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Abstract

Drug shortages are a problem widely documented around the world. We develop a simple method allowing to identify shortage events and their intensity using sales data at a national level. In the case of prescription drugs, shortages occur when the quantities supplied do not meet demand at regulated prices. Using sales data only, shortages that are driven by supply shocks affect only the lower distribution of sales quantities and can be identified using a demand prediction model estimated on sales observed above a given quantile threshold. We can then measure the likelihood and the magnitude of shortage events. We provide evidence that lower French prices increase the likelihood and magnitude of shortages in France. However, higher prices in the UK seem to have positive spillover effects on reducing the likelihood of shortages, while a negative one when shortages happen and there is competition for scarce resources internationally. Finally, we provide evidence on the heterogeneous effects of shortage reductions achievable through higher regulated prices in France.

Keywords: Drug Shortages, Prices, Regulation, Econometrics.

JEL codes: L5, L65, I18.

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1 Introduction

Drug shortages are a problem widely documented around the world. Acosta et al. (2019) reviewed the recent literature and found 56 studies describing the drug shortage situation in a regional context (Europe, Latin America), as well as country specific analyses: covering the US (26 studies), EU markets (e.g. France, Spain, Ireland), Brazil, Venezuela, Australia, and a few Asian countries. In a survey of 537 European hospital pharmacies, over 85 % of respondents agreed that drug shortages are a current problem in their country (EAHP, 2014).

The main implications of shortages include disruption to the treatment (in particular, switching to an inferior alternative therapy (Becker et al., 2013)), additional costs (e.g. increased workload for hospital pharmacies (Kaakeh et al., 2011) and price increases of affected drugs (Dave et al., 2018)), and the emergence of illicit drug trade (Fittler et al., 2018). While uncertainty of supply chains may be impossible to fully eradicate or way too costly with oversized production capacities to cover demand whenever there are factory disruptions, it is important to measure the right trade-off between spending on drug manufacturing and shortage risk.

In this paper, we develop a methodology allowing to identify shortage events and their intensity using sales data at a national level. Intuitively, shortages occur when the quantities supplied do not meet demand for prescription drugs whose prices are typically regulated in most European countries. Using sales data only, identifying these events is not trivial, as sales during the shortage periods do not reflect the underlying demand and supply curves, and using these periods to estimate these functions would produce biased results.

Our method relies on the assumption that the shortages are driven by supply shocks, and that the size of the market studied is small in comparison to the global market, making the shortage events exogenous to local demand. Indeed, these shocks correspond to production capacities disruption events that can alter significantly the production level of a drug during enough time so that stocks are insufficient to smooth the shock. Under these circumstances, large sales quantities in a small country compared to the world demand are not affected by shortages because the largest possible demand in a small country cannot be causing a shortage at the world level. Thus, we can define a threshold level of sales above which shortages do not happen. In the limit case where demand is constant, this method simply uses the fact that if sales are smaller than the regular demand when there are no shortages it means that there is a shortage and thus a supply lower than the country's demand. Then, the question is simply to identify the frequency of shortages that can be identified using the frequency of the largest sales value of the drug in the country. Of course, the demand for a drug in France may not be constant but vary with prices, drug diffusion, innovation, and our method thus needs to account for varying demand.

We consider a threshold depending on the quantile of the observed sales distribution, fixed at the drug class level. We choose the threshold level comparing the resulting predicted demand (estimated using time periods when sales are above the threshold) to the realized sales. We define shortages as periods when the observed sales are below the threshold and the predicted demand. The magnitude of the shortage is the sum of the differences between the predicted demand and the realized sales in these periods.

We apply the methodology to monthly data covering purchases of hospital pharmacies in France in the period 2016-2021 provided by the GERS association. We find that the drugs probability of shortage is on average 26% but with large heterogeneity.

With these estimates, we proceed to study the determinants of shortages. We focus on prices, both domestically and in other countries (here we use the example of the UK) as drugs and their ingredients are traded globally. We find that higher prices in France lead to a lower probability of a shortage and a higher supply of the drug in case of a shortage. On the other hand, while higher prices in the UK are also associated with a lower probability of a shortage in France, conditional on a shortage they lead to lower supply in France. These results suggest a trade-off between low prices and the probability and magnitude of shortages. The effects of the UK prices suggest that in the event of a shortage, firms shift the remaining supply towards countries with higher prices. But they also suggest a positive spillover effects of prices on the shortage probability, probably through the production capacity that higher global prices allow to build.

Our counterfactual exercise suggests that prices have some power as a tool for reducing shortages, and that the positive spillover effects across countries call for cooperative price setting to reduce the likelihood of such events. However, we find that while appropriate unilateral price increases can substantially reduce shortages, their welfare implications are not obvious if we account for the decrease in demand they cause in non-shortage periods.

In the existing literature on drug shortages, the problem is most often analyzed by medical professionals, discussing clinical implications of the shortages, case studies of particular drugs, and surveys of the personnel directly affected by them. Some policy-oriented studies feature informal discussions of the economic forces in place (Acosta et al., 2019; Woodcock and Wosinska, 2013; Parsons et al., 2016; Dave et al., 2018).

Yurukoglu et al. (2017) uses the sterile injectable products market to study the relationship between reimbursement and shortages. In 2003 and 2005 Medicare substantially reduced the amounts reimbursed to practitioners administering the drugs. The paper hypothesizes that drugs with lower fixed costs and serving more Medicare patients are affected more severely by the decline in reimbursement. The empirical model, a quasi-DiD setting using a measure of the drug's Medicare market share (as treatment intensity), suggests that drugs more exposed to this policy change experienced longer durations of shortages. A theoretical model in Kim and Morton (2015) lends support to this conclusion, while Yang (2020) finds spillovers of the policy on the Californian Medicaid system. Stomberg (2016) focuses on non-injectables drugs and how shortages react to the changes in the intensity of FDA's quality control. When the probability of inspection increases, manufacturers not meeting the standards might experience disruptions.

Parsons et al. (2016) confirms a positive correlation between the probability of shortage and the generic status of the drug. Low margins in the generic market mean that the manufacturing sites are used at their capacity. The lack of spare capacity limits the ability to perform regular maintenance, increasing the risk of disruptions. At the same time, without backup production lines, any disruption can translate into a shortage. The weak failure-to-supply clauses existing in this market aggravate this problem, as the manufacturer faces a low cost of undersupplying. Finally, limited capacity makes the producers shift to the most profitable products - Haninger et al. (2011) show that drugs experiencing shortages in 2008-2011, faced, on average, decreasing sales volumes and prices in 2006-2008.

Apart from generic competition, prices can be driven down if the buyer has substantial bargaining power. Half of the childhood vaccines in the US are paid for by the government. The CDC acquires them directly from the manufacturers and uses strict price caps. Ridley et al. (2016) estimate that a 1% increase in price is associated with a 0.086 pp decrease in probability of shortage in the following year. In the period studied, the shortages reach a peak in 2007, with 7 vaccines unavailable. A study of generics dispensed in outpatient pharmacies, confirms the relationship between price and risk of shortage, finding that lower priced generics are more often in shortage (Dave et al., 2018). In Europe, unlike the US, branded drugs are relatively more often affected by shortages, with reference pricing policies quoted as the cause (Pauwels et al., 2014). Pauly (2005) suggests that vaccine shortages stem mostly from firms' underspending on the quantity and quality of labor needed to ensure the lack of errors and disruptions.

Other studies assess how regulatory dispositions across countries affect shortages. Lee et al. (2021) analyze mandates on reporting shortages from regulatory agencies in the US and Canada. Using a DiD design, in which Canada is the treatment group, they find that compulsory mandates on reporting shortages decrease 41% the number of days to end the shortage of that drug compared to non-compulsory reporting. They explain this is due to positive pressure to end the shortage in a short time because competitors are now aware of this shortage. Kortelainen et al. (2023) study the effects of different regulatory regimes across the Nordic countries on generic drug expenditure and pharmaceutical availability. While the most stringent price regulation regime decreases drug expenditure by 40% compared to the less stringent regime, they find no effects on the availability of drugs. The paper is structured as follows: Section 2 presents our methodology to identify drug shortages from sales data; in Section 3 we discuss the results of our analysis, and in Section 4 the determinants of shortages and the implications of possible counterfactual price changes; Section 5 concludes.

2 Identifying Shortages from Sales Data

The main policy response to the shortage problem so far has been to increase transparency, allowing the practitioners as well as competing manufacturers to anticipate disruptions to their operations. In 2019, Acosta et al. (2019) counted 28 countries with systems of reporting shortages in place, mostly coordinated by the national regulator. Despite these efforts, the data on the reported shortages is not always available and differences in the definitions used can make international comparisons difficult.

We develop a methodology that allows to identify drug shortages and their magnitudes using only sales data at the product level, which are typically available at a national level, without relying on auxiliary datasets of shortage notifications to regulators. Another advantage of using sales data directly is that we can estimate also the magnitude of the shortages, i.e. the size of the gap between the quantities demanded and the quantities supplied. We will show explicitly in which cases this method is valid and when it cannot be used.

A shortage can be defined as a situation in which the quantities supplied (so the quantities observed in the sales data) are less than the quantities demanded. Identifying shortages requires then having an estimate of the demand function. In a market where we know shortages occur, obtaining the correct demand function is complicated by the fact that including the shortage periods when sales do not correspond to the quantities demanded, will bias the demand estimates. Therefore, we need a way of selecting only the time periods without shortages for demand estimation.

Our method relies on defining a threshold, which we will denote τ, and assuming that shortages can happen only below this threshold. In other words, we are only interested in shortages driven by supply shocks that bring sales to abnormally low levels. The importance of supply shocks as drivers of shortages is confirmed in the literature, e.g. the review in Acosta et al. (2019) identifies four main, interconnected, categories of causes of shortages: the market, supply chain management, manufacturing process, and political and ethical issues. Indeed, even if demand variations at the world level exist, the supply side production and storage capacities should normally be important enough to smooth demand shocks and provide drugs where needed. However, shocks on the supply side can happen (e.g. accidents in the supply chain, factory closures) and lead to shortages even with constant demand.

2.1 Set-up

Consider a national market, for example, France. The world capacity of production of a drug is very large compared to the demand from France. Indeed it should be commensurate with aggregate world demand, from which France is a small share (around €30 billion annual spending in France in 2020 while world pharmaceutical sales were around €1,250 billion, thus France is less than 2.5%). Of course, the world demand may vary over time as well as French demand, but we assume that the maximum possible demand from France is small compared to the world production capacity.

Denoting q^d_{jt} and Q^d_{jt} respectively the French and rest of the world demands for drug j during t, we assume that the world capacity of production is $K_j + \kappa_{jt}$ where κ_{jt} is a random variable representing possible supply shocks with support $[\underline{\kappa}, \bar{\kappa}]$.

A world level shortage happens if the world production is insufficient that is if:

$$q^d_{jt} + Q^d_{jt} > K_j + \kappa_{jt}$$

Assuming that κ_{jt} is independent of the distribution of demands q^d_{jt} and Q^d_{jt}, a shortage will happen with probability $P(q^d_{jt} + Q^d_{jt} > K_j + \kappa_{jt}) = \int_{\underline{\kappa}}^{\bar{\kappa}} f_\kappa(\kappa) 1_{\{\kappa < q^d_{jt} + Q^d_{jt} - K_j\}} d\kappa = F_\kappa(q^d_{jt} + Q^d_{jt} - K_j)$ where f_κ and F_κ are the pdf and cdf of κ_{jt}.

Denoting $\underline{Q}^d$ the minimum rest-of-the-world demand, we then assume that F_κ is strictly less than one and flat on $[\underline{Q}^d - K_j, \bar{\kappa}[$ which implies that the shortage probability is $F_\kappa(\underline{Q}^d - K_j)$ and is independent of the French demand, but depends only on the supply shocks relative to the rest of the world excess capacity of production. This assumption on the distribution of the supply shock means that the density of κ_{jt} is such that $\kappa_{jt} = \bar{\kappa}$ with probability $1 - F_\kappa(\underline{Q}^d - K_j) \equiv \mu$ and otherwise $\kappa_{jt} < \underline{Q}^d - K_j$. κ_{jt} is such that $P(\kappa_{jt} = \bar{\kappa}) = \mu > 0$ and $P(\kappa_{jt} \leq \underline{Q}^d - K_j) = 1 - \mu$.

This assumption means that $\kappa_{jt} = \bar{\kappa}$ is at maximum production capacity with some non zero probability and that if $\kappa_{jt} < \bar{\kappa}$ then the production capacity shock is large enough compared to french demand and such that $\kappa_{jt} \leq \underline{Q}^d - K_j$. This means that even if the French demand is zero, the shock on production capacity is such that there is a world shortage. The probability of a shortage at the world level $P(q^d_{jt} + Q^d_{jt} > K_j + \kappa_{jt})$ is then exogenous to the French demand. However, when there is a world shortage, part of the shortage likely affects the French market.

2.2 Identifying Drug Shortages

In order to identify shortages and their magnitude, we first specify a demand model for drugs in France. The demand for a given drug in French hospitals depends on the identity of the product because of its quality and need in therapeutic choices, but also the time period because of population and diseases variations, and finally on some other unobservable factors. Moreover, the demand for a drug may depend also at the monthly level on its dynamics because treatments sometimes last longer and the diffusion of the drug may depend on its use. As prices may also affect demand, we allow them to affect demand. We thus specify a demand model for drug j composed of molecule $m(j)$ in

ATC4 class $c(j)$ during month t as follows:

$$\log q_{jt}^d = \alpha_{m(j)} + \delta_{c(j)t} + \sum\nolimits_{k=1}^{K} \rho_k \log q_{jt-k}^d - \beta \log p_{jt} + \varepsilon_{jt}^d \qquad (1)$$

where q_{jt}^d is the quantity of demand of drug j at period t that depends on a fixed component $\alpha_{m(j)}$, a class-specific time effect $\beta_{c(j)t}$, on lagged demands up to K periods, its price p_{jt}, and some unobservable demand shock ε_{jt}.

However, the quantity sold at period t may be lower than the quantity theoretically demanded q_{jt}^d if there is some supply shortage. We thus denote by q_{jt} the quantity sold in month t for each product j that is such that $q_{jt} = q_{jt}^d$ if there is no shortage and $q_{jt} < q_{jt}^d$ if there is shortage.

We then define a threshold τ_j for drug j as being the threshold such that we can consider there is no shortage if sales are larger than this threshold. This threshold is not necessarily equal to the theoretical supply capacity as it could be that there is no shortage even if sales are smaller. However, it is a threshold that represents the maximum possible supply of a drug j where shortages are still possible.

Indeed, with the assumptions done earlier on the variability of the demand in France, shortages cannot be caused by unexpected high demand shocks in France but are caused by world level shortages because of negative supply shocks or large rest-of-the-world demand shocks. Thus, if sales volumes in France are larger than some threshold, we cannot be in the case of a shortage.

In particular, if the French and rest-of-the-world demand were proportional with a factor N such that $Q_{jt}^d = N q_{jt}^d$, then we know there is no shortage if $q_{jt}^d + Q_{jt}^d < K_j + \kappa_{jt}$ that is $q_{jt}^d < \dfrac{K_j + \kappa_{jt}}{N+1}$. This implies that, defining the threshold as $\tau_j \equiv \dfrac{K_j + \kappa}{N+1}$, there is no shortage if $q_{jt} > \tau_{jt}$ and then $q_{jt} = q_{jt}^d$.

We now make the following assumption:

$$E[\varepsilon_{jt}^d | \alpha_{m(j)}, \delta_{c(j)t}, \beta, \rho, q_{jt-k}, .., q_{jt-1}, q_{jt} > \tau_j] = 0, \qquad (2)$$

meaning that unobservable demand shocks are mean independent of observable demand determinants if sales are larger than the threshold of maximum sales compatible with shortages. It means that if sales are large enough such we that can assume there were no shortages during that time period, then the demand is equal to observed sales even if unobservable demand shocks are large because we assume the supply is able to meet the demand in those cases. Another interpretation of the consequences of our assumption is that we cannot have shortages of a drug because of unobserved large deviations of demand if that drug was sold in quantities that are above the threshold. We believe this assumption is reasonable because large demand increases are in general either permanent or predictable by lagged demand increases[1].

Then, using (2), we can estimate the demand equation conditional on the observation of τ_j and predict the demand $\widehat{q}_{jt}^{d}(\tau_j)$ using:

$$\log \widehat{q}_{jt}^{d}(\tau_j) = \widehat{\alpha}_{m(j)} + \widehat{\delta}_{c(j)t} + \sum\nolimits_{k=1}^{K} \widehat{\rho}_k \log q_{jt-k}^{d} - \widehat{\beta} \log p_{jt} \tag{3}$$

Given the realized quantity sold q_{jt}, we can then define the shortage probability quantity $s_{jt}(\tau_j)$ as a function of τ_j and equal to the difference between realized sales and demand (if demand is larger than supply) and the shortage probability as the probability that the shortage quantity is non zero.

In order to account for the demand estimation precision, we also compute the estimated variance of the predicted demand of equation (3), denoted $var(\widehat{q}_{jt}^{d}(\tau_j))$ and infer that there is a shortage if the observed sales quantity is less than the lower bound of the 95% confidence interval for the predicted quantity, that is:

$$\widehat{q}_{jt}^{d}(\tau_j) - 1.96\sqrt{var(\widehat{q}_{jt}^{d}(\tau_j))}$$

Remark that we can also infer the absence of shortage with a 5% maximum error of not detecting a shortage assuming there is no shortage when observed sales are larger than the upper bound of the 95% confidence interval of predicted demand which is $\widehat{q}_{jt}^{d}(\tau_j) + 1.96\sqrt{var(\widehat{q}_{jt}^{d}(\tau_j))}$.

In case of shortage, the shortage quantity is then

$$s_{jt}(\tau_j) = \max\left\{0, \widehat{q}_{jt}^{d}(\tau_j) - q_{jt}\right\} \times 1_{\left\{q_{jt} \leq \widehat{q}_{jt}^{d}(\tau_j) - 1.96\sqrt{var(\widehat{q}_{jt}^{d}(\tau_j))}\right\}} \tag{4}$$

Given our assumptions on the supply shocks source of shortage, we define τ_j as the λ quantile of

[1] To illustrate the rationale of the assumption of equation (2), simplifying to the case where $q_{jt}^{d} = \alpha_j + \varepsilon_{jt}^{d}$ and when $\tau_{jt} \equiv \dfrac{K_j + \kappa}{N+1}$, the assumption (2) is satisfied if ε_{jt}^{d} is bounded below by $\dfrac{K_j + \kappa}{N+1} - \alpha_j$ because then $E[\varepsilon_{jt}^{d}|\alpha_j, q_{jt} > \tau_{jt}] = E[\varepsilon_{jt}^{d}|\alpha_j, \varepsilon_{jt}^{d} > \dfrac{K_j + \kappa}{N+1} - \alpha_j] = E[\varepsilon_{jt}^{d}|\alpha_j] = 0$.

demand of product j

$$\tau_j(\lambda) = \arg\max_{\tau}\{\ P_j[q^d_{jt} \geq \tau] \geq 1-\lambda\}$$

As we initially don't observe the demand function q^d_{jt} but only the realized sales, for any given value of the parameter λ, $\tau_j(\lambda)$ being defined as the λ quantile of $\widehat{q}^d_{jt}\,(\tau_j)$, we look for the solution in λ of the fixed point equation:

$$\tau_j(\lambda) = \arg\max_{\tau}\{P_j[\widehat{q}^d_{jt}\,(\tau_j(\lambda)) \geq \tau] \geq 1-\lambda\}$$

where $\widehat{q}^d_{jt}$ is the predicted demand using equation (3).

The intuition of this method consists in using the fact that if there are no shortages when $q_{jt} > \tau_j$, then the cumulative distribution function of q^d_{jt} above τ_j should be equal to the cumulative distribution function of the observed quantity q_{jt} above τ_j. As $q^d_{jt} > q_{jt}$ when there is a shortage, the cumulative distribution function of q_{jt} should be to the left of the one of the demand function below τ_j. We thus compute for each $\lambda \in (0,1)$ the corresponding quantile q_{jt} denoted $\tau_j(\lambda)$, predict $\widehat{q}^d_{jt}(\lambda)$ and then the $\lambda \in (0,1)$ quantile $\widehat{q}^d_{jt}$ and use the minimum λ such that the predicted quantile is closest to the initial one.

In Appendix A.2 we run a Monte Carlo exercise to test the performance of our method. We find the we predict correctly 60% of shortages, missing mostly shortage events in which the gap between demand and supply is less than 10%.

3 Analysis of Drug Shortages in France

3.1 The French Context

In France, a shortage is defined by the French National Agency of Medicine and Health Product Safety (ANSM) as the inability of a pharmacy to deliver a drug within 72 hours. Additionally, shortages are classified according to the context: they can be either a supply problem, resulting from issues in the supply chain (*rupture d'approvisionnement*), or a stock problem, meaning that the medicine cannot be manufactured (*rupture de stock*). The landscape of drug shortages in France is well documented since 2012, when marketing authorization holders of pharmaceuticals became obliged

Figure 1: Reported Drug Shortages in France

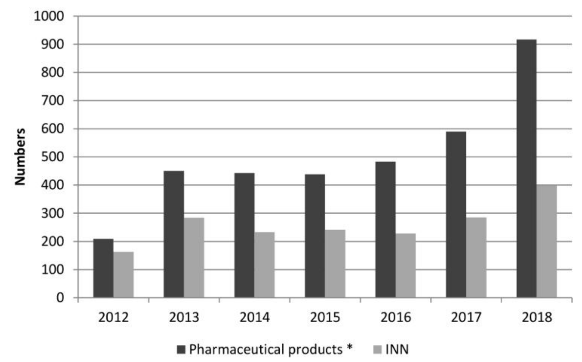


Figure 1 Trends in shortages by numbers of pharmaceutical products and international non-proprietary name drugs (INN) (2012–2018) in France. *Pharmaceutical products: defined by a combination of the INN, the formulation and the packaging.

Source: Benhabib et al. (2020)

by law to report effective or predicted shortages to the ANSM. As shown in Figure 1, shortages are increasingly a problem in France.

Quantitative evidence on drug shortage in France is very limited. Benhabib et al. (2020) uses measures of shortage reports to the ANSM to analyze their occurrence and evolution. Benhabib et al. (2020) find that there were 3,530 pharmaceutical products reported on shortage during 2012-2018, including 1,833 different active substances. Drugs on shortage were mostly old products (63.4%) with national marketing authorization procedures (62.8%), as well as injectable and oral forms (47.5% and 43.3%, respectively). Anti-infectives for systemic use ranked first (18%), followed by nervous and cardiovascular system drugs and by antineoplastic and immunomodulating agents (17.4%,12.5% and 10.4%, respectively). The number of reported shortages presented a fourfold increase between 2012 and 2018 and a sharp rise in 2017 and 2018, along with a rise in the number of active substances on shortage. The therapeutic classes concerned remained similar over time. Manufacturing and material supply issues were the main reported reasons for the shortage each year (30%) and there was an overall rise in pharmaceutical market reasons.

3.2 Data and Descriptive Statistics

We analyze drug shortages using monthly data covering purchases of hospital pharmacies in France in the period from September 2016 to August 2021 provided by GERS. These data report sales per month to hospitals, with values and quantities by drug defined as a single delivery unit denoted

UCD.[2] As the monthly variation may be subject to variations in the timing of purchase decisions of hospitals that can store products for a month, we test the robustness of our results using bimonthly data, and smoothing the end of year effect aggregating bimonthly starting in December. All our results are robust to this aggregation and reported in appendix A.1.

The data cover 1,730 molecules (ATC level 5 class in the WHO classification) corresponding to 12,123 unique products (UCD) with a total of 556,661 observations. Table 1 presents an overview of the data by ATC level 1 class - the most general level of the WHO drug classification. Three classes: B (Blood and blood forming organs), J (Antiinfectives for systemic use) and L (Antineoplastic and immunomodulating agents) generate substantially more revenue than the others, with class L revenue being almost 150 times higher than that of the smallest revenue class S for Sensory Organs.

A similar pattern can be seen when we look at the mean revenue generated by products within a class. Again, the products in ATC level 1 classes B, J and L stand out with the revenues they generate. This is reflected also in the high average product prices within these classes, although less so for the antiinfectives in class J.

Classes with the lowest mean annual revenues, G and S, have also the lowest mean product revenues but while the mean price in the class G is also among the lowest, drugs in the class S have the second highest mean price among all ATC 1 classes.

Finally, in the L class there are on average fewer brands per ATC level 5 class (molecule) which is a proxy for generic penetration, but the variation across the classes is much smaller than in the case of prices or revenues.

[2]UCD stands for *Unité Commune de Dispensiation* that are unique codes for the most disaggregate description of a drug.

Table 1: Mean sales, prices and number of brands per ATC5 (molecule) by ATC1 class

ATC	Class Revenue	UCD Revenue	Mean UCD Units	UCD Price	Brands per ATC5
A Alimentary tract and metabolism	472.6	0.4	398,412.3	18.1	8.2
B Blood and blood forming organs	2,041.7	2.7	415,428.1	268.5	7.0
C Cardiovascular system	312.1	0.2	193,290.7	2.6	9.0
D Dermatologicals	67.6	0.1	63,226.0	7.1	6.7
G Genito urinary system	49.2	0.1	73,004.7	7.1	7.8
H Systemic hormonal preparations	162.0	0.7	199,253.8	118.2	5.5
J Antiinfectives for systemic use	2,027.3	2.0	108,589.9	52.9	7.6
L Antineoplastic and immunomodulating agents	4,906.3	5.4	26,534.0	773.8	4.2
M Musculo skeletal system	233.1	0.6	108,557.3	240.3	8.8
N Nervous system	803.3	0.4	390,656.9	6.7	10.1
R Respiratory system	63.4	0.1	111,661.5	14.8	8.1
S Sensory organs	34.5	0.1	149,276.4	390.2	8.3

Notes: Class revenue is the mean annual revenue of all drugs in the class in millions of euros. UCD revenue is the mean annual product revenue in millions of euros. UCD price is the mean product price in euros.

3.3 Drug shortages estimation results

We apply the methodology described in Section 2 to identify shortages in our dataset. Strictly speaking, our method allows to identify the probability of a shortage, but for simplicity of exposition we use a dummy variable denoting a shortage whenever we identify a “any” shortage with a probability that is above 95% (given that it could still be a small drug shortage).

Table 2 presents the demand estimation using time periods where we infer no shortage using the selected τ_j's following the model in equation (1). Column (1) is a simple OLS regression, while in column (2), the price p_{jt}^{FR} is instrumented for with its 5th and 6th lags p_{jt-5}^{FR} and p_{jt-6}^{FR}. We use the estimates in Column (2) to fit a demand curve for the whole time period of our dataset[3].

[3]Table 10 in appendix A.1 shows the results of the same method and demand for bimonthly data. Results are similar.

Table 2: Demand prediction

	(1)	(2)
$\log q_{t-1}$	0.917***	1.027***
	(0.002)	(0.002)
$\log q_{t-2}$	-0.075***	-0.092***
	(0.002)	(0.003)
$\log q_{t-3}$	0.016***	0.053***
	(0.002)	(0.002)
$\log p_{jt}$	0.031***	-0.006***
	(0.005)	(0.001)
Adj. R-Square	0.9852	.
N	241902	206807
Molecule fixed effects	✓	✓
ATC4 × Time fixed effects	✓	✓
Instruments for price		✓

Note: The dependent variable is $\log \widehat{q}^{d}_{jt}(\tau_j)$. Standard errors in parenthesis. OLS regressions when no instruments. 2SLS regressions when instrumenting price $\log p_{jt}$ by lagged prices $\log p_{jt-5}, \log p_{jt-6}$. * for $p < .05$, ** for $p < .01$, and *** for $p < .001$.

Having selected τ_j's and predicted the demand for each product, we can find the time periods in which every drug is subject to a shortage following the definition in equation (4). As the predicted log demand is normally distributed with an estimated mean and variance, a product is said to be on shortage at a given month if the observed sales are lower than the lower bound of the 95% confidence interval, meaning there is 95% chance that the demand was larger than observed sales. This means there is 5% chance that we infer a shortage while there is none. We could also use the upper bound of the 95% confidence interval and infer there is no shortage when the observed sale is larger or equal to this upper bound. Table 3 presents the estimates of shortages in France predicted by our method. We report the mean of inferred shortages with a 5% error maximum error of wrongly inferring a shortage for each observation in the first column and the mean absence of shortage with a 5% maximum error per observation of not detecting a shortage. In the following analysis, we will use only the inferred shortage (with a 5% maximum error) and not the inferred absence of shortage.

Shortages affect different ATC 1 classes to a varying degree, with products in ATC 1 class G facing an average 20% probability of a shortage and drugs in classes L and S a 33% and 29% probability of a shortage respectively.

Table 3: Shortage Estimates

ATC	Mean Shortage	Mean No Shortage	Nb UCD with Shortage	Nb UCD
A Alimentary tract and metabolism	0.27	0.61	1,053	1,298
B Blood and blood forming organs	0.28	0.65	801	889
C Cardiovascular system	0.24	0.64	1,557	1,898
D Dermatologicals	0.28	0.55	447	546
G Genito urinary system	0.20	0.61	382	585
H Systemic hormonal preparations	0.23	0.65	259	315
J Antiinfectives for systemic use	0.24	0.66	1,030	1,243
L Antineoplastic and immunomodulating agents	0.33	0.56	987	1,181
M Musculo skeletal system	0.23	0.62	413	508
N Nervous system	0.25	0.65	2,078	2,467
R Respiratory system	0.27	0.56	493	664
S Sensory organs	0.29	0.63	289	319

Note: The mean shortage column corresponds to the mean of the inferred shortage variable (probability of inferring a shortage while there is none being 5%) which is when $q_{jt} \leq \widehat{q}^{d}_{jt}(\tau_j) - 1.96\sqrt{var(\widehat{q}^{d}_{jt}(\tau_j))}$. The mean no shortage column corresponds to the mean of the inferred absence of shortage variable (probability of not detecting a shortage while there is being 5% which is when $q_{jt} \geq \widehat{q}^{d}_{jt}(\tau_j) + 1.96\sqrt{var(\widehat{q}^{d}_{jt}(\tau_j))}$.

Figure 2 shows the distribution, across all the 12,123 products in our sample, of the average probability that the product is on shortage across the 5 years of data. We see that many products are rarely on shortage, but the bulk of them that are on shortage, have a shortage probability that is rarely above 40%.

Figure 2: Frequency of Shortage by Product

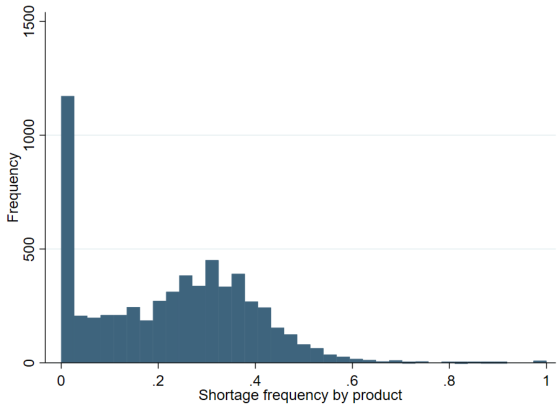


Table 4 shows the mean shortage probability for different categories of products. It shows that branded products have a smaller shortage probability of 25% instead of 31% for unbranded products. The branded products are products whose molecule is still on patent or have not experienced entry of generics of the same molecule[4]. They represent around 17.5% of all products and 14.3% of ob-

[4]Here branded product corresponds to molecules marketed under a single brand. If we observe multiple brands per

servations. The shortage probability is larger for injectables than for oral drugs and other modes of administration.

Table 4: Shortage Estimates by Type of Product

Groups of drugs	Shortage Probability
By type of administration	
Injectable	0.30
Oral	0.24
Other	0.28
By number of brands	
Single brand	0.25
Multiple brands	0.31

Then, conditional on a shortage being identified, one can look at the extent of the shortage as a share of the predicted demand. Table 5 shows some statistics on the distribution of these shortage shares of demand with the mean, and 25%, 50% and 75% quantiles, by ATC1 class. The shortage share is on average by class between 32% and 46%. The quantiles vary across classes showing a distribution more to the right (with a higher shortage share) on the different quantiles when the mean is higher. For all classes the median is lower than the mean meaning there are more shortage shares below the mean than above.

Table 5: Shortage Share Condition on Shortages

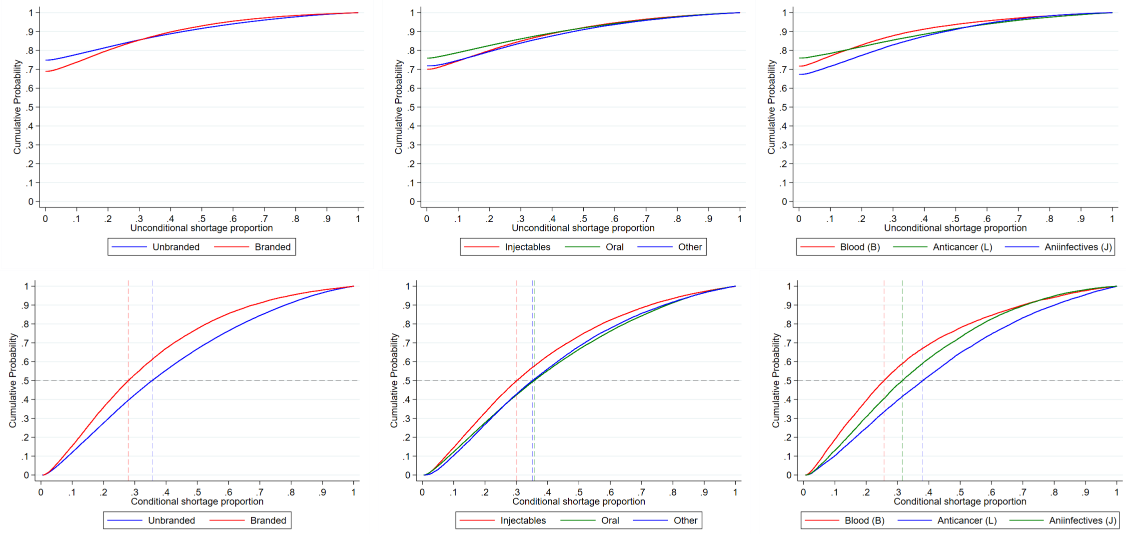
	Shortage Share			
ATC	Mean	P25	P50	P75
A Alimentary tract and metabolism	0.37	0.17	0.33	0.55
B Blood and blood forming organs	0.32	0.13	0.26	0.46
C Cardiovascular system	0.40	0.19	0.36	0.59
D Dermatologicals	0.43	0.21	0.39	0.61
G Genito urinary system	0.43	0.23	0.41	0.62
H Systemic hormonal preparations	0.42	0.21	0.37	0.61
J Antiinfectives for systemic use	0.42	0.20	0.38	0.60
L Antineoplastic and immunomodulating agents	0.36	0.17	0.32	0.52
M Musculo skeletal system	0.46	0.24	0.43	0.66
N Nervous system	0.37	0.16	0.32	0.56
R Respiratory system	0.41	0.21	0.38	0.60
S Sensory organs	0.36	0.17	0.31	0.51

Note: The shortage share conditional on having a shortage is the estimated share of demand that is not satisfied by supply conditionally on having a shortage. P25, P50 and P75 represent respectively the 25, 50 and 75 the percentiles of the distribution.

Figure 3 shows the cumulative distribution functions of these conditional shortage shares of demand for different categories of products. It first shows CDFs for the branded and unbranded products. When there is a shortage, the distribution of the shortage share of demand for unbranded drugs

molecule, we infer the product is unbranded first-order stochastically dominates the one of branded drugs, which means that the shortage proportion is larger for unbranded drugs (conditional on having a shortage). The values at the median show for example that half of the shortages are more than 35% of demand for unbranded products while only more than 28% for branded ones. Then, the distributions show that the shortages proportion is larger for oral drugs than for injectables, while the shortage probability is smaller. For the three largest ATC classes, they are larger for anticancer than for antiinfectives and for blood and blood forming organs.

Figure 3: Cumulative Distribution Function of Shortage Shares Unconditional and Conditional on Shortage



Note: Cumulative distribution functions of shortage share of demand unconditional on shortages on first row and conditional on shortage on second row.

As our method is detecting shortages in the periods with the lowest sales, if sales of some drugs displayed seasonality, we might be risking over-predicting shortages in the periods of (seasonally) low demand. In Appendix A.1 we smooth the sales data by aggregating it to the bimonthly level and find similar results.

4 Drug Shortages Determinants and Counterfactuals

4.1 The Determinants of Drug Shortages

Having identified the shortage events, we can study their determinants. In particular, we are interested in how prices affect the probability of a shortage. Studies in the US context suggest that downward pressure on prices is correlated with more frequent shortages (Yurukoglu et al., 2017; Yang, 2020; Parsons et al., 2016; Haninger et al., 2011; Ridley et al., 2016; Dave et al., 2018). In Europe, this mechanism especially merits close investigation, since prices are often set by regulators (as is the case in France, UK and other countries).

Drugs are globally traded goods, and the prices in all countries can affect the probability of a shortage in France. There are several mechanisms that can lead to different effects of prices on shortages. First, for a given predicted demand shape, the supply side adapts its capacity of production to the anticipated drug prices. Everything else equal, higher prices lead to higher profits and larger incentives to build large enough production capacities. This will reduce the likelihood of shortages, which may happen when a factory needs maintenance or some other factor disrupts the supply chain. Thus, higher prices are likely to reduce the likelihood of shortages, and higher prices in a country can exert a positive externality on other countries by reducing shortage events everywhere because of larger production capacities. Second, higher prices normally lead to higher supply whatever the demand, but if capacity is limited and prices can not adjust upward (because of regulation) then shortages will happen, but to a lower extent if prices are larger (holding everything else equal). However, in such a case, prices in other countries can exert a negative externality. Indeed, when geographical markets compete for limited supply, higher prices will attract supply, and everything else equal, will reduce the supply of the drug in other places. Thus, external prices can have either a positive or negative effect on shortages in France. Which effects matter and dominate in practice is an empirical question that we now try to investigate.

Whenever possible, we match our dataset with information on prices from other countries. We could do this thanks to the publicly available data on drugs prices in the UK from the website of the NHS.

We model the shortage probability s^*_{jt} as a function of the price(s) of the product:

$$s^*_{jt} = \sigma_j + \delta_t + \alpha_{FR} \log p^{FR}_{jt} + \alpha_{UK} \log p^{UK}_{jt} + \epsilon_{jt} \tag{5}$$

Table 6 presents the results of the estimation of equation (5) either on the full sample without the UK price or on the restricted sample to which we could match the UK price. All regressions include drug fixed effects to control for any unobservable fixed characteristic explaining the shortage probability of a drug. We also include time fixed effects at the month level to control for seasonal variation. In column (1) we focus on the effect of the French price on the shortage probability of all drugs in our sample using and Ordinary Least Squares regression. Our estimate suggests that a 10% increase in the price is associated with a 0.76 pp decrease in the shortage probability. In column (2), we also add dummies for the number of brands supplying the molecule, given the reference case is when the drug is in a monopoly situation for the molecule, because of its on-patent status. We can see that the more brands supply the molecule the higher the shortage probability. Theoretically, having more suppliers for a single molecule can have either positive or negative effects on shortages. Indeed, on the one hand, a larger number of suppliers may reduce the risk of plant production disruptions to impact the global supply and allow diversifying the risk of the supply chain production. On the other hand, more suppliers for the same molecule means stronger competition, lower margins and lower profits for suppliers. Lower profit per supplier may lead to lower capacity to cope with supply production risk and to build larger production capacity because of fixed costs of production. Empirically, we find that this second effect seems to dominate and that more suppliers increase the risk of shortage substantially as it is 15.7pp higher when there are more than 5 brands and even 9.6pp higher when there are 2 to 5 brands versus a monopoly. Then, we introduce the UK price as an additional explanatory variable for the subsample of drugs for which it was possible to match the French data with the UK prices. This represents around half (46%) of the initial sample and in fact more than half for the years 2017 to 2020 and only 21% for 2021. Focusing on this subsample in column (3), we see a stronger effect of the French price – a 0.98 pp reduction in the shortage probability per 10% increase in the French price and a small but significant negative effect of the UK price on the shortage probability, showing that higher prices in the UK also lower the probability of a shortage in France. This shows that the effect of higher external prices exerting a positive externality, probably through the ability of the supply chain to build larger production capacity, dominates.

Finally, recognizing that prices of drugs may change over time with unobserved factors that may explain the shortage probability and be correlated with prices, we implement an instrumental variables method using instruments for prices. For that with use the number of drugs and formats by level 3 or 4 or 5 ATC class, which varies across products and time periods and is correlated with prices. The Two Stages Least Squares estimates are reported in columns (4) and (5) for the full sample

Table 6: Shortage probability

	(1)	(2)	(3)	(4)	(5)
$\log p_{jt}^{FR}$	-0.076***	-0.073***	-0.098***	-0.306***	-0.311***
	(0.004)	(0.004)	(0.007)	(0.055)	(0.091)
$\log p_{jt}^{UK}$			-0.008**		-0.008**
			(0.003)		(0.003)
2-5 brands		0.096***	0.097***	0.073***	0.081***
		(0.008)	(0.017)	(0.010)	(0.018)
More than 5 brands		0.157***	0.175***	0.127***	0.154***
		(0.009)	(0.018)	(0.012)	(0.020)
Constant	0.333***	0.215***	0.124***		
	(0.002)	(0.007)	(0.019)		
N	444399	444399	220204	444425	220266
Instrumental variables				✓	✓
Sargan (df)				2	2
Sargan Statistics				2.74	30.3
Drug fixed effects	✓	✓	✓	✓	✓
Time fixed effects	✓	✓	✓	✓	✓

Note: Standard errors in parenthesis. * for $p < .05$, ** for $p < .01$, and *** for $p < .001$. Column (3) includes only drugs for which the UK price can be observed. Columns (4) and (5) use instrumental variables and the Sargan statistic with its degrees of freedom are reported in the table.

and the subsample matched with UK prices. The results show that the price coefficient increases in magnitude three fold, which is consistent with an endogeneity issue in the OLS regressions. The Sargan statistic shows that overidentifying restrictions are satisfied on the full sample but not on the subsample matched with UK data, which is due to the fact the instrumental variables are correlated with the ability to match the subsample. Nevertheless, the price coefficient of columns (4) and (5) are similar and thus confirm the effect of prices on drug shortages.

Then, we look at the effect of prices on the magnitude of shortages, conditional on shortage ($s_{jt} = 1$). Indeed, observed sales rarely go to zero even in periods of shortages and the magnitude of shortages is important in terms of welfare effects. We thus use the quantities supplied, q_{jt}^s, during the shortage periods as our dependent variable and estimate the equation:

$$\log q_{jt}^s = \sigma_j + \delta_t + \alpha_{FR} \log p_{jt}^{FR} + \alpha_{UK} \log p_{jt}^{UK} + \epsilon_{jt} \tag{6}$$

for all j, t such that $s_{jt} = 1$.

Table 7 presents the results of estimation of equation (6). Column (1) contains the results for all observations of drugs experiencing shortages in our data, while column (2) focuses on the subsample matched to the UK price data. In both specifications, we include drug and time fixed effects. Results show that the effect of the French price is positive, which means that drugs with higher prices in France are supplied in larger quantities during shortages, or that higher prices reduce the magnitude of shortages. On the other hand, drugs with higher UK prices, are supplied in lower quantities when there is a shortage. Contrary to the effect on shortage probability where higher external prices as the one of the UK reduce the probability of shortage, when there is a shortage, higher UK prices reduce the supplied quantity of the drug in France, showing that competition for scarce supply across countries seems to play a role in the magnitude of shortages.

Table 7: Supply in case of shortage

	(1)	(2)
$\log p_{jt}^{FR}$	0.199***	0.393***
	(0.011)	(0.019)
$\log p_{jt}^{UK}$		-0.025**
		(0.008)
Constant	6.102***	6.622***
	(0.005)	(0.029)
N	134911	64087
Drug fixed effects	✓	✓
Time fixed effects	✓	✓

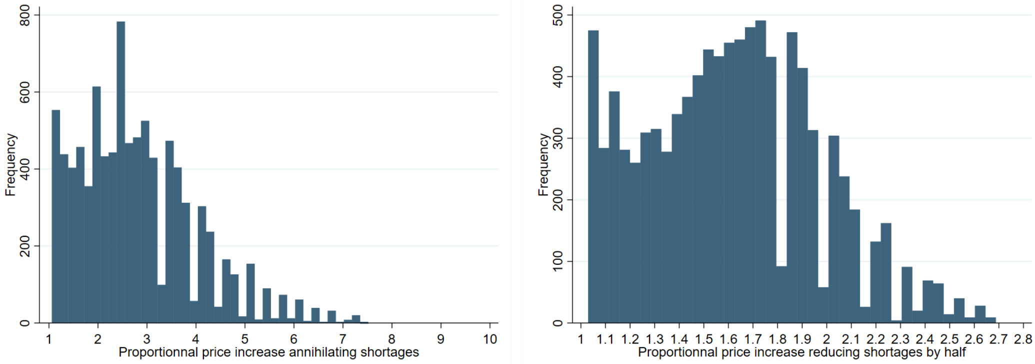
Note: Standard errors in parenthesis. * for $p < .05$, ** for $p < .01$, and *** for $p < .001$. Columns (2) includes only the drugs for which the UK price can be observed.

4.2 Counterfactuals

As we use a linear probability model with log price for the shortage probability estimate in equation (5), using instrumental variables, the coefficient implies that a 10% price increase in France reduces the shortage probability by 3 percentage points, and a doubling of price (an increase of 100%) reduces the shortage probability by 21 percentage points. This gives an idea of the counterfactual effect on shortages that a price increase would have. Moreover, given the shortage state inference obtained for each product, we can compute the average shortage probability at the product level, or at the ATC class level, and given the average product price, infer what price increase would allow to reduce the shortage probability to zero or to divide this probability by half.

Thus defining $s_j = \frac{1}{T}\sum_t s_{jt}^*$ the product level mean shortages and $p_j^{FR} = \frac{1}{T}\sum_t p_{jt}^{FR}$, the price increase needed to eliminate shortages is $(\exp(\frac{s_j}{-\alpha_{FR}}) - 1)p_j^{FR}$ while the one needed to reduce the shortage probability to a half is $(\exp(\frac{s_{j/2}}{-\alpha_{FR}}) - 1)p_j^{FR}$. Figure 4 shows the distribution of these price increases across the 9,789 products that experience some shortage (17% of products never have any

Figure 4: Increase in proportion of price needed to eliminate or divide by two shortages



shortage and don't need any price change to reduce shortages). It shows that to eliminate shortages, price would have to be seven times larger for some products but less than 2.7 times larger for half of the products. Moreover, reducing shortages by half would be doable with price increases that mostly do not need to be more than twice larger.

We then compute the counterfactual supply in case of shortage using equation (6), and the counterfactual demand in case of no shortage using equation (1). We do so for prices that are all double ($\tilde{p}_{jt} = 2p_{jt}^{FR}$), or larger prices that are such that the shortage probability by product is half of what it is at current prices ($\tilde{p}_{jt}^{0} = (\exp(\frac{s_j}{-\alpha_{FR}}) - 1)p_{jt}^{FR}$), or larger prices that are such that the shortage probability becomes zero ($\tilde{p}_{jt}^{\frac{1}{2}} = (\exp(\frac{s_j}{-2\alpha_{FR}}) - 1)p_{jt}^{FR}$).

Table 8 shows the mean quantity changes resulting from these price changes, either keeping the shortage probability fixed or accounting for its change according to the effect of prices on shortages. Table 9 shows the same for expenses.

When keeping shortage probabilities fixed, the price effects increase supply in case of shortages as demonstrated in Table 7 and decrease demand in case of no shortage because of the demand elasticity as estimated in column (2) of Table 2. The two effects go in opposite directions on total sales, but as the supply elasticity in case of shortage is much larger than the demand elasticity, the overall effect is to increase the quantity sold, mostly from larger sales in the shortage states and very small decreases of demand in case of no shortage. As a consequence, when prices double (column (1)), the total quantity increases on average between 7% and 20% across ATC classes, being the larger increase for anticancer drugs (ATC1 class L). When prices increase to lead to half fewer shortages, the quantity increase varies between 5% and 19% (column (2)) and when prices increase sufficiently to eliminate shortages, quantities increase on average between 12% and 44%.

Then, accounting for the reduction in shortage probability , Table 8 shows that the total quantity increase is much smaller and sometimes even negative because of the demand elasticity effect.

Table 8: Counterfactual quantities

	Fixed Shortage Probability			With Shortage Probability Change		
ATC	(1)	(2)	(3)	(4)	(5)	(6)
A Alimentary tract and metabolism	0.08	0.07	0.17	0.08	0.09	0.11
B Blood and blood forming organs	0.15	0.11	0.25	-0.12	-0.06	-0.24
C Cardiovascular system	0.07	0.05	0.12	0.10	0.10	0.13
D Dermatologicals	0.19	0.17	0.40	-0.18	-0.12	-0.42
G Genito urinary system	0.10	0.09	0.20	0.00	0.03	-0.02
H Systemic hormonal preparations	0.10	0.08	0.17	-0.04	0.00	-0.08
J Antiinfectives for systemic use	0.13	0.10	0.22	-0.08	-0.03	-0.16
L Antineoplastic and immunomodulating agents	0.20	0.19	0.44	-0.19	-0.14	-0.46
M Musculo skeletal system	0.12	0.09	0.20	-0.07	-0.02	-0.13
N Nervous system	0.07	0.05	0.12	0.10	0.09	0.12
R Respiratory system	0.14	0.13	0.30	-0.05	-0.01	-0.16
S Sensory organs	0.14	0.12	0.27	-0.09	-0.05	-0.22

Note: Columns (1), (2) and (3) represents the change in quantity due to a price change, keeping shortage event fixed but accounting for demand elasticity in case of no shortage and supply elasticity in case of shortage. Columns (4) (5) and (6) also account for the change in the probability of shortage. Columns (1) and (4) correspond to a doubling of price. Columns (2) and (5) correspond to a price increase for each product that leads to half fewer shortages. Columns (3) and (6) correspond to a price increase for each product that leads to zero shortages. Numbers indicate the mean relative change of quantities such that .10 means a 10% increase of quantity.

Table 9 shows the changes in expenses relative to initial ones corresponding to the changes in quantities of Table 8. When doubling prices, expenses increase on average between 113% and 141% if we keep shortage probabilities fixed (Column 1) but only by 61% to 121% when accounting for changes in shortage probabilities. The price increase leading to half shortages (columns 2 and 5) leads to lower expenses increase (between 75% and 128% with shortage probabilities fixed and between 63% and 98% when accounting for probabilities changes. When prices increase to the level such that shortages are eliminated (columns 3 and 6), expenses increase between 230 and 401% with fixed shortage probabilities but only between 95 and 299% when accounting for the effect of prices on shortages probabilities.

These counterfactual results show that shortages can be reduced if one accepts to pay higher prices, but the quantity effects also show that it would not be necessarily welfare improving to increase prices up to the point where shortages disappear unless we value much more the per unit limited availability during shortages than the per unit reduced demand because of higher prices when the drug is not on shortage.

Table 9: Counterfactual expenses

	Fixed Shortage Probability			With Shortage Probability Change		
ATC	(1)	(2)	(3)	(4)	(5)	(6)
A Alimentary tract and metabolism	1.17	0.91	3.02	1.15	0.98	2.99
B Blood and blood forming organs	1.30	0.89	2.80	0.75	0.60	1.40
C Cardiovascular system	1.13	0.78	2.40	1.21	0.87	2.51
D Dermatologicals	1.38	1.20	4.45	0.64	0.62	1.00
G Genito urinary system	1.21	0.92	3.26	1.00	0.83	2.36
H Systemic hormonal preparations	1.20	0.75	2.38	0.93	0.63	1.56
J Antiinfectives for systemic use	1.25	0.84	2.82	0.84	0.63	1.65
L Antineoplastic and immunomodulating agents	1.41	1.28	4.77	0.61	0.64	0.95
M Musculo skeletal system	1.24	0.84	2.66	0.86	0.66	1.61
N Nervous system	1.13	0.76	2.30	1.19	0.83	2.29
R Respiratory system	1.29	1.12	4.01	0.90	0.86	2.13
S Sensory organs	1.29	0.94	3.08	0.81	0.64	1.37

Note: Columns (1), (2) and (3) represents the change in expenses due to a change in price, keeping shortage event fixed but accounting for demand elasticity in case of no shortage and supply elasticity in case of shortage. Columns (4), (5) and (6) also account for the change in the probability of shortage. Columns (1) and (4) correspond to a doubling of price. Columns (2) and (5) correspond to a price increase for each product that leads to half fewer shortages. Columns (3) and (6) correspond to a price increase for each product that leads to zero shortages. Numbers indicate the mean relative change of expenses such that .10 means a 10% increase of expense.

Determining formally welfare maximizing prices is beyond the scope of this paper but these results show that regulatory institutions should account for shortages effects when determining the regulated price levels of drugs. Too low prices may lead to frequent shortages and affect welfare but large enough prices to annihilate shortages may be too high for welfare. This implies that some level of shortages may be needed when seeking prices that maximize welfare.

5 Conclusion

Shortages affect most major pharmaceutical markets. Their prevalence among drugs needed for especially vulnerable patients (emergency medicine, oncology) has translated into a sizeable medical and policy literature scrutinizing their incidence and clinical implications. The peculiarities of the pharmaceutical market have been hinted as the underlying causes of the shortages, but very few studies have undertaken their formal analysis, and rarely reached beyond the American context.

We show that in the case of France, shortages depend on prices and increase with lower prices, adding a short term trade-off between expenses and shortages to the usual dynamic long term efficiency trade-offs between current expenditures and future innovation. The usual argument for higher prices of drugs is that higher rents for the industry generate higher incentives for innovation (Acemoglu and Linn, 2003; Dubois et al., 2015), but this argument falls short for generics and for small countries whose contribution to total industry revenue is small. However, we have shown that shortages increase with lower prices such that in the short run there is still a trade-off between expenses and availability even in the case of non innovative products (for which long run benefits of higher rents can be neglected) and thus even more for innovative ones.

Another example of international spillover effects of price regulation, also related to the phenomenon of shortages, is the parallel trade of drugs within Europe. It has been shown that it also affects price negotiations and returns for the industry (Kyle, 2011; Dubois and Sæthre, 2020). The spillover effects of prices across countries may not only come from the manufacturers decision to supply only those demands with higher prices in case of global shortages but also through parallel traders even if manufacturers do not strategically supply countries with higher prices.

We show that prices in the UK affect the negatively the probability of drug shortages and positively their intensity in France. One interpretation is that higher prices in any place contribute to the profitability of the industry and to its ability to build larger production capacity, thus reducing the frequency of shortage events. However, we show that drugs with higher prices in the UK are supplied with lower quantities in France during shortage events. This can be explained by the fact that conditional on not being able to supply all countries demands, firms may choose to provide larger quantities to higher prices places. This analysis is possible after being able to identify shortage events from a method that relies on assumptions that come from observations of the industry.

Consistently with our results, sterile injectable oncology drugs has been one of the most affected by shortages in the US. This market is well penetrated by generics, which results in low margins, which in turn reduces the firms' incentives and ability to invest in maintaining their manufacturing sites and keeping up with the stringent quality standards. Lack of appropriate maintenance leads to disruptions and with inelastic demand, those translate into shortages. Existing policies focus on increasing transparency and alleviating the effects of shortages. Further proposals targeting the root causes of shortages include introducing pricing floors for generic chemotherapy drugs and accelerating FDA review of generic applications (Kantarjian, 2014) as well as more frequent quality controls to enforce compliance with standards (Scott Morton and Boller, 2017).

Our paper suggests that the trade-off between prices and shortage probability should be well taken into account when regulating prices. In a counterfactual exercise, we increase drug prices, taking into consideration the changes in demand and supply driven by the price change as well as the change in shortage probabilities. Our findings suggest that higher prices in France could reduce the occurrence of shortages and allow a larger share of demand being supplied but also that obtaining zero shortages may be too costly. This means that, on the one hand, regulatory authorities may need to concentrate in choosing price levels to reduce as much as possible shortages of drugs that have no or few therapeutic alternatives. On the other hand, those authorities may need to accept shortages of drugs that have therapeutic alternatives. Finally, the international "cooperative" price effect found on the frequency of shortages calls for coordination across regulators within Europe in order to account for the positive effects of price setting on capacity building. This interesting effect needs however to be confirmed with data on more countries allowing to test fully the existence of these international positive spillover effects.

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A Appendix

A.1 Results using bimonthly data

Table 10: Demand prediction $\widehat{q}^{d}_{jt}(\tau_j)$

	(1)	(2)
$\log q_{t-1}$	0.683***	0.887***
	(0.002)	(0.001)
$\log p^{FR}_{jt}$	0.012	-0.051***
	(0.008)	(0.002)
Adj. R-Square	0.9724	.
N	135993	96853
Molecule fixed effects	✓	✓
ATC4 × Time fixed effects	✓	✓
Instruments for price		✓

Note: Standard errors in parenthesis. OLS regressions when no instruments. 2SLS regressions when instrumenting price $\log p_{jt}$ by lagged prices $\log p_{jt-5}, \log p_{jt-6}$. * for $p < .05$, ** for $p < .01$, and *** for $p < .001$.

Figure 5

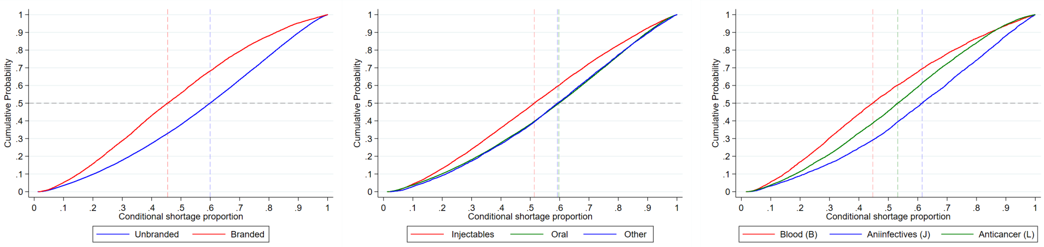

Table 11: Shortages estimates

ATC	Shortage Probability	Nb UCD with Shortage	Nb UCD
A Alimentary tract and metabolism	0.19	1,032	1,284
B Blood and blood forming organs	0.33	796	879
C Cardiovascular system	0.27	1,587	1,874
D Dermatologicals	0.28	439	532
G Genito urinary system	0.21	403	571
H Systemic hormonal preparations	0.18	238	313
J Antiinfectives for systemic use	0.20	995	1,230
L Antineoplastic and immunomodulating agents	0.30	982	1,161
M Musculo skeletal system	0.23	404	500
N Nervous system	0.28	2,089	2,431
R Respiratory system	0.19	484	646
S Sensory organs	0.21	275	315

Table 12: Shortage probability

	(1)	(2)	(3)
$\log p_{jt}^{FR}$	-0.093***	-0.089***	-0.152***
	(0.005)	(0.005)	(0.010)
$\log p_{jt}^{UK}$			-0.008*
			(0.004)
2-5 brands		0.101***	0.076**
		(0.011)	(0.024)
More than 5 brands		0.144***	0.129***
		(0.013)	(0.026)
Constant	0.328***	0.217***	0.129***
	(0.002)	(0.010)	(0.027)
N	221583	221583	107024
Drug fixed effects	✓	✓	✓
Time fixed effects	✓	✓	✓

Note: Standard errors in parenthesis. * for $p < .05$, ** for $p < .01$, and *** for $p < .001$. Column (2) includes only drugs for which the UK price can be observed.

Table 13: Supply in case of shortage

	(1)	(2)
$\log p_{jt}^{FR}$	0.140***	0.337***
	(0.017)	(0.031)
$\log p_{jt}^{UK}$		-0.032**
		(0.011)
Constant	5.520***	6.004***
	(0.007)	(0.041)
N	64123	30285
Drug fixed effects	✓	✓
Time fixed effects	✓	✓

Note: Standard errors in parenthesis. * for $p < .05$, ** for $p < .01$, and *** for $p < .001$. Columns (2) and (4) include a selection control term for the probability to be on shortage. Columns (3) and (4) include only the drugs for which the UK price can be observed.

A.2 Monte Carlo

We provide evidence on how the algorithm works to predict shortages using only data on sales. We define a data generating process to construct quantities demanded and supplied across time. We assume shortages in France only come from the supply side and therefore define the supply as the demand plus a negative shock. The shock has some persistence to capture that, if there is a shortage, there will be a shortage in the following periods. The error of the shock follows a Bernoulli process with probability 0.2. We generate 1,000 products across 65 periods. We also define 5 ATC levels randomly: there are 10 categories for ATC level 1 and 334 for ATC level 5.

A.2.1 DGP

Demand is given by:

$$\log q_{jt}^{d} = \alpha_j + \beta_t + \gamma x_{jt} + \sum_{k=1}^{K} \rho_k \log q_{jt-k} + \epsilon_{jt} \tag{7}$$

with $q_{jt} = 0$ for $t < 0$

- J=1000, T=65
- $\alpha_j \sim U[10, 1000]$
- $\gamma = 0$
- $\beta_t = \beta_0 t + \beta_1 t^2 + \beta_2 sin(\frac{t}{\pi})$ with $\beta_0 = 0.8, \beta_1 = 0.001, \beta_2 = 0.6$[5]
- $\rho_1 = 0.554, \rho_2 = 0.179, \rho_3 = 0.071$
- ϵ follows a logistic distribution with location parameter equal to 0 and scale parameter equal to 0.53 [6]. ϵ is independent across products and time.

Supply is defined as:

$$q^s_{jt} = q^d_{jt} + shock_{jt} \tag{8}$$

$$shock_{jt} = 0.5 shock_{jt-1} + error_{jt}$$

with $error_{jt} = \eta_{jt} * \nu_{jt}$

$\eta_{jt} \sim Bernoulli(0.2)$ and $\nu_{jt} \sim U[-200, 0]$.

More details:

We drop the first 10 periods of time to allow the dynamics in the demand model to fully take place. We define a shortage if $q^s < 0.99 q^d$ or if $q_s = 0$ because the persistence of the shock makes the supply slightly lower even after the shortage period. Figure 6 provides an example of a product with a generated supply and demand that shows in which periods the product is experiencing shortages.

A.2.2 Results

Table 14: Shortage prediction precision: full sample

	Simulated		
Predicted	No shortage	Shortage	Total
No shortage	25,648	10,617	36,265
Shortage	9,868	8,867	18,735
Total	35,516	19,484	55,000

Table 14 counts the observations by their shortage status, both true shortages observed in the simulation ("Simulated") and as predicted with our methodology ("Predicted"). As our methodology

[5]The last term gives seasonality to the series

[6]Comes from the distribution of residuals of the estimated demand with data (distribution not exactly logistic but similar)

Figure 6: Generated Demand and supply for product 10

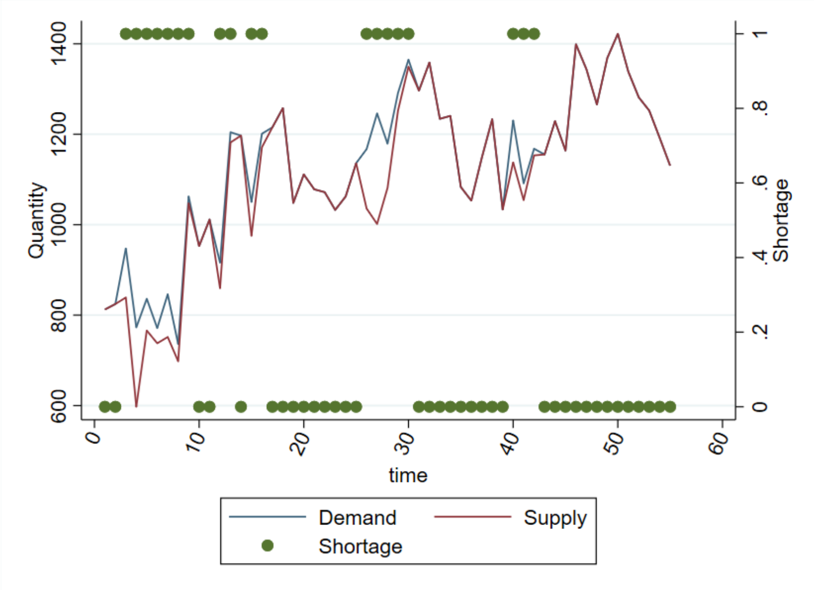

Table 15: Shortage prediction precision: observed units $< \tau$ only

	Simulated		
Predicted	No shortage	Shortage	Total
No shortage	11,848	6,071	17,919
Shortage	9,868	8,867	18,735
Total	21,716	14,938	36,654

can only detect shortages below a certain threshold and the simulation DGP allows shortages to happen at any level of demand, we do not detect more than a half of the simulated shortages. To provide a more meaningful analysis of the precision of our method, we focus on the observations where the observed sales are below the threshold τ. Table 15 shows the precision of the methodology for that subsample.

Our method predicts correctly 60% of the simulated shortages. Figure 7 plots the cumulative density of the relative magnitude (as percent of the true demand) of the shortages that we do not predict. The figure shows that these are mostly small shortages: 75% of the false negatives correspond to shortages that are less than 4.97% of the demand and 90% of the false negatives correspond to shortages that are less than 10.6% of the demand.

Table 15 shows also that our method predicts a substantial number (9,868) of false positives: shortages when there is no shortage in the underlying simulated data. This is not surprising given that all observations below τ are susceptible to being defined as shortage. Moreover, a large fraction of these false positives correspond to periods directly before or after a true simulated shortage: 28% of them are predictions within one period of the shortage events and 47% of the false positives are predictions within two periods. Finally, 50% of the false positives have a relative difference between the demand predicted with our method and units observed of less than 3%.

Figure 7: CDF for $(q^d - q^s)/q^d$ for non-predicted shortages when observed units $< \tau$