin using Equation (5), which we plot in Figure 3, (c) and (d), respectively. We find that heparin supply chain disruption has a significant effect on medication errors of enoxaparin. We estimate that 29.63 more medication error events occur for enoxaparin in each quarter on average after the heparin supply disruption (118.52 more errors per year), a 98% increase relative to the predisruption period. Similarly, the normalized medication error rates of enoxaparin increased by 1.15 on average during the postperiod, a 114% increase relative to the predisruption period. In summary, we find that the supply chain disruption of heparin has a spillover effect on another substitute drug, enoxaparin, by increasing medication errors. Thus, the results support Hypothesis 2.

4.3. Inference About the Effects of the Supply Chain Disruption on Medication Error Rates

To evaluate the statistical significance of our treatment effect estimates, we follow the synthetic control literature by using permutation inference (Abadie et al. 2010, 2015; Lu et al. 2021). We run a series of placebo tests by iteratively applying the synthetic control method to estimate the effects of the heparin supply chain disruption on every other drug in the donor pool. For each iteration, we reassign the supply chain disruption to 1 of 32 drugs in the donor pool as if the reassigned drug would have experienced a supply disruption while shifting the original treated units, heparin and enoxaparin, to the donor pool.

Figure 4 shows the results of the placebo tests. The gray lines in Figure 4 represent the estimated gap associated with each placebo test. That is, the gray lines in Figure 4 show the difference in medication error rates between each drug in the donor pool and its respective synthetic control unit. The superimposed black solid and dotted-dashed lines in Figure 4 illustrate the gap estimated for heparin and enoxaparin, respectively. As placebo tests with poor fit before the heparin supply chain disruption (dashed vertical lines in Figure 4) do not provide information to measure the relative rarity of estimating a large postdisruption gap (Abadie et al. 2010), we plot different versions by excluding drugs that exceed 10 times the MSPE of heparin in Figure 4(b) and excluding drugs that exceed 5 times the MSPE of heparin in Figure 4(c). Figure 4 shows that the gap lines of heparin and enoxaparin are clearly the unusual lines that show consistently substantial positive gaps after the disruption.

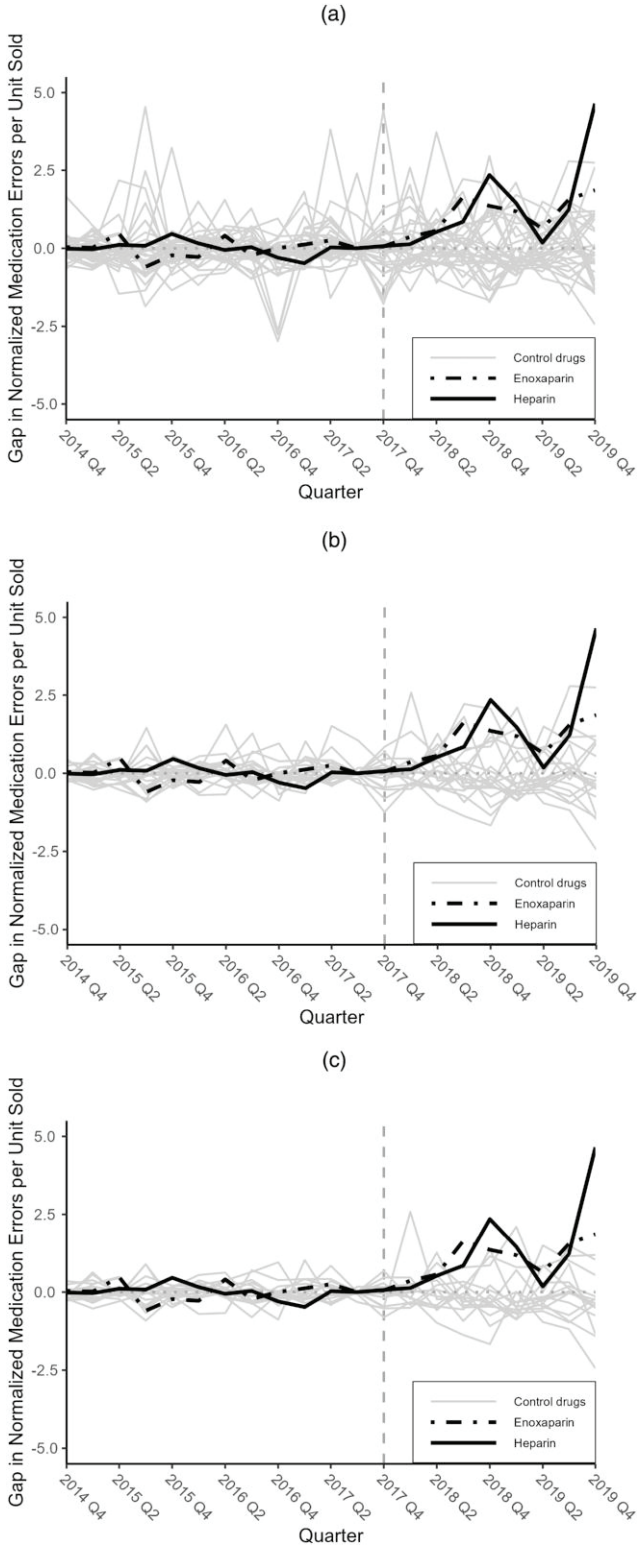
We evaluate the significance of the true effects by looking at the distribution of the ratios of post-/predisruption root mean squared prediction error (RMSPE). Because a large outcome gap is not indicative of a large effect of the supply chain disruption if the synthetic control does not closely reproduce the preperiod outcome, this method can make a more robust inference comparing the postperiod RMSPE with the preperiod RMSPE. Abadie et al. (2015) and Abadie (2021) suggest using RMSPE to measure the preperiod fit between the outcome variable of any particular unit and its synthetic counterpart. Specifically,

$$\mathrm{RMSPE}_{i,pre} = \left(\frac{1}{T_0}\sum_{t=1}^{T_0}(Y_{it} - \hat{Y}_{it}^N)^2\right)^{\frac{1}{2}}, \quad \text{for } i = 1, \ldots, J+1, \qquad (6)$$

where $\hat{Y}_{it}^N$ is defined as in Equation (3) when unit i is coded as treated and using all other J units to estimate $\hat{Y}_{it}^N$. In our inference, we replace $Y_{it} - \hat{Y}_{it}^N$ in Equation (6) with their positive parts $(Y_{it} - \hat{Y}_{it}^N)^+$ to make a one-sided inference that results in a substantial gain of power (Abadie 2021). Likewise, $\mathrm{RMSPE}_{i,post} = \left(\frac{1}{T-T_0}\sum_{t=T_0+1}^{T}((Y_{it} - \hat{Y}_{it}^N)^+)^2\right)^{\frac{1}{2}}$. For brevity, we discuss here only the results for the outcome variable *error rate*, and the results of the outcome variable *error* are reported in Online Appendix E.

Figure 5 displays the distribution of ratios between the postdisruption RMSPE and the predisruption RMSPE for heparin, enoxaparin, and all drugs in the donor pool. It shows that heparin has the highest RMSPE ratio and that enoxaparin has the second-highest RMSPE ratio, whereas no control drug achieves such large ratios. The results suggest that the probability of obtaining a post-/predisruption RMSPE ratio as large as heparin or enoxaparin is $1/33 = 0.030$. Therefore, we can infer that the effects of the supply chain disruption on medication error rates of both the supply-disrupted

Figure 4. Placebo Tests (Outcome Variable: *error rate*)



Notes. The figure plots the gap in *error rate*$_{it}$ between each control drug and its respective synthetic control unit (gray solid lines), between enoxaparin and its synthetic control unit (black dotted-dashed lines), and heparin and its synthetic control unit (black solid lines). The dashed vertical lines represent the heparin supply chain disruption. (a) Normalized medication error rate gaps of heparin, enoxaparin, and placebo of 32 control drugs. (b) Normalized medication error rate gaps of heparin, enoxaparin, and placebo of 19 control drugs (discarding drugs with pretreatment MSPE 10 times higher than that of heparin). (c) Normalized medication error rate gaps of heparin, enoxaparin, and placebo of 15 control drugs (discarding drugs with pretreatment MSPE five times higher than that of heparin).

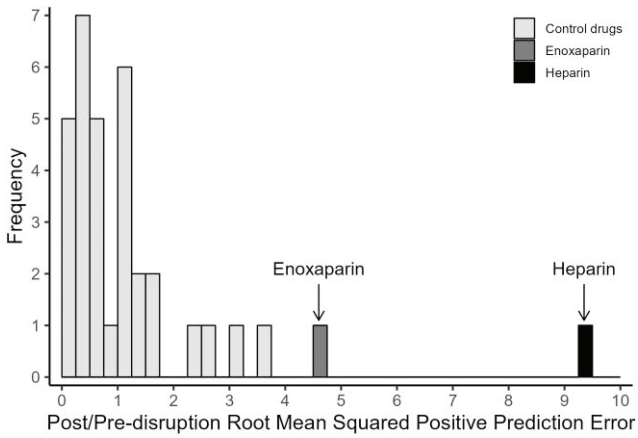
drug (heparin) and the substitute drug (enoxaparin) are significant at a 5% significance level.

4.4. Underlying Mechanism: Increase in Errors at Later-Stage Steps in Medication Administration Processes

To gain a deeper understanding of what may be causing the increased medication errors, we analyze errors by step in the medication administration process: (1) prescribing, (2) preparation, (3) dispensing, and (4) administration. For classification, we followed the MedDRA. We seek to illuminate which process steps are most vulnerable during drug shortages. We plot the changes in medication errors by period (pre- versus postdisruption) and process step in Figure 6. For the medication error rates, we present the results in Online Appendix F for brevity.

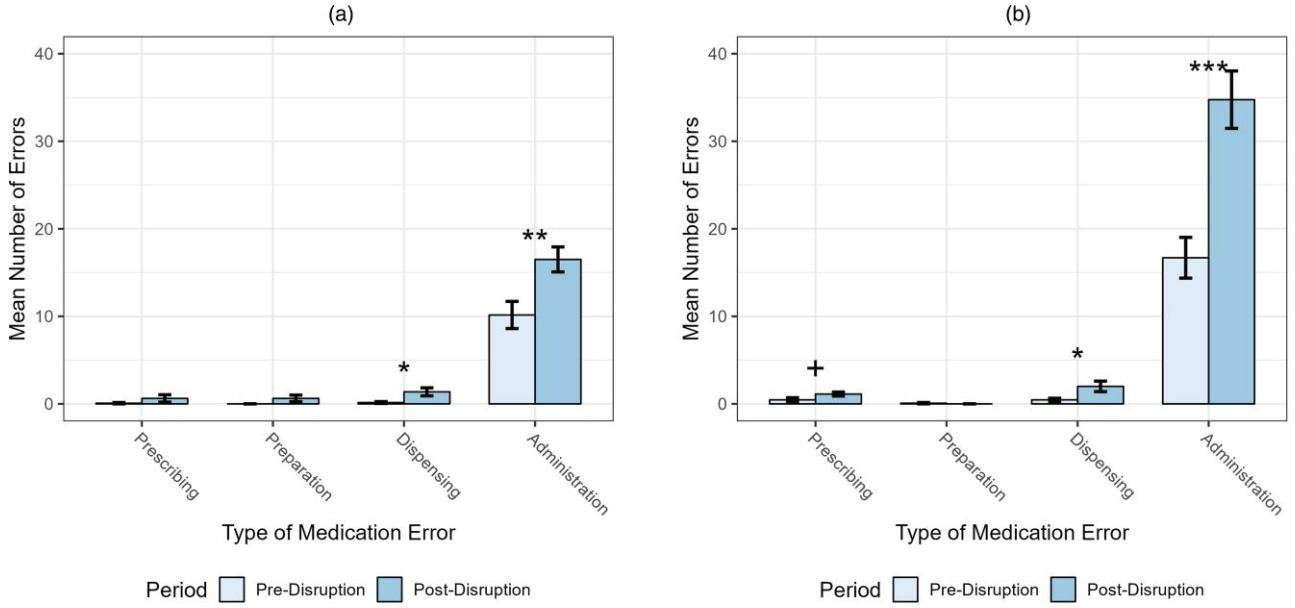
For both heparin and enoxaparin, in the postperiod, we find that medication errors increased only for the last two process steps of dispensing and administration. This result reinforces prior research that finds that medication errors during prescribing and preparation are more likely to be intercepted before reaching patients than those that occur during dispensing and administration because of less remaining time and opportunity to prevent later-stage errors from reaching patients (Bates et al. 1995). More specifically, Bates et al. (1995) find that 48% of the errors at the prescribing stage are intercepted in contrast to zero at the

Figure 5. Ratio of Postdisruption RMSPE to Predisruption RMSPE



Note. The figure plots the distribution of the ratio of postdisruption root mean squared positive prediction error to predisruption root mean squared positive prediction error.

Figure 6. (Color online) Changes in Medication Errors by Error Type



Notes. Panels (a) and (b) plot the average quarterly medication errors reported (bars) by period (color) and by error type (x axes) for heparin and enoxaparin, respectively. The error bar indicates the standard error of the mean. The predisruption period is from 2014 Q4 to 2017 Q4, and the postdisruption period is from 2018 Q1 to 2019 Q4 as in our analysis. (a) Heparin. (b) Enoxaparin. Asterisks indicate the t-test significance.
$^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; $^{+}p < 0.1$.

administration stage. Thus, our results suggest that during supply chain disruptions, clinicians and managers should pay extra attention to the later stages of medication processes, such as dispensing and administration, because of the high likelihood of errors.

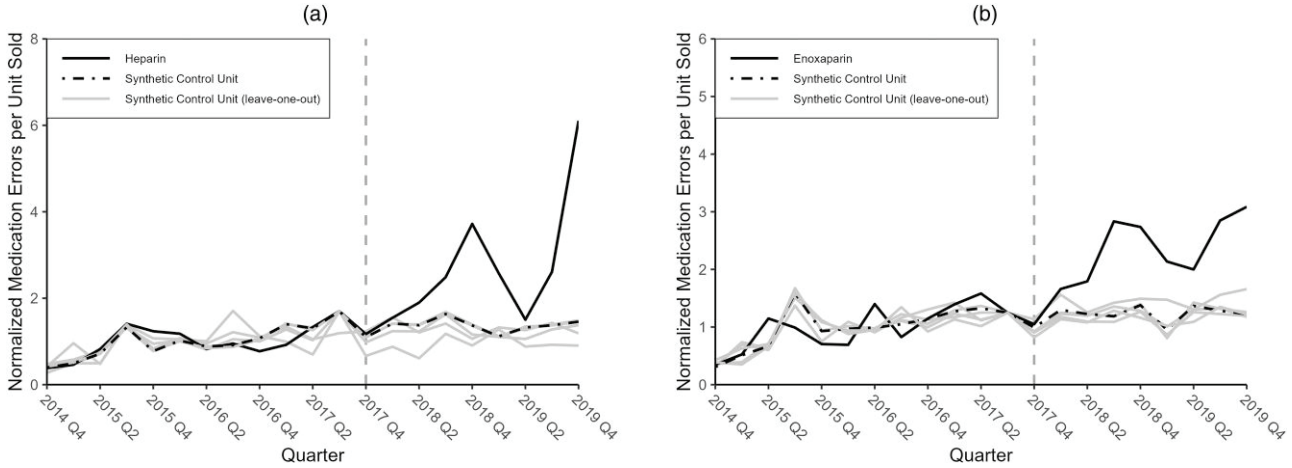
5. Robustness Checks

We run multiple robustness checks to test the credibility of our results. First, we run an in-time placebo study following Abadie et al. (2015). We rerun the model for the case when the supply chain disruption is reassigned to the middle of the pretreatment period in 2016 Q2, about 1.5 years earlier than the actual heparin supply chain disruption. We use the same procedures to construct the synthetic control by matching the predictor variables accordingly. We find that the outcome values of heparin and enoxaparin do not diverge significantly after the placebo supply chain disruption, whereas the synthetic control units produce matched outcome values before the placebo supply chain disruption (Figure OA.5 and Figure OA.6 in the Online Appendix). In stark contrast to the actual supply chain disruption in 2017 Q4, the 2016 Q2 placebo supply chain disruption has no perceivable effect. The finding suggests that the gaps estimated in Figures 2 and 3 reflect the impact of supply chain disruption and not a potential lack of predictive power of the synthetic control (Abadie et al. 2015).

Second, we iteratively rerun the analysis to construct a synthetic control unit, omitting in each iteration one of the drugs that received the top five largest weights in Tables OA.3 and OA.4 in the Online Appendix. Doing so, we lose some goodness of fit, but this allows us to test whether our results are driven by any particular control drug (Abadie et al. 2015). Figure 7 displays the results and confirms that our main results are robust to excluding any particular drug from the donor pool. The results for *error* are summarized in Online Appendix H.

Third, following other research using the synthetic control method, we estimate the effects of supply chain disruptions on medication error by matching only the pretreatment outcome values (Conti and Valentini 2018, Guo et al. 2020). We find consistent results with our main analyses (Online Appendix I). For heparin, we estimate that about 18.1 more medication errors occurred in each quarter on average during the postperiod (89% increase relative to the predisruption period), and this effect is statistically significant at the 5% level. Likewise, the normalized medication error rate of heparin increases by 1.3 (140% increase relative to the predisruption period), with statistical significance at the 5% level. For the substitutable drug, enoxaparin, we estimate that about 25.8 more medication errors occurred in each quarter on average after the heparin supply chain disruption (85% increase relative to the predisruption period), with statistical significance at the 10% level. The normalized medication error rate of enoxaparin increases by 0.9 (97% increase relative to the predisruption period), with statistical significance at the 5% level.

Figure 7. Leave-One-Out Distribution of the Synthetic Control Unit



Notes. Panel (a) plots the quarterly normalized medication errors per units sold, *error rate*$_{it}$, of heparin (solid line), synthetic control unit (dotted-dashed line), and leave-one-out synthetic control units (gray lines). Panel (b) plots the quarterly normalized medication errors per unit sold, *error rate*$_{it}$, of enoxaparin (solid line), synthetic control unit (dotted-dashed line), and leave-one-out synthetic control units (gray lines). The vertical dashed lines represent the heparin supply chain disruption. (a) Heparin. (b) Enoxaparin.

Fourth, we test the sensitivity of our estimates using other estimators. Arkhangelsky et al. (2021) develop a new estimator, SDID, by combining attractive features of the synthetic control method and the difference in differences. Compared with the synthetic control method, this estimator adds unit-specific fixed effects and time-specific fixed effects and uses both unit and time weights to match the pretreatment outcomes of control groups with the treated unit. Specifically, consider the following difference-in-differences specification with two-way fixed effects, $Y_{it} = \alpha + \beta_i + \gamma_t + \tau D_{it} + \varepsilon_{it}$, where Y_{it} denotes the outcome for unit i (drug) in period t (quarter-year); $D_{it} \in \{0,1\}$ represents the binary treatment,; α is the intercept; and β_i and γ_t denote unit fixed effects and time fixed effects, respectively. The SDID estimator adds unit weights, ω_i, that align pretreatment outcomes of the control group with those of the treated unit and time weights, λ_t, that balance pretreatment periods with posttreatment periods (Arkhangelsky et al. 2021). That is, SDID solves the following problem to estimate the average causal effect: $(\hat{\tau}, \hat{\alpha}, \hat{\beta}, \hat{\gamma}) = \arg\min_{\tau,\alpha,\beta,\gamma} \{\sum_{i=1}^{N} \sum_{t=1}^{T} (Y_{it} - \tau D_{it} - \alpha - \beta_i - \gamma_t)^2 \hat{\omega}_i \hat{\lambda}_t\}$.

We estimate the effects of supply chain disruptions on medication error rates, *error rate*$_{it}$, by using SDID and differences in differences (without and with control variables) in Table 3. In summary, we find consistent results with our main analyses where the estimates are comparable in magnitudes with estimates from the synthetic control method and statistically significant across different estimators.

6. Discussion and Conclusion

6.1. Summary

We find that the supply chain disruption of the medication heparin caused by Hurricane Maria in 2017 significantly increased medication errors of the supply-disrupted drug heparin. In addition, we find a spillover effect of the supply chain disruption; it increases medication errors of an alternative drug enoxaparin, which did not experience coincident supply chain disruptions. Using a rigorous comparative case study method, the synthetic control method, we estimate that supply chain disruption caused by Hurricane Maria increases medication error rates of the supply-disrupted drug, heparin,

Table 3. Estimates Using Alternative Estimators

	Treated unit: Heparin			Treated unit: Enoxaparin		
	(1) SDID	(2) DID	(3) DID with controls	(4) SDID	(5) DID	(6) DID with controls
Estimate	1.54**	1.34**	1.47***	0.79*	0.94***	0.96***
Standard error	(0.43)	(0.48)	(0.10)	(0.38)	(0.18)	(0.10)

Notes. The table reports the estimates for the average effect of the heparin supply chain disruption on medication error rates (*error rate*) of heparin and enoxaparin using *synthetic difference in differences (SDID)*, difference in differences (DID), and DID with control variables. The control group includes 32 drugs as in the main analysis. We report standard errors using the placebo method standard error estimator in Arkhangelsky et al. (2021) in columns (1) and (4), and we report standard errors clustered by the unit in columns (2), (3), (5), and (6). $N = 693$.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

and a substitute drug, enoxaparin, by about 152% (104.4 more errors per year) and 114% (118.52 more errors per year), respectively. Our results are consistent with previous reports that provide anecdotal evidence of increases in medication errors because of drug shortages (McBride et al. 2013, McLaughlin et al. 2013, Caulder et al. 2015).

6.2. Contributions to Literature

This paper contributes to the supply chain management literature by empirically showing the causal effects of supply chain disruptions on the quality of medical services. Previous literature focuses on the economic impacts of supply chain disruptions on firms' financial performance (Hendricks and Singhal 2003, 2005a, 2005b). Using medication error as a measure of service quality, we show that variations in service supplies, such as medicines, harm service quality. Additionally, our paper contributes to the operations management literature and medical literature studying drug shortages (e.g., McBride et al. 2013, McLaughlin et al. 2013, Caulder et al. 2015, Jia and Zhao 2017, Vail et al. 2017, Lee et al. 2021, Galdin 2024, Swinney et al. 2024, Noh et al. 2025). Our paper is one of the few studies that provides a causal estimate of the impact of drug shortages on healthcare services. In addition, we show a spillover effect; supply chain shortages affecting one drug trigger an increase in medication errors for a substitute drug.

6.3. Managerial Implications

The risk of supply chain disruptions is increasing (Council of Economic Advisers 2022). Therefore, our results should be of interest to clinicians, healthcare managers, and policymakers. Previous authors posit that within- and across-drug substitutions could lead to medication errors because of a lack of familiarity with proper dosing, administration procedures, and contraindications (Fox et al. 2014, Mazer-Amirshahi et al. 2014, Kehl et al. 2015). Our results empirically support these concerns by showing that both within- and across-drug substitutions during shortages are associated with increased medication error events.

We find in Section 4.4 that errors made during the later stages of dispensing and administration are more likely to reach patients. Thus, our study suggests that it is important to notify pharmacists, nurses, and physicians about supply chain shortages and the resulting substitutions along with the heightened risk of error. To illustrate, a hospital that we collaborate with regularly emails its staff, including pharmacists, nurses, and physicians, about drug shortages and substitute therapy options. The hospital also posts labels on drugs alerting nurses about the potential for medication errors. Similarly, during the heparin shortage, Massachusetts General Hospital (MGH) created alert messages for physicians in their Epic electronic health record system with detailed, tailored clinical guidance on the alternatives and information on indications and dosing (Rosovsky et al. 2020). MGH developed alternative therapy guidelines for physicians tailored to specific patient populations (e.g., cancer patients), which helped surface where additional education was needed to prevent medication errors, such as providing initial starting rates for dosing regimens for substitute drugs (Rosovsky et al. 2020). Furthermore, during the heparin supply shortage, MGH's Emergency Operations Plan included frequent meetings of service leads made up of physician, nursing, and pharmacy representations from many areas, including perioperative services, cardiology, cardiac surgery, neurology, hematology, oncology, and pediatrics, to stay abreast of the effectiveness of the hospital's response plan (Rosovsky et al. 2020). As a result of these efforts, MGH could rapidly standardize updated anticoagulant use practices during the heparin shortage (Rosovsky et al. 2020). Hospitals could emulate these practices to manage and mitigate the impact of drug shortages. In addition, collecting data on medication errors during drug shortages could help surface problems quickly.

6.4. Limitations

This paper has a few limitations. First, as we study shortages of a single, albeit clinically important, prescription drug, we cannot test the external validity of our results. Because the impact of drug supply chain disruptions varies according to the drug that is affected and the duration and severity of the supply disruption (Vail et al. 2017, Lee et al. 2021), not all pharmaceutical supply chain disruptions will lead to increases in medication errors. Nonetheless, we focus on the heparin supply disruption case because we aim to use the exogenous event to estimate an unbiased causal effect. Our results could be generalized for shortages of essential drugs, like heparin, because healthcare providers need to find substitutes to continue patient care. Second, because our unit of analysis is at the aggregate drug level, we cannot identify medication errors at the product or patient levels. The lack of individual-level data limits understanding of heterogeneous effects across patients and products. We hope that future research can explore the effects of supply disruptions on medication errors with more granularity. Third, because the adverse events are reported voluntarily to the FAERS, the database is not free from errors (Veronin et al. 2020), and information in each report has not been verified by the FDA (Food and Drug Administration 2018). Nevertheless, the FAERS is used by the FDA to monitor the safety of pharmaceutical products (Food and Drug Administration 2018) and is widely used by medical research (Raschi et al. 2014, Kimura et al. 2015, Tkachenko et al. 2019) and

management studies (Diestre et al. 2020, Gao et al. 2022). Future research could use alternative sources to measure adverse events, such as social media posts (Gao et al. 2022).

6.5. Conclusion

Global supply chains, including medical supply chains, are facing more disruptions because of increased natural disasters and geopolitical upheavals around the world (Council of Economic Advisers 2022, National Academies of Sciences et al. 2022). Our study finds that supply chain disruptions in essential medications may have downstream negative consequences on patient care quality. Hence, clinicians and hospital managers need to develop proactive response measures that protect patients from suffering harm because of drug shortages. We hope that our paper contributes to the research body that helps build more resilient pharmaceutical supply chains.

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