Drug Shortages: Evidence from France

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Introduction

- Drug shortages lead to disruption of treatment, health costs, additional treatment costs, increased workload for hospital pharmacies, illicit drug trade
- Drug shortages are widely documented around the world (reported for Europe, Latin America, US, Australia, some Asian countries in Acosta et al. (2019))
- Drug shortages refer to supply disruption, discontinuation, out of stock somewhere in supply chain, excess demand, supply delays
- Definition of interest: potential demand of patients not satisfied by supply
- Many studies focus on the US that experienced a sharp increase of shortages in the early 2010s and a decrease after 2014 (FDA, 2020)

Drug Shortages Literature: Which drugs?

- Some drug classes are particularly sensitive to supply disruptions, but differences across countries of most severely affected drug classes
- Shortages are common in injectables, especially cancer drugs, antibiotics and anesthesia (especially in the US), but also for essential medicines and oncology drugs in Europe (Pauwels et al. 2014)
- Nervous system medicines in Belgium, US, Canada and China
- Anti-infectives in Australia and Latin America it is anti-infectives Acosta et al. (2019)
- Antimicrobials, oncology medicines, and, to a lesser degree, emergency and cardiovascular medicines in Europe (EAHP, 2014)

Drug Shortages in France

- In France, ANSM defines a shortage as the inability of a pharmacy to deliver a drug within 72 hours
- Benhabib et al. (2020) analyzed ANSM shortage data 2012-2018:
  - Trends similar to those observed internationally
  - Mostly older drugs experience shortages
  - Drug classes with more frequent shortages: anti-infectives, cardiovascular, oncology (mirrors the experiences of other countries)
- Measurement issues: counts of shortages but no measure of magnitude, knowledge of supply problems may affect medical choices attenuating shortage measures

Drug Shortages in France

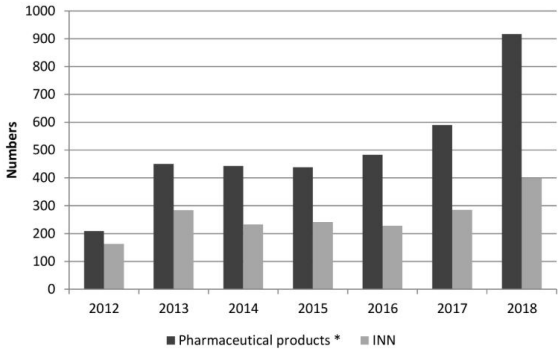


Figure 1 Trends in shortages by numbers of pharmaceutical products and international non-proprietary name drugs (INN) (2012–2018) in France. *Pharmaceutical products: defined by a combination of the INN, the formulation and the packaging.

Source: Benhabib et al. (2020)

Mechanisms and Evidence from the US

- Short term manufacturing capacity is fixed
- Existing manufacturers cannot easily expand production capacities
- In markets penetrated by generics, competition in prices with low margins, little incentives to invest in maintaining their manufacturing sites (Woodcock and Wosinska, 2013)
- Low margins in generic market mean manufacturing sites used at their capacity, increasing the risk of disruptions
- Weak failure-to-supply clauses aggravate this problem

Mechanisms and Evidence from the US

- Limited capacity makes producers shift to most profitable products - Haninger et al. (2011) show that drugs experiencing shortages in 2008-2011 faced decreasing sales volumes and prices in 2006-2008
- Intensity of FDA's quality control increase disruptions (Stomberg, 2018)
- Market Structure and regulatory rules
  - Low number of suppliers higher probability of shortage (Parsons et al (2016), Lee et al. (2020))
  - Regulatory and administrative requirements discouraging entry (Kantarjian, 2014)
- Low prices: Ridley et al. (2016) on vaccines, Dave et al. (2018) on generics, Yurukoglu et al. (2017) on shortages in sterile injectables after Medicare reimbursement decreases

An New Study of Drug Shortages at Hospital in France

- ANSM measure may be noisy and does not measure the magnitude of shortages
- Use of exhaustive Sell In data from GERS (2016-2021) to quantitatively measure (estimate) occurrence and magnitude of shortages
- Data by UCD (30,267 different UCD), hospital or pharmacies, monthly values and quantities (1,956,108 observations)
- Measure magnitude of shortage
- Measure expense/value lost due to shortage
- Matching with NHS data on prices in the UK

Methodology to Identify Drug Shortages

- Demand model allows to predict counterfactual demand and compare it to sales (equal to demand without shortage but higher and equal to supply when shortage)
- Demand model for drug j at month t in hospitals:

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

  where q_{jt}^d is the quantity of demand of drug j at period t that depends on a fixed component α_j, a time effect β_t, some other observable demand shifters γx_{jt}, on lagged demands up to K periods and some unobservable demand shock ε_{jt}.
- The quantity sold q_{jt} may be lower than the quantity theoretically demanded q_{jt}^d if there is some supply shortage
- Thus $q_{jt} = q_{jt}^d$ if there is no shortage and $q_{jt} < q_{jt}^d$ if there is shortage

Methodology to Identify Drug Shortages

- Assumption: shortages because of supply shocks are absent when sales are "large"
- Define a threshold τ_{jt} such that $q_{jt} = q_{jt}^d$ if $q_{jt} > \tau_{jt}$.
- Estimate demand equation conditional on τ_{jt} and predict using:

$$\widehat{q}_{jt}^{d}\left(\tau_{jt}\right) = \widehat{\alpha}_j + \widehat{\beta}_t + \widehat{\gamma} x_{jt} + \sum_{k=1}^{K} \widehat{\rho}_k q_{jt-k}^{d}$$

- Define quantity shortage $s_{jt}\left(\tau_{jt}\right)$ as the difference between realized sales and demand:

$$s_{jt}\left(\tau_{jt}\right) = \max\left(0, \widehat{q}_{jt}^{d}\left(\tau_{jt}\right) - q_{jt}\right) \times 1_{\{\widehat{q}_{jt}^{d}(\tau_{jt}) < \tau_{jt}\}}$$

Methodology to Identify Drug Shortages

- Recover $\tau_{jt}(\lambda)$ as solution of the following fixed point equation:

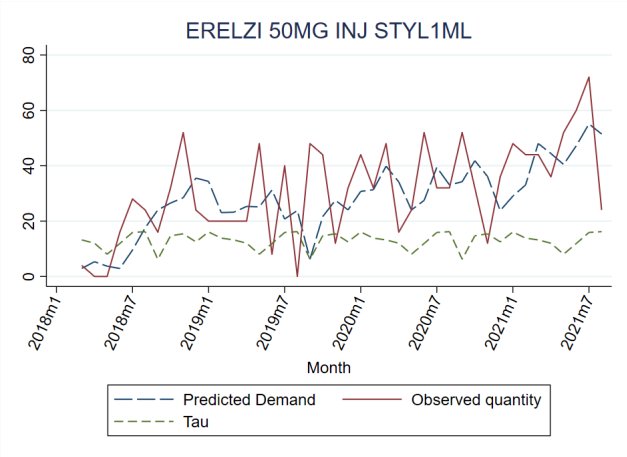
$$\tau_{jt} = E[\widehat{q}^d_{jt}(\tau_{jt})\,|m(t)] - \lambda\gamma_c(\tau_{jt})\sqrt{E_{j|j\in c}[V(\widehat{q}^d_{jt}(\tau_{jt})\,|j)]}$$

  where

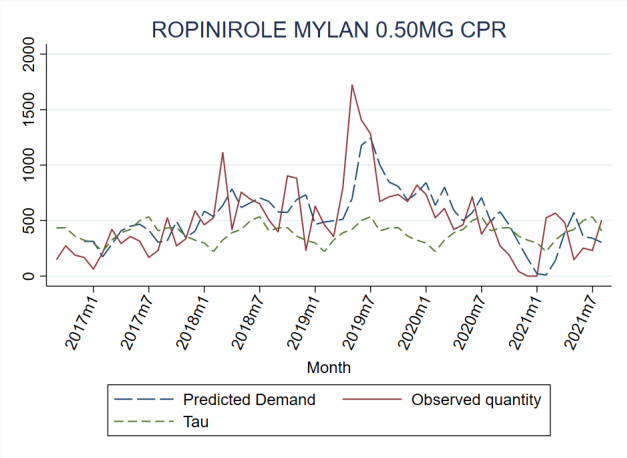
$$\gamma_c(\tau_{jt}) = E_{j|j\in c}\left[\frac{\sqrt{V(\widehat{q}^d_{jt}(\tau_{jt})\,|j)}}{E(\widehat{q}^d_{jt}(\tau_{jt})\,|j)}\right]$$

- We calibrate λ by minimizing the the prediction error of demand under the threshold τ_{jt} when sales are larger than the predicted demand (no shortage), and the prediction error of demand above the threshold τ_{jt} (no shortage)

Example


ERELZI 50MG INJ STYL1ML
0
20
40
60
80
2018m1
2018m7
2019m1
2019m7
2020m1
2020m7
2021m1
2021m7
Month
Predicted Demand
Observed quantity
Tau

Example



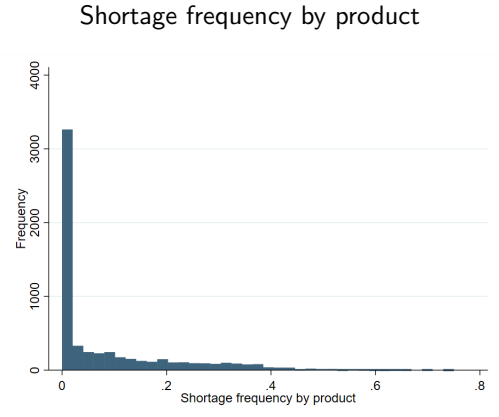
Note: ANSM shortage indication Sept 2020.

Drug Shortages in France

- Estimated average drug shortage probability by UCD at hospital (mean over 2016-2021)

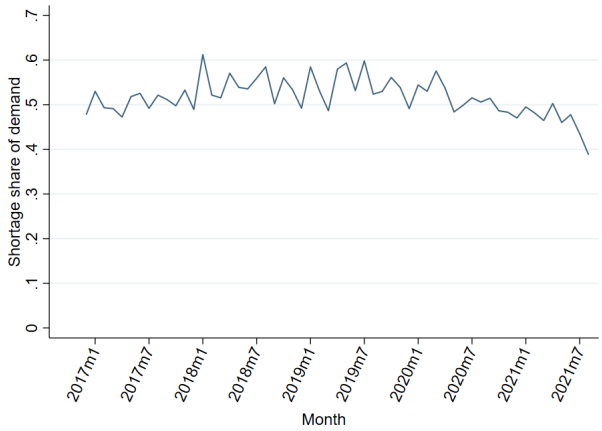
ATC	Shortage Probability	Nb UCD with Shortage	Nb UCD
A Alimentary tract and metabolism	0.00	0	1,317
B Blood and blood forming organs	**0.33**	644	893
C Cardiovascular system	**0.05**	953	1,918
D Dermatologicals	0.03	220	558
G Genito urinary system	**0.20**	382	591
H Systemic hormonal preparations	0.00	14	321
J Antiinfectives for systemic use	0.01	222	1,263
L Antineoplastic and immunomodulating agents	**0.09**	743	1,188
M Musculo skeletal system	0.08	334	514
N Nervous system	**0.26**	2,007	2,491
R Respiratory system	0.01	77	672
S Sensory organs	**0.13**	278	327

Drug Shortages in France



Drug Shortages in France

Shortage share of demand by UCD, conditional on shortage



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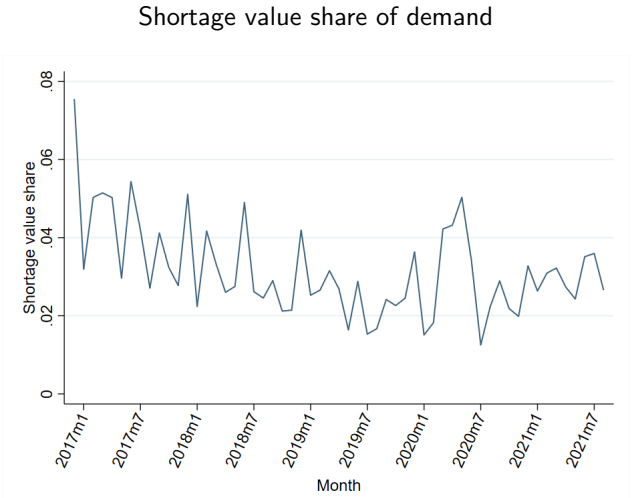

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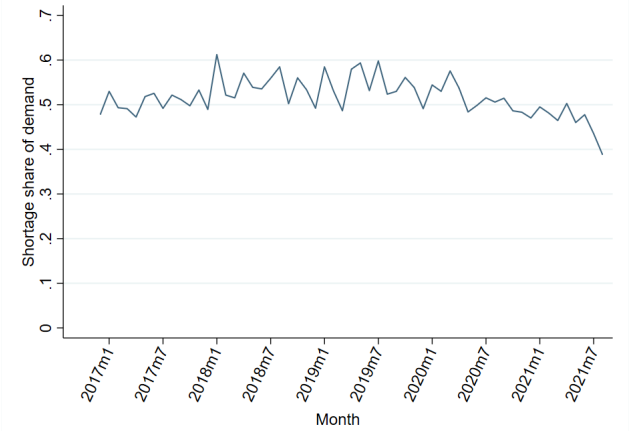

Analysis of Drug Shortages Determinants

- Shortages of drug may depend on price in France but also in other countries (like UK) because limited aggregate supply compared to aggregate demand
- Shortage probability s_{jt}^* as a function of the price(s) of the product

$$s_{jt}^* = \sigma_j + \delta_t + \alpha_{FR} \log p_{jt}^{FR} + \alpha_{UK} \log p_{jt}^{UK} + \epsilon_{jt}$$

- Shortage amount conditional on shortage is the opposite of the supply, function of the price(s) of the product, conditional on shortage ($s_{jt} = 1$)

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

Drug Shortages in France

Shortage probability

	(1)	(2)	(3)	(4)
Log price FR	-0.022***	-0.062***	-0.138***	-0.394***
	(0.002)	(0.004)	(0.010)	(0.063)
Log price UK		0.005**	0.007***	0.004*
		(0.002)	(0.002)	(0.002)
Constant	0.003	-0.071***	-0.140***	-0.216***
	(0.003)	(0.012)	(0.014)	(0.030)
N	473347	234521	213357	234521
UCD fixed effects	✓	✓	✓	✓
Time fixed effects	✓	✓	✓	✓
Instruments for price			✓	✓

Note: Standard errors. * for $p < .05$, ** for $p < .01$, and *** for $p < .001$.

Drug Shortages in France

Supply in case of shortage

	(1)	(2)	(3)	(4)
Log price FR	0.153***	1.636***	1.882***	1.636***
	(0.019)	(0.130)	(0.142)	(0.130)
Log price UK		-0.078***	-0.069***	-0.078***
		(0.011)	(0.011)	(0.011)
Constant	6.527***	9.695***	10.189***	9.695***
	(0.023)	(0.235)	(0.277)	(0.235)
N	53242	26912	24670	26912
UCD fixed effects	✓	✓	✓	✓
Time fixed effects	✓	✓	✓	✓
Selection control			✓	✓

Note: Standard errors. * for $p < .05$, ** for $p < .01$, and *** for $p < .001$.

Drug Shortages in France

Shortage probability - ATC class N

	(1)	(2)	(3)	(4)
Log price FR	-0.069***	-0.124***	-0.215***	-0.717***
	(0.007)	(0.009)	(0.017)	(0.163)
Log price UK		0.007*	0.013***	0.005
		(0.003)	(0.004)	(0.004)
Constant	-0.047***	-0.138***	-0.270***	-0.507***
	(0.011)	(0.027)	(0.031)	(0.105)
N	101787	71925	65620	71925
UCD fixed effects	✓	✓	✓	
Time fixed effects	✓	✓	✓	✓
Instruments for price			✓	✓

Note: Standard errors. * for $p < .05$, ** for $p < .01$, and *** for $p < .001$.

Drug Shortages in France

Supply in case of shortage - ATC class N

	(1)	(2)	(3)	(4)
Log price FR	0.171***	0.345***	2.020***	1.296***
	(0.026)	(0.034)	(0.180)	(0.100)
Log price UK		-0.049***	-0.061***	-0.055***
		(0.013)	(0.013)	(0.013)
Constant	7.340***	7.685***	11.076***	8.930***
	(0.031)	(0.095)	(0.378)	(0.155)
N	25052	17381	16257	17381
UCD fixed effects	✓	✓	✓	✓
Time fixed effects	✓	✓	✓	✓
Selection control			✓	✓

Note: Standard errors. * for $p < .05$, ** for $p < .01$, and *** for $p < .001$.

Counterfactuals

Back of the envelope counterfactual calculations
If prices were 10% higher, trade-off:

- Reduction in shortages both in probability and in extent: larger expenses to satisfy demand (increase in consumer welfare)
- Larger expenses even when no shortages
- Ratio of total increase in spending over demand increase says how much it costs to satisfy demand because of shortage

Counterfactuals: 10% higher prices in 2021

Spending increase ATC	Available Drugs (A)	Drugs on Shortage (S)	Ratio $(\frac{S+A}{S})$
A Alimentary tract and metabolism	31	0	∞
B Blood and blood forming organs	122	112	2.08
C Cardiovascular system	14	7	3.12
D Dermatologicals	4	1	8.15
G Genito urinary system	1	44	1.03
H Systemic hormonal preparations	11	8	2.50
J Antiinfectives for systemic use	154	23	7.68
L Antineoplastic and immunomodulating agents	413	508	1.81
M Musculo skeletal system	18	10	2.80
N Nervous system	42	92	1.46
R Respiratory system	3	1	7.38
S Sensory organs	3	0	7.62

Note: Total yearly expenses (million €).

Conclusion

- Shortages of drugs in France are important:
  - Shortage value is between 2 and 6 % of total demand
  - Shortage quantity between 40 and 60% of demand (conditional on shortage)
- Prices are one of the determinants
- Price negotiation should account for the tradeoff between higher spending and availability