CMI COMMUNICATIONS 1 (2024) 105037

Contents lists available at ScienceDirect

CMI Communications

journal homepage: www.elsevier.com/locate/cmicom

Original Article

Post-pandemic consumption of outpatient antibiotics in Switzerland up to pre-pandemic levels, 2018–2023: An interrupted time series analysis

Catherine Plüss-Suard [a,*], Olivier Friedli [a], Anton Labutin [b], Michael Gasser [a], Yolanda Mueller [c], Andreas Kronenberg [a], on behalf of the Swiss Centre of Antibiotic Resistance (ANRESIS)

[a] Swiss Centre for Antibiotic Resistance, Institute for Infectious Diseases, University of Bern, Bern, Switzerland
[b] Federal Office of Public Health, Communicable Diseases Division, Bern, Switzerland
[c] Department of Family Medicine, Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland

ARTICLE INFO

Editor: Dr. Navaneeth Narayanan

Keywords:
Antibacterials
Outpatient
COVID-19
Surveillance
Switzerland

ABSTRACT

Background: The COVID-19 pandemic has been a challenge for health-care systems and antibiotic stewards as uncertainty regarding treatment and bacterial coinfections raised concern.
Methods: This retrospective observational study examined the association of the pandemic on outpatient antibiotic sales and prescriptions in Switzerland using interrupted time series (ITS) analyses. Data from IQVIA™ and the Sentinella Network were used to analyze antibiotic consumption and prescription patterns over a 72-month period from January 2018 to December 2023, divided into pre-pandemic, pandemic, and post-pandemic periods.
Results: Antibiotic consumption decreased during the pandemic and returned to pre-pandemic levels in the post-pandemic period. A decrease in level was most pronounced in the French-speaking region (−2.82 defined daily doses per 1,000 inhabitants per day (DID) per month, 95 %CI [−4.34, −1.30], $p < 0.001$) and the Italian-speaking region (−2.80 DID per month, 95 %CI [−4.78, −0.82], $p < 0.01$), followed by the German-speaking region (−1.72 DID per month, 95 %CI [−2.71, −0.74], $p < 0.01$). Similarly, in the ITS, the relative change of model estimates in antibiotic prescriptions by GPs and pediatricians for upper respiratory tract infections, was of −36.0 % and −50.3 % resp. in the pandemic period and +10.1 % and −2.6 % in the post-pandemic period compared with the pre-pandemic period.
Conclusions: A decrease of antibiotic prescriptions was observed in GPs and pediatricians during the COVID-19 pandemic, followed by a return to pre-pandemic levels. The patterns in antibiotic prescriptions aligned with the epidemiology of respiratory infections and demonstrated a pronounced association with the implementation and subsequent removal of non-pharmaceutical interventions.

Introduction

Inappropriate prescribing of antibiotics is a major cause of resistance development with consequences for patient morbidity and mortality [1]. The COVID-19 pandemic posed a challenge to health-care systems and antibiotic stewards [2]. It raised concerns about antibiotic use because of the difficulty in diagnosing bacterial pneumonia and, at least early in the pandemic, the fear of bacterial co-infection [2]. However, decreases of outpatient antibiotic consumption during the COVID-19 pandemic have occurred in most European countries, most likely due to changes in the epidemiology of respiratory tract infections as a result of control measures, such as physical distancing, mask use and hand hygiene [3]. In addition, Switzerland has shown more liberal government responses, relaxing COVID-19 mitigation measures faster and more than other European countries [4].

Based on existing literature, it was hypothesised that the COVID-19 pandemic would be associated with an immediate steep decline in outpatient antibiotic sales and in prescriptions for respiratory tract infections during the pandemic period [5]. The aim of the study was to investigate (i) the impact of the COVID-19 pandemic on outpatient antibiotic prescribing patterns in Switzerland using interrupted time series analyses and (ii) how rates have evolved at the end of non-pharmaceutical interventions (NPIs).

* Corresponding author at: Institute for Infectious Diseases, University of Bern, Friedbühlstrasse 25, 3001 Bern, Switzerland.
E-mail address: Catherine.Pluess@unibe.ch (C. Plüss-Suard).

https://doi.org/10.1016/j.cmicom.2024.105037
Received 16 July 2024; Received in revised form 17 September 2024; Accepted 17 September 2024
Available online 5 October 2024

Methods

Study setting

Switzerland confirmed the first case of COVID-19 on February 25th 2020 in the Italian-speaking region. New cases then rapidly emerged in the Italian- and French-speaking regions, and a state of Extraordinary Situation was declared on March 16th 2020 under the Federal Law of Epidemics, with NPIs being recommended: banning gatherings for more than 5 people, staying at home and closing of schools, restaurants and non-essential stores, and later wearing a mask [4]. The measures were gradually removed beginning in late April until June 2020, but new measures were imposed on October 19th 2020 as new cases were detected. The vaccination campaign started on December 20th 2021. A second national lockdown was reintroduced from January 18th to February 16th 2021 with less stringent measures (partial containment: face masks on public transport, ban on gatherings of more than five people, home office requirement). At the end of March 2022, the Swiss Federal Council lifted the last remaining measures, ending the extraordinary situation.

Study design

Interrupted time series (ITS) analyses were performed using outpatient antibiotic sales and prescription data over a 72-month period, from January 2018 to December 2023. The time period was splitted in a pre-pandemic period (January 2018–February 2020), a pandemic period (March 2020–March 2022) and a post-pandemic period (April 2022–December 2023), with temporal segments following the introduction and removal of NPIs.

Data collection and sources

This retrospective observational study was based on two data sources:

(i) Sales (Sell-In) data provided by IQVIA™

Antibiotic sales data were provided on behalf of the Swiss Federal Office of Public Health (FOPH) through the IQVIA™ database, which provides a dataset of antibiotic quantities sold by the pharmaceutical industries to community pharmacies and self-dispensing physicians (IQVIA™ channels: APO/SD). As IQVIA™ uses the European Pharmaceutical Marketing Research Association (EphMRA) classification, antibiotic sales data (referring as consumption data throughout this study) were collected from the classes A7A, D10B, G1A1, G4A1, G4A9, J1 and J4A. Table S1 have been added to better illustrate the concordance between the EphMRA and the ATC classification, the latter being used to classify antibiotic families in our study. Antibiotic consumption in grams was converted to defined daily doses (DDD) using the 2024 release of the DDD by the World Health Organization (WHO) and classified according to their Access, Watch and Reserve (AWaRe) categories [6,7]. Linguistic regions were stratified as follows: the Italian-speaking part (Canton Tessin and Italian-speaking Grisons), the French-speaking part (Cantons Geneva, Neuchâtel, Jura, Vaud, Valais, French-speaking Fribourg and French-speaking Bern) and the German-speaking part (all other cantons, including Liechtenstein).

(i) Prescription data from the Swiss Sentinel Surveillance Network, Sentinella

Data collection was conducted on behalf of the FOPH as part of Sentinella, the Swiss Sentinel Surveillance Network (www.sentinella.ch). Distribution of physicians' age, gender, specialty and region is compared on an annual basis to the national medical statistics, following the methodology used in [8]. Given that this is a voluntary system that is likely to select physicians with a particular interest in infectious diseases, it is considered fairly representative of the population of primary care physicians in Switzerland. Reliability has not been assessed formally. Observations from members who reported irregularly (i.e., less than 39 weeks per year and fewer than one prescription per week) were excluded. In 2023, 121 GPs and 22 pediatricians completed a weekly questionnaire on number of consultations (including face-to-face consultations and home visits) and their antibiotic choice and indication, as judged by the physician. The respiratory tract infections included acute bronchitis, chronic obstructive pulmonary disease and pneumonia, as well as otitis media, sinusitis, pharyngitis and other upper respiratory tract infections. The urinary tract infections included upper and lower urinary tract infections.

Outcomes

For the IQVIA™ dataset, monthly antibiotic consumption in DDD per 1,000 inhabitants per day (DID) was measured using quarterly population estimates from the Swiss Federal Statistical Office for the period 2018–2023. For the Sentinella dataset, the monthly number of antibiotic prescriptions per 1,000 consultations was used. Antibiotic consumption was measured overall, by linguistic region, by antibiotic family and AWaRe category for the IQVIA™ dataset and overall, by GPs/pediatricians and by indication for the Sentinella dataset.

Statistical analysis

We used interrupted time series (ITS) linear regression assuming a normal distribution to test whether the antibiotic consumption fell below its expected value during and after the COVID-19 pandemic [9,10]. A statistical model was created to investigate whether a change in level was observed at the start of the pandemic and in the post-pandemic period, as follows:

$$\text{Model 1} <\text{-} \text{ Antibiotic consumption} \sim \text{Time} + \text{Period} + \text{Seasonality}$$

The model 1 included the independent variables ``Time'', a variable which coded for time (from 1 to the time point t), with a coefficient corresponding to the slope of the change in consumption over time and ``Period'', a variable coded as A, B and C (A for pre-pandemic, B for pandemic and C for post-pandemic time points), with a coefficient corresponding to the change in level after the start of the pandemic or post-pandemic period compared to the pre-pandemic period. In addition, we adjusted for seasonality by including a harmonic term using sine and cosine transform functions. Proportion of change in model estimates were the level changes derived from model 1. A model 2 was created to investigate whether a change in slope was observed during the pandemic and the post-pandemic period, including an interaction term ``Time * Period''. R version 4.3.2. was used to perform the analyses and generate the graphs.

Results

Consumption of systemic antibiotics, overall and by linguistic region, by antibiotic family and AWaRe category using the IQVIA™ dataset

During the pre-pandemic period, the mean monthly antibiotic consumption in Switzerland was 9.36 DID (95 %CI [8.73, 10.00]). After the start of the pandemic period, the estimated mean antibiotic consumption dropped abruptly by 2.07 DID per month (95 %CI [−3.16, −0.97], $p < 0.001$). This was a relative change of model estimates of −22.1 % compared to the pre-pandemic period.

During the pandemic, a decrease in level was most pronounced in the French-speaking region (−2.82 DID per month, 95 %CI [−4.34, −1.30], $p < 0.001$) and the Italian-speaking region (−2.80 DID per month, 95 % CI [−4.78, −0.82], $p < 0.01$), followed by the German-speaking region

(−1.72 DID per month, 95 %CI [−2.71, −0.74], $p < 0.01$), corresponding to relative changes of model estimates of −22.6 %, −22.9 % and −21.6 %, resp. (Fig. 1). In the Italian-speaking region, the estimated mean antibiotic consumption was 1.00 DID per month (95 %CI [−2.38,4.38], $p = 0.56$) higher in the post-pandemic than in the pre-pandemic period (corresponding to a relative increase by 8.2 %). In the French- and the German-speaking regions, the level in antibiotic consumption was very similar as in the pre-pandemic period (resp. +0.06 and −0.17 DID per month). The decrease in DID during the pandemic period does not appear to be affected by the actual incidence of COVID-19 cases (Fig. S1). Table S2 show the observed monthly trend of DID and the counterfactual based on the best-fitted model.

There was an upward trend in antibiotic consumption during both the pandemic and the post-pandemic periods, without being significant for both (Table S3).

Considering antibiotic families in Switzerland, the overall analysis showed the most significant decrease during the pandemic phase in level for combinations of penicillins and beta-lactamase inhibitors (mainly amoxicillin-clavulanic acid, ATC Code J01CR) (−0.76 DID per month, 95 %CI [−1.21, −0.32], $p < 0.01$), followed by extended-spectrum penicillins (mainly amoxicillin, J01CA) (−0.38 DID per month, 95 % CI [−0.60, −0.17], $p < 0.001$), macrolides (J01FA) (−0.37 DID per month, 95 %CI [−0.56, −0.19], $p < 0.001$) and fluoroquinolones (J01MA) (−0.18 DID per month, 95 %CI [−0.28, −0.07], $p < 0.01$) (Fig. 2). Levels for all antibiotic families during the post-pandemic period have returned to pre-pandemic levels.

Fig. S2 shows the trends in antibiotic consumption by AWaRe category. During the pandemic period we observed a higher decrease in level for the use of Access group antibiotics (−1.33 DID per month, 95 %CI [−2.07, −0.58], $p < 0.001$), then for the use of Watch (−0.78 DID per month, 95 %CI [−1.15, −0.40], $p < 0.001$). The use of antibiotics in the Reserve group did not show a statistically significant change in level. A reason might be the low baseline use of these medications in the outpatient setting.

Antibiotic prescriptions by GPs or pediatricians and by indications using the Swiss Sentinel Surveillance Network ``Sentinella'' database

In the ITS analysis, the mean monthly prescriptions per 1,000 consultations by GPs decreased by 3.96 (95 %CI [−6.73, −1.19], $p < 0.01$) after the start of the pandemic period. In the post-pandemic period, the mean monthly prescriptions per 1,000 consultations by GPs was 2.12 (95 %CI [−2.60, 6.84], $p = 0.38$) higher than the pre-pandemic period (Fig. 3). This represented a relative change of model estimates of −12.0 % in the pandemic period and +6.4 % in the post-pandemic period compared to the pre-pandemic period.

During the pandemic compared to the pre-pandemic phase, the level of prescription decreased for upper respiratory tract infections (−3.15 prescriptions per 1,000 consultations, 95 %CI [−4.64, −1.65], $p < 0.001$), and for lower respiratory tract infections (−2.95 prescriptions per 1,000 consultations per month, 95 %CI [−4.03, −1.86], $p < 0.001$), and slightly increased for urinary tract infections by 1.26 prescriptions per 1,000 consultations per month (95 %CI [0.48, 2.04], $p < 0.001$) (Fig. 4A). For upper respiratory tract infections, the relative change of model estimates was of −36.0 % in the pandemic period and +10.1 % in the post-pandemic period compared to the pre-pandemic period, for lower respiratory tract infections, it was resp. −46.5 % and +2.6 %.

Considering pediatricians, the mean monthly prescriptions per 1,000 consultations decreased by 17.74 (95 %CI [−25.43, −10.05], $p < 0.001$) after the start of the pandemic period. In the post-pandemic period, the mean monthly prescriptions per 1,000 consultations by pediatricians was 3.2 (95 %CI [−16.36, 9.89], $p = 0.63$) lower than the pre-pandemic

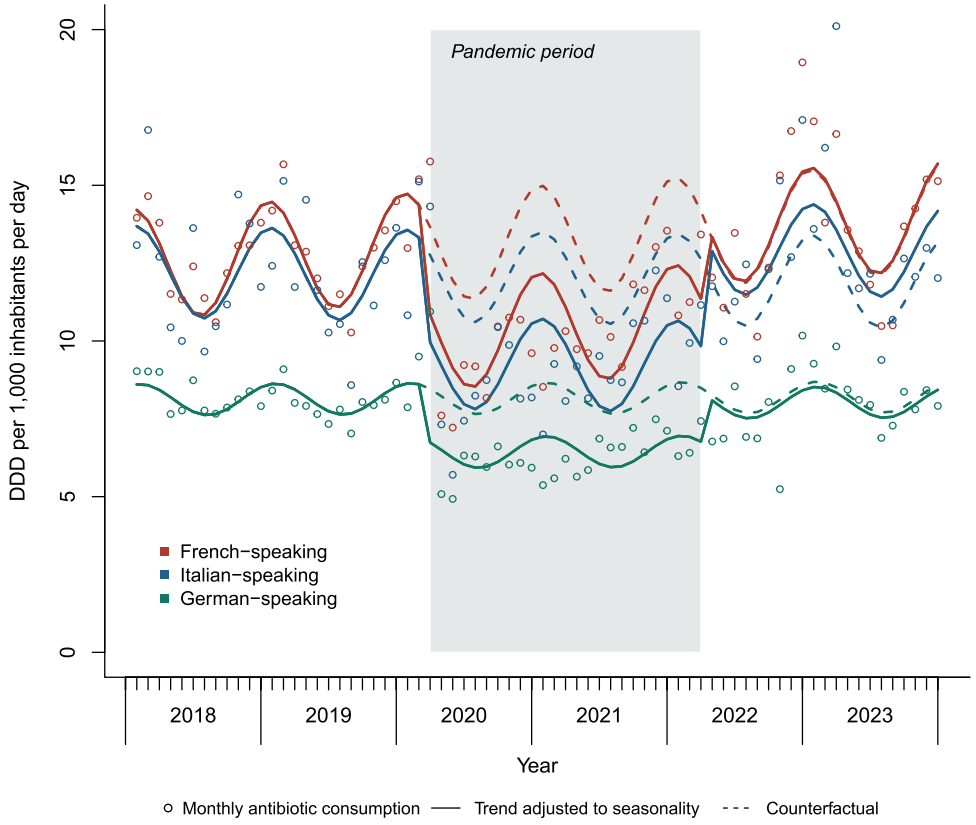

Fig. 1. Outpatient global antibiotic consumption by linguistic region expressed in defined daily doses (DDD) per 1,000 inhabitants per day using monthly sales data from IQVIA™, Switzerland. Pre-pandemic period: January 2018–February 2020; pandemic period: March 2020–March 2022; post-pandemic period: April 2022-December 2023.

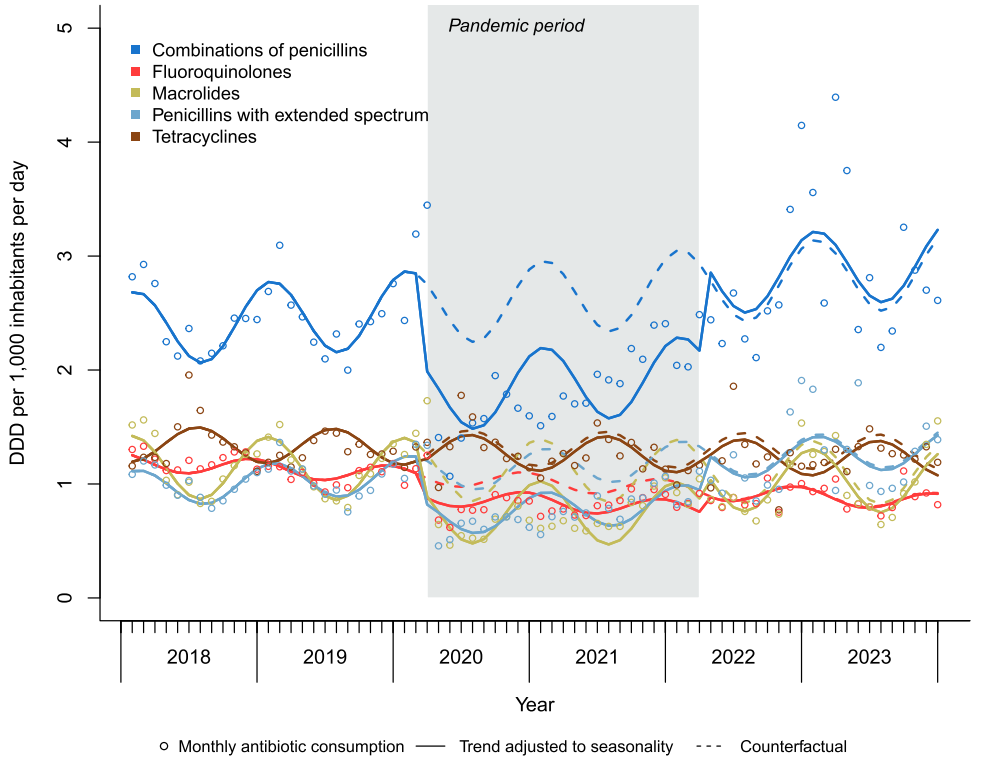

Fig. 2. Outpatient consumption per antibiotic families expressed in defined daily doses (DDD) per 1,000 inhabitants per day using monthly sales data from IQVIA™, Switzerland.
Pre-pandemic period: January 2018–February 2020; pandemic period: March 2020–March 2022; post-pandemic period: April 2022–December 2023. Combinations of penicillins for Combinations of penicillins with beta-lacatamase inhibitors.

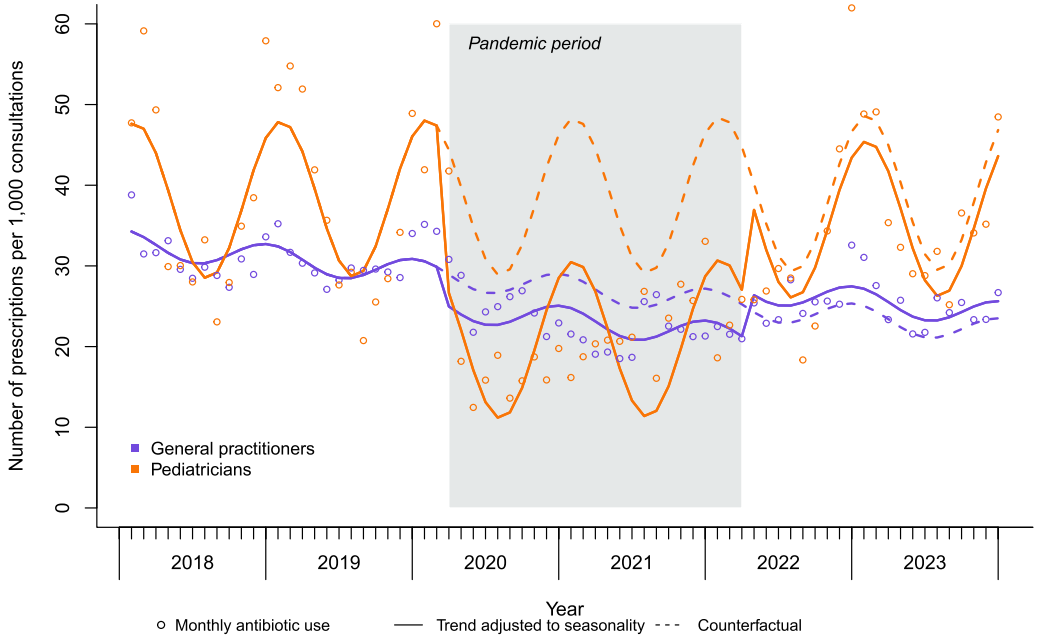

Fig. 3. Outpatient antibiotic use per general practitioners and pediatricians expressed in a number of prescriptions per 1,000 consultations using monthly prescription data from Sentinella network, Switzerland. Pre-pandemic period: January 2018–February 2020; pandemic period: March 2020–March 2022; post-pandemic period: April 2022–December 2023.

period (Fig. 4B). This corresponded to a relative change of model estimates of −46.7 % in the pandemic period and −8.5 % in the post-pandemic period. During the pandemic period, the level of prescription decreased for upper respiratory tract infections (−14.81 prescriptions per 1,000 consultations, 95 %CI [−21.65, −7.98], $p < 0.001$), and for lower respiratory tract infections (−2.86 prescriptions per 1,000 consultations per month, 95 %CI [−4.10, −1.61], $p < 0.001$). For upper respiratory tract infections, the relative change was of −50.3 % in the pandemic period and −2.6 % in the post-pandemic period compared to the pre-pandemic period.

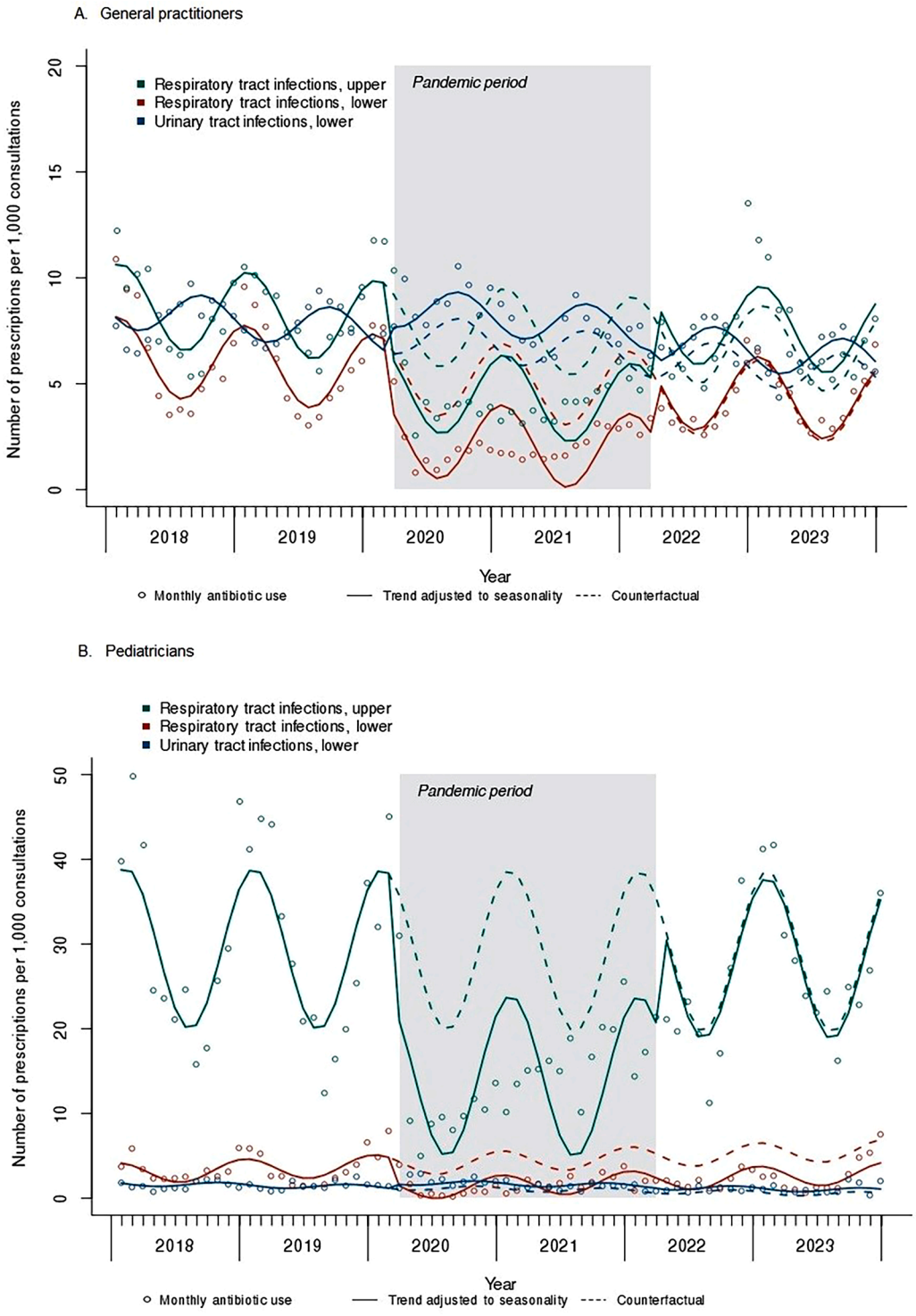

Fig. 4. Outpatient use per general practitioners (A) and pediatricians (B) by indications expressed in a number of prescriptions per 1,000 consultations using monthly prescription data from Sentinella network, Switzerland. Pre-pandemic period: January 2018–February 2020; pandemic period: March 2020–March 2022; post-pandemic period: April 2022–December 2023.

Changes in prescription of antibiotic families by GPs and pediatricians during the three periods are shown in Figs. 5, S3 and S4.

Of note, a slight decrease in the numbers of GPs and pediatrician consultations in the Sentinella network was observed in 2020 compared to 2019 (−2.3 % and −6.9 %, resp).

Discussion

Antibiotic consumption decreased during the pandemic and returned to pre-pandemic levels in the post-pandemic period. This was observed when measuring in DDD per 1,000 population per day as well as in a number of prescriptions per 1,000 consultations. The antibiotic consumption seemed to be better correlated with the ``period'' corresponding to non-pharmaceutical interventions rather than to the

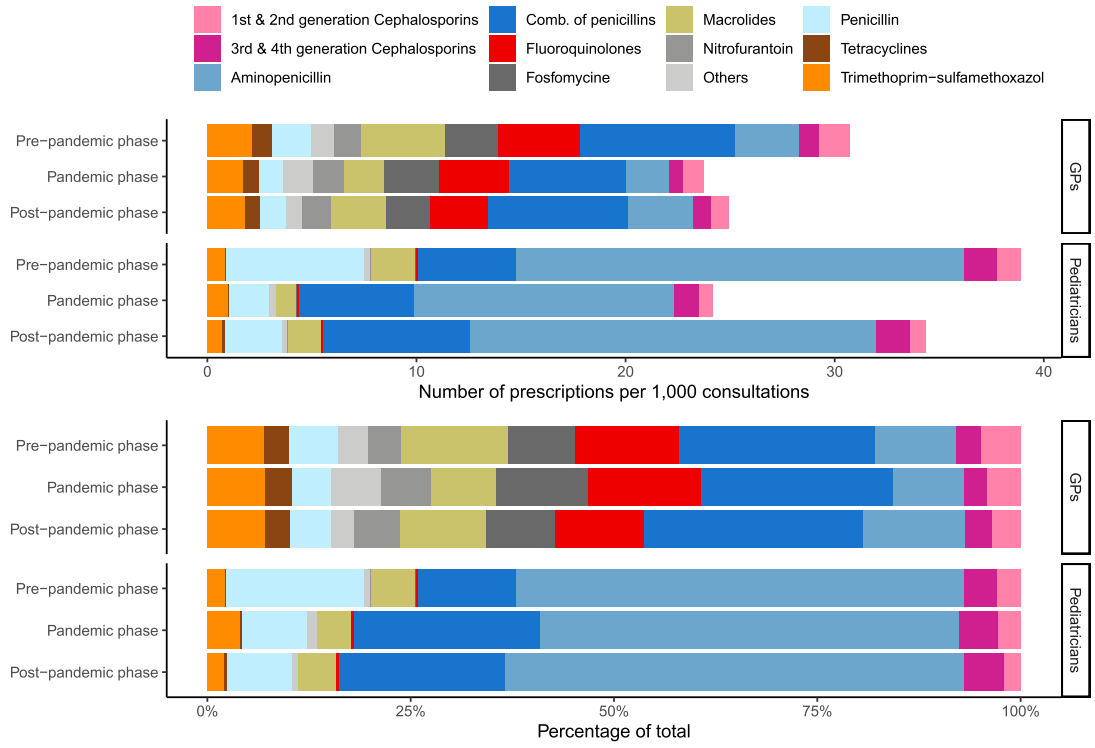

Fig. 5. Outpatient use per general practitioners (GPs) and pediatricians by antibiotic categories expressed in a number of prescriptions per 1,000 consultations and in percentage of total using prescription data from Sentinella network, Switzerland. Pre-pandemic phase: January 2018–February 2020; pandemic phase: March 2020–March 2022; post-pandemic phase: April 2022–December 2023.

number of positive COVID-19 identified cases.

A significant decrease in antibiotic prescriptions during the pandemic period was observed for both GPs and pediatricians. A slight decrease in consultations was also observed in Swiss primary care settings participating to the FIRE project where weekly consultation counts of the total general practice population were 17.2 % lower than expected during the lockdown period, with consultation numbers quickly returning to normal for the rest of 2020 [11]. These findings suggest that the reduction in antibiotic prescription rates is truly reflects a reduction in antibiotic prescribing and not an increase in consultations.

A large decrease in antibiotic prescriptions was observed in the Sentinella network for upper and lower respiratory tract infections during the pandemic period. Reductions in respiratory infections have also been reported due to NPIs such as face mask mandates and social distancing which lead to reduced inter-person transmission of bacteria and viruses [12-15]. Then, the removal of NPIs led to a resurgence of infectious diseases in many high-income countries [16]. A surge of scarlet fever above baseline levels was described in Switzerland (Joint Annual Meeting Swiss Society of Infectiology and Hospital Hygiene 2023, abstract 004), in France and in UK [17,18]. Influenza and respiratory syncytial virus transmission rates increased in autumn 2022 in Europe and in Switzerland, where antibiotics might have been prescribed in viral infections [19,20]. Immunity debt in children seemed to explain the increase in infections in the post-pandemic period [13,21]. Also, while people were working from home, they may have had less need to seek medical consultations for leave certificate, but they returned to their usual behaviors once back in the office.

During the pandemic, the decrease in antibiotic prescription was most pronounced in the French- and Italian-speaking region compared to the German-speaking region. Those were also the regions where COVID-19 cases first appeared in the country, and where the situation deteriorated rapidly. In these regions with higher COVID-19 incidence and mortality than in the German-speaking region, Moser et al. observed a stricter adherence to mitigation measures during the first lockdown [4, 22].

This study highlights a resurgence in antibiotic prescribing in the Swiss outpatient setting during the post-pandemic period. While the reduction in antibiotic use during the pandemic likely stemmed from a decrease in circulation of respiratory viruses, this was probably due most to the societal disruptions and physical distancing measures. Although preventive measures like vaccination, hand hygiene, and mask usage can contribute to reducing virus circulation, it is unlikely that the same levels of reduction seen during the pandemic can be achieved with only such measures. Therefore, future efforts, as key message of this study, should focus on reducing unnecessary antibiotic prescriptions for viral respiratory infections, emphasizing the importance of antimicrobial stewardship to ensure the appropriate use of antibiotics in the community.

Some limitations might influence our conclusions. The Sentinella network is a surveillance system comprising a non-exhaustive group of physicians. When compared with all physicians in the Swiss Medical Association, the Sentinella network proved however to be a representative sample of physicians, even if participation is voluntary, which introduces a degree of bias [8,23]. Their consultation counts only slightly decreased in 2020 compared with 2019 (−2.3 %). This was not the case in another study in Swiss medium- to high-prescribers where Aghlmandi et al. showed a 43 % reduction in consultations during 2020 compared with 2017 [24]. The shortage of important first-line antibiotics, such as amoxicillin, led to a shift in prescribing towards cephalosporins, penicillin V, macrolides and ceftriaxone in some European countries in autumn 2022 [25]. It cannot be ruled out that this may have also contributed to changes in prescribing habits [26].

Conclusions

Our study on outpatient antibiotic consumption in Switzerland during the COVID-19 pandemic revealed a significant decrease, observed both in GPs and pediatricians, followed by a return to pre-

pandemic levels. The patterns in antibiotic prescriptions align closely with the epidemiology of respiratory infections and demonstrated a pronounced association with the implementation and subsequent removal of non-pharmaceutical interventions.

Funding and transparency declaration

ANRESIS is partially financed by the FOPH and the University of Berne, Switzerland. CPS and AK received fees for lecturing at the University of Bern.

For projects not related to this study, YM received grants from the Swiss National Fund (grant no. 212429) and the Faculty of Biology and Medicine (transition grant), University of Lausanne, Switzerland. YM is a member of Cantonal Parliament of the Canton of Vaud, Switzerland, and holds stock options in Swiss Alternative Bank. AK has received fees for consulting to the FOPH in the framework of the Strategy Antibiotic Resistance (StAR), Switzerland and payment for lecture on data presentation within ANRESIS for Abbott in January 2024. OF have no conflicts of interest and no external funding to declare.

CRediT authorship contribution statement

Catherine Plüss-Suard: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Olivier Friedli:** Writing – review & editing, Investigation. **Anton Labutin:** Writing – review & editing, Investigation. **Michael Gasser:** Writing – review & editing, Investigation. **Yolanda Mueller:** Writing – review & editing, Investigation. **Andreas Kronenberg:** Writing – review & editing, Investigation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Catherine Pluess-Suard reports a relationship with University of Bern that includes: employment, speaking and lecture fees, and travel reimbursement. Catherine Pluess-Suard reports a relationship with Federal Office of Public Health that includes: funding grants. Olivier Friedli reports a relationship with University of Bern that includes: employment and travel reimbursement. Olivier Friedli reports a relationship with Federal Office of Public Health that includes: funding grants. Anton Labutin reports a relationship with Federal Office of Public Health that includes: employment. Michael Gasser reports a relationship with University of Bern that includes: employment and travel reimbursement. Michael Gasser reports a relationship with Federal Office of Public Health that includes: funding grants.

Yolanda Mueller reports a relationship with Swiss National Science Foundation that includes: funding grants. Yolanda Mueller reports a relationship with University of Lausanne Faculty of Biology and Medicine that includes: funding grants. Yolanda Mueller reports a relationship with University Centre for General Medicine and Public Health of Lausanne that includes: employment and travel reimbursement. Andreas Kronenberg reports a relationship with University of Bern that includes: employment, speaking and lecture fees, and travel reimbursement. Andreas Kronenberg reports a relationship with Federal Office of Public Health that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to thank the GPs and pediatricians who take part in the Sentinella network allowing us to conduct research projects with their reported data.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cmicom.2024.105037.

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