Changes in the Ambulatory Use of Antibiotics in France Due to the COVID-19 Pandemic in 2020-2022: A Nationwide Time-Series Analysis

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ABSTRACT

We estimated the changes in the ambulatory use of antibiotics in France due to the COVID-19 pandemic in 2020-2022 by conducting time-series analyses using nationwide data from French health insurance databases. We examined all systemic antibiotics dispensed from January 1, 2010 through March 31, 2022. Use of most antibiotics decreased during the 3-month period following the start of first lockdown (March 17, 2020), and these decreases persisted 12 months later. Some initial increases indicated potential stockpiling for antibiotics used for chronic indications. Azithromycin constituted a noticeable exception. In a context of reduced circulation of non–COVID-19 viruses, the observed decreases compared with forecasts could partly reflect habitual overuse of certain antibiotics.

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INTRODUCTION

In early 2020, France was the fourth highest antibiotic consumer in Europe.[1] The COVID-19 pandemic and associated containment measures negatively impacted health care access and drug prescriptions.[2-4] In France, ambulatory antibiotic use decreased by 25% in 2020 compared with 2019.[3] This is equivalent to the gradual decrease observed over the prior decade, calling for more detailed explorations.[5] The reduction in antibiotic use, whose overuse or inappropriate use is difficult to limit, is a major concern due to high and increasing microbial antibiotic resistance.[5]

Our objective was to estimate the changes in ambulatory use of individual antibiotics in France during the COVID-19 pandemic, starting with the first national lockdown (March 17, 2020 through May 11, 2020) through roughly 2 years later.

METHODS

We used the Medic'AM open database of the French national health care system that covers about 67 million people.[6] The national database aggregates quantitative information on all non-hospital drug reimbursements on a monthly basis. No ethic committee approval was required for using these publicly accessible anonymized aggregated open data.

From January 2010 through March 2022, we estimated the monthly number of reimbursed delivered daily doses for individual systemic antibiotics. Delivered daily dose is defined by the World Health Organization as the average daily dose for a drug being used for its main indication in adults.

Interrupted time series were used to estimate the impact of the pandemic and associated containment measures on the use of each antibiotic with 3-month, 12-month, and 24-month follow-up periods. March 2020, when the first French national lockdown started, served as the predefined change point. Interrupted time-series analyses were conducted using autoregressive integrated moving average models to estimate changes in observed antibiotic use after this change point compared with what would have been expected without the pandemic (Supplemental Appendix). These models account for previously existing trends and eliminate the influence of seasonality.[7] All analyses were conducted using SAS 9.4 (SAS Institute).

Table 1. Change in Use of Specific Antibiotics Due to the COVID-19 Pandemic 3 and 12 Months After First Lockdown in France

	Pre-pandemic DDDs		Change in DDDs observed vs expected at 3 months		Change in DDDs observed vs expected at 12 months	
Antibiotic class and name	**No.**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**
Penicillins						
Amoxicillin	**2,914**	**2,372 to 3,455**	**−27.5**	**−35.1 to −17.9**	**−55.5**	**−71.8 to −39.2**
Amoxicillin-clavulanic acid	147	−125 to 420	**−10.9**	**−19.5 to −0.3**	**−24.9**	**−32.2 to −17.6**
Cloxacillin	**−91**	**−104 to −78**	−6.6	−27.5 to 31.4	−6.3	−17.0 to 4.4
Oxacillin	**−57**	**−70 to −44**	−41.6	−94.1 to 10.9	16.5	−68.1 to 84.6
Benzylpenicillin	**−1**	**−2 to −1**	**−13.8**[a]	**−22.8 to −4.9**	5.5[a]	−3.9 to 14.9
Phenoxymethylpenicillin	**65**	**58 to 72**	**26.1**	**2.5 to 49.7**	11.8	−2.5 to 26.1
Piperacillin	**1**	**1 to 1**	−15.9	−39.6 to 7.8	−11.8	−35.3 to 11.7
Pivmecillinam	**188**	**175 to 200**	**−10.2**	**−14.4 to −5.6**	**−105.5**	**−136.5 to −74.5**
Cephalosporins						
Cefuroxime	**−151**	**−194 to −107**	−15.6	−40.8 to 10.7	**−32.0**	**−41.4 to −22.6**
Cefaclor	**−37**	**−43 to −30**	−6.2	−21.7 to 9.2	**−14.4**	**−18.6 to −10.2**
Cefpodoxime	**−280**	**−367 to −193**	−16.6	−42.4 to 9.2	**−25.6**	**−33.1 to −18.1**
Cefixime	16	−18 to 51	−7.8	−24.3 to 8.7	**−6.8**	**−14.7 to −1.1**
Ceftriaxone	**10**	**2 to 18**	−2.7	−10.3 to 4.9	**−27.5**	**−35.6 to −19.4**
Cefepime	**1**	**1 to 1**	−22.0	−40.4 to 3.6	**−8.3**	**−10.7 to −5.9**
Ceftazidime	**2**	**1 to 2**	**−17.0**	**−28.8 to −6.6**	−6.9	−21.2 to 7.4
Cefadroxil	**−14**	**−16 to −12**	−23.9	−63.7 to 15.9	**−3.1**	**−15.6 to −12.1**
Tetracyclines						
Doxycycline	67	−105 to 239	−21.7	−43.0 to 0.4	−3.5	−17.5 to 10.5
Minocycline	**−47**	**−54 to −40**	−6.1	−25.9 to 13.7	−0.3	−2.4 to 1.8
Tetracycline	20	−4 to 44	−12.4	−29.5 to 4.7	5.4	−11.6 to 22.4
Macrolides						
Azithromycin	**276**	**236 to 315**	−6.3	−24.7 to 12.1	**2.7**	**0.1 to 5.3**
Clarithromycin	**−347**	**−425 to −270**	−9.8	−29.6 to 10.0	**−26.9**	**−34.8 to −19.0**
Erythromycin	**−19**	**−22 to −16**	−13.1	−25.5 to 0.8	−3.3	−17.2 to 10.6
Josamycin	**−104**	**−133 to −75**	−22.2	−45.6 to 1.2	**−39.0**	**−50.5 to −27.5**
Roxithromycin	**−55**	**−91 to −18**	**−17.7**	**−32.7 to −2.7**	**−44.7**	**−67.8 to −21.6**
Spiramycin	−3	−11 to 5	−7.1	−16.7 to 2.5	**−34.4**	**−44.5 to −24.3**
Spiramycin in combinations	**−78**	**−89 to −66**	**−16.1**	**−29.3 to −2.7**	−5.8	−19.0 to 7.4
Fluoroquinolones						
Ciprofloxacin	**−25**	**−40 to −9**	−4.5	−10.9 to 2.9	−2.6	−9.8 to 4.6
Levofloxacin	−15	−36 to 6	−6.2	−18.9 to 6.0	**−23.6**	**−30.5 to −16.7**
Moxifloxacin	**−70**	**−79 to −61**	−7.3	−23.1 to 8.5	−2.0	−7.4 to 3.4
Ofloxacin	**37**	**17 to 57**	−3.9	−12.1 to 5.8	−3.4	−18.1 to 14.7
Other antibiotics						
Tobramycin	**3**	**0 to 5**	−5.3	−12.7 to 2.1	−5.3	−12.7 to 2.1
Clindamycin	**44**	**42 to 46**	**−5.6**	**−11.2 to 0.0**	**−7.7**	**−10.0 to −5.4**
Sulfadiazine	**−4**	**−4 to −3**	**−41.9**	**−52.3 to −25.9**	−8.7	−21.3 to 3.9
Sulfamethoxazole-trimethoprim	**29**	**24 to 35**	8.4	−1.8 to 18.6	−5.5	−17.1 to 6.1
Trimethoprim	**2**	**2 to 3**	−0.2	−4.8 to 4.4	**79.6**	**56.2 to 103.0**
Pristinamycin	−41	−104 to 21	**−15.9**	**−24.1 to −7.6**	**−29.1**	**−47.7 to −10.5**
Fosfomycin	**70**	**66 to 73**	**−10.4**	**−13.9 to −6.8**	**−8.6**	**−16.1 to −1.1**
Colistin	**1**	**1 to 2**	**8.1**	**1.5 to 14.7**	−2.1	−9.2 to 5.0
Nitrofurantoin	**−60**	**−70 to −51**	**−185.1**	**−246.5 to −123.7**	−21.3	−55.6 to 13.0

DDDs = delivered daily doses.

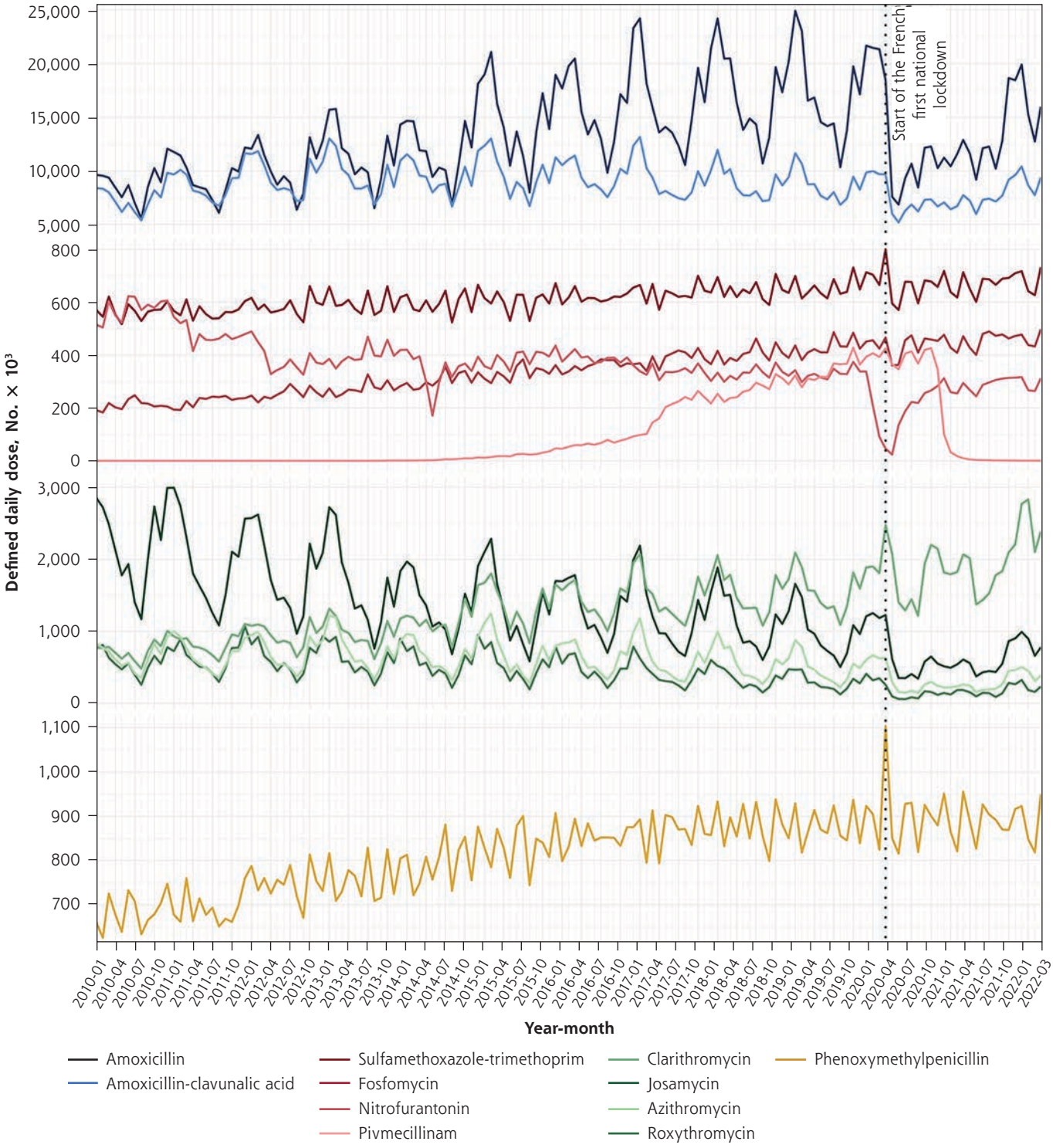
Note: Prior trend is the overall evolution of the monthly number of reimbursed DDDs for each antibiotic in France from January 2010 to near the start of first lockdown in March 2020 (roughly 10 years of data). Values in bold are significant at the level of $\alpha = .05$

[a] Estimated since June 2018.

RESULTS

Over the 3-month period starting with lockdown, the number of monthly reimbursed delivered daily doses decreased significantly for most antibiotics (Table 1, Figure 1, Supplemental Table 1); for example: amoxicillin (−27.5%; CI, −35.1% to −7.9%), amoxicillin-clavulanic acid (−10.9%; CI, −19.5% to −0.3%), cefepime (−22%; CI, −40.4% to −3.6%), roxithromycin (−17.7%; CI, −32.7% to −2.7%), pivmecillinam (−10.2%; CI, −14.4% to −5.6%), or fosfomycin (−10.4%; CI, −13.9% to −6.8%). Conversely, colistin (8.1%; CI, 1.5% to 14.7%) and phenoxymethylpenicillin use (26.1%; CI, 2.5% to 49.7%) initially increased significantly. Results appeared similar over the 12-month period starting in March 2020, indicating a prolonged impact of the pandemic on ambulatory antibiotics use (Supplemental Table 2). For the overall the 24-month follow-up period, most antibiotics use levels remained significantly

Figure 1. Monthly Number of Defined Daily Doses for Antibiotics in France January 2010 Through March 2022



Note: Selected antiobiotics include amoxicillins, drugs with indication for urinary tract infections (reds), macrolides (greens), and phenoxymethylpenicillin (for chronic conditions).

decreased (Supplemental Table 3) but trends in monthly reimbursements tended to move back to their pre–COVID-19 values. Unlike the observed overall and for other macrolides, azithromycin use level did not decrease during the 3-month period starting with lockdown (–6.3%; CI, –24.7% to 11.1%) and conversely increased over 12-month (2.7%; CI, 0.1% to 5.3%).

DISCUSSION

As observed in other countries,[8,9] a significant and prolonged decrease in the ambulatory use of most systemic antibiotics in France was observed over the COVID-19 pandemic period (2020-2022). The decrease in antibiotics specifically intended for the treatment of ear, nose, throat, and respiratory tract infections, such as amoxicillin, was especially noticed. The decrease could be partly related to restricted access to care caused by the lockdowns.[2,4] It could also be a direct effect of the decrease in viral infections which was observed during this period as a result of containment measures, that led to fewer secondary bacterial infections and potentially less antibiotic misuse.[8-11] For antibiotics with indications for urinary tract infections (eg, fosfomycin), the decrease in use might be related to restricted access to care, but potentially also to a reduction of some traditional urinary tract infections risk factors during the lockdowns. For example, people had fewer sexual activities, and people working from home may have been able to hydrate and urinate more easily than when in the workplace.

Some antibiotics had different patterns of use. Reimbursements for antibiotics with chronic indications, such as colistin, phenoxymethylpenicillin, and trimethoprim-sulfamethoxazole, temporarily increased during the first lockdown. This could be due to precautionary stockpiling by patients with chronic comorbidities, as observed for cardiovascular drugs.[4] Finally, unlike other macrolides, use of azithromycin did not decrease in the months following the first lockdown start and increased persistently. This is likely because azithromycin was considered as an anti–COVID-19 drug by some French microbiologists despite any robust evidence, an item of misinformation that was widely relayed by the media. This finding was consistent with internationally reported results.[12]

To our knowledge, no event other than the pandemic and associated containment measures could explain the changes observed during the study period. No important antibiotic drug shortage occurred during this period, except for nitrofurantoin between December 2019 and April 2020 which might have led to an overestimation of the initial impact of the pandemic for this drug.

An important strength of the study resides in its use of national data of ambulatory drug reimbursements, which included all reimbursements in France. The findings, however, do not allow for identifying and quantifying antibiotic indications and misuse. Another strength relates to the use of interrupted time-series models that allowed the analyses to account for seasonal variations and pre-existing trends in antibiotic use.

In conclusion, the early COVID-19 period was marked by significant reductions in the use of most antibiotics, particularly those with indications for ear, nose, throat, respiratory, and urinary tract infections. The observed changes in use differed for antibiotics with indications for chronic use, however, and for azithromycin. In a context of reduced circulation of non–COVID-19 viruses, the decreases observed compared with forecasts could partly reflect the habitual overuse of certain antibiotics.

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Key words: ambulatory care; anti-bacterial agents; COVID-19; interrupted time-series analysis.

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Supplemental materials

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