Marked Reductions in Pediatric Outpatient Antibiotic Prescribing in Portugal During the Pandemic

José Miguel Cunha de Alarcão (josecunhaalarcao@gmail.com)
Hospital Pediátrico de Coimbra: Centro Hospitalar e Universitario de Coimbra EPE
https://orcid.org/0000-0002-4649-9500

Ana Teresa Gil
Hospital Pediátrico de Coimbra: Centro Hospitalar e Universitario de Coimbra EPE

Bárbara Oliveiros
University of Coimbra Faculty of Medicine: Universidade de Coimbra Faculdade de Medicina

Fernanda Rodrigues
Hospital Pediátrico de Coimbra: Centro Hospitalar e Universitario de Coimbra EPE

Short Report

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Abstract

The COVID-19 pandemic brought unexpected effects on healthcare systems access and usage. Some of the measures implemented by governments to try and contain it, such as confinement periods, social distancing, widespread use of masks and other hygiene practices led to unprecedented epidemiological changes in several common infectious diseases.

We describe changes in antibiotic prescribing in pediatric outpatients before and during the pandemic in a dynamic population analysis context during a study period of three years in mainland Portugal.

There was a marked reduction in antimicrobial prescribing in all regions, particularly in younger children and during the lockdown periods.

This reduction was much sharper for those antimicrobials most commonly used to treat respiratory-tract infections, as Amoxicillin (with and without β-lactamase inhibitor) and Macrolides, and considerable less accentuated in other commonly prescribed antibiotics as Co-Trimoxazole and Fosfomycin, usually associated with the treatment of urinary tract infections.

**Conclusion**: Our findings indicate that the COVID-19 pandemic has had profound effects on antibiotic use in ambulatory care in children in Portugal.

Further monitoring is necessary to ascertain whether this reduction in antibiotic prescription will persist and whether these changes may impact antimicrobial resistance.

**What Is Known**

- The COVID-19 pandemic led to unprecedented epidemiological changes, with a decrease in common pediatric infectious diseases and to a reduction in visits to the emergency room department.

**WHAT IS NEW**:

- There was a marked reduction in antimicrobial prescribing during the pandemic, particularly in younger children, during lockdown periods and for antimicrobials mostly used to treat respiratory-tract infections.
- These results enhance the importance of non-medical interventions in fighting other infections beyond SARS-CoV-2 and call for a more rational use of health care services and antibiotic prescription.

**Introduction**:

COVID-19 was first identified in Portugal on 12/03/2020, with the government declaring a State of Emergency shortly after, that lasted until 02/05/2020. Later, a new wave, led to a new State of Emergency declared on 24/11/2020, lasting until 01/05/2021. Schools were closed from the 16/03/2020 until the
end of that school year, and again from the 21/01/2021 to the 15/03/2021 (pre-school and 1st cycle),
5/04/2021 (2º and 3º cycles) or until the 19/04/2021 (high-school).

A significant nationwide impact on healthcare system usage was observed, with a particular impact on
acute care, and a reduction in visits to the emergency room department. [1–4]

A sudden decrease in presentations of other pediatric infectious diseases was reported [1–3], and a
reduction in antibiotic consumption in the general population was observed in some settings. [5–7]

Inappropriate and widespread use of antibiotics is established as a main cause of emergence of resistant
strains [8], with antimicrobial resistance (AMR) being recognized as a global public health threat.

Portugal, despite recent improvements, still has very high rates of outpatient antibiotic usage [9], and in
the pediatric age, Amoxicillin/Clavulanic Acid is the most prescribed antimicrobial (https://bicsp.min-saude.pt/pt).

The aim of this study was to describe the profile and trends in antibiotic use in the pediatric outpatient
setting before and during the pandemic, assessing how prescribing was impacted by the Covid-19
pandemic and by the different measures implemented to contain.

**Materials And Methods:**

This is a retrospective, observational cohort study. Pediatric (< 18 years) antibiotic prescription data, in
Defined Daily Dose (DDD), was obtained from the Ministry of Health Primary Health Care Identity Card
“BI-CSP” (https://bicsp.min-saude.pt), a public-access platform, that includes information about
ambulatory prescribing from all primary care centers and public and private hospitals in mainland
Portugal. It does not include data on inpatient hospital prescribing.

We established a pre-pandemic period from March/2018 to February/2020 and a pandemic period from
March/2020 to February/2021. DDD values are in accordance with the World Health Organization (WHO)
Anatomical Therapeutic Chemical (ATC) index 2019 and the consumption of systemic antibiotics is
hereinafter expressed in DDD per 1000 children/adolescents per day (DHD).

The classification of different antibiotic groups was done according to the national pharmaco-
therapeutical classification (Classificação Farmaco-Terapeutica-CFT).

Different regions were assessed according to the common nomenclature of territorial units for statistical
purposes (NUTS II - Eurostat regions), which simultaneously corresponds to the organizational regions of
the national health service (Serviço Nacional de Saúde - SNS).

Covid-19 incidence rates were obtained from public-access data from Directorate-General Health (Direção
Geral da Saúde-DGS) (https://covid19.min-saude.pt), during the study period, and the population values
used are estimates made available by the National Institute of Statistics (Instituto Nacional de Estatística-INE) in its “Estimativas da População Residente” yearly report (https://www.ine.pt).

Since data was provided irreversibly anonymized for research purposes in compliance with European data protection regulations, there was no ethics approval or informed consent.

Analysis was performed in a dynamic population context as data was related to the antibiotic prescription in the entire Portuguese pediatric population, although converted to DHD in order to be interpretable.

**Results:**

During the pandemic, antibiotics decreased from 13.9–9.0% of the total prescribed drugs, with an average prescription of 6.4DHD, decreasing from 14.4DHD in 2018 and 2019, which represents a reduction of 55.8%.

Amoxicillin/Clavulanic Acid (2.58DHD) and Amoxicillin (1.22DHD) accounted for more than half (59.5%) of all antibiotic prescribing in pediatrics during the pandemic, despite marked reductions of -70.0% and −56.4%, respectively. Macrolides also showed reductions (Azithromycin − 66.1% and Clarithromycin − 60.5%). Other frequently prescribed antibiotics showed smaller changes, including Cefuroxime (-43.0%), Flucloxacinil (-38.9%), Fosfomycin (-15.8%) and Co-trimoxazole (-14.1%), with a slight increase for Tetracyclines (+ 1.56%). (Table 1)
Table 1
DHD (DDD$^1$ per 1000 children and adolescents per day) in pre-pandemic (March 2018-February 2020) and pandemic periods (March 2020-February 2021)

|                         | Pre-pandemic period | Pandemic period | Percentage of Reduction |
|-------------------------|---------------------|-----------------|-------------------------|
| **Global**              | 14.43               | 6.38            | − 55.8                  |
| **By antibiotic**       |                     |                 |                         |
| Amoxicillin + Clavulanic Acid | 5.91               | 2.58            | − 56.4                  |
| Amoxicillin             | 4.09               | 1.23            | − 70.0                  |
| Azithromycin            | 1.06               | 0.36            | − 66.1                  |
| Clarithromycin          | 0.51               | 0.20            | − 60.5                  |
| Cefuroxime              | 0.85               | 0.49            | − 43.0                  |
| Co-trimoxazole          | 0.13               | 0.11            | − 14.1                  |
| Fosfomycin              | 0.03               | 0.02            | − 20.4                  |
| Flucloxacillin          | 0.26               | 0.16            | − 38.9                  |
| Doxycycline/Minocycline | 0.93               | 0.94            | + 0.91                  |
| **By region**           |                     |                 |                         |
| North                   | 16.44               | 7.15            | − 56.5                  |
| Center                  | 9.69               | 4.39            | − 54.7                  |
| Lisbon and Tagus Valley | 16.14               | 7.21            | − 55.3                  |
| Alentejo                | 10.37               | 4.28            | − 58.7                  |
| Algarve                 | 13.75               | 6.22            | − 54.7                  |
| **By age group**        |                     |                 |                         |
| 0 - <1Y                 | 10.88               | 4.54            | −58.27                  |
| 1 - <5Y                 | 21.77               | 6.73            | −69.06                  |
| 5 - <10Y                | 13.95               | 5.70            | −59.11                  |
| 10 - <14Y               | 9.44                | 5.26            | −44.31                  |
| 14 - <18Y               | 12.54               | 9.17            | −26.90                  |

$^1$ DDD - Defined Daily Dose

Comparing the pre-pandemic and pandemic periods, there was a reduction in prescribing in all months. Falls greater than 50% were observed between April and June/2020 and again between November/2020.
and February/2021, corresponding to the 2 lockdown periods, with September/2020 being the least impacted with a reduction of only 24.5%. (Fig. 1)

During the pandemic, the month with the highest prescription rates was March/2020, with the lowest period being from April to June/2020 (4.04-4.82DHD), and with slightly higher values from September to November/2020 (7.03-7.82DHD), after which a new downward trend started, reaching 5.31DHD in February/2021.

Percentage falls in prescribing were similar across the country, ranging from −58.7% in Alentejo to -54.7% in both the Central Region and the Algarve, despite widely different pre-pandemic and pandemic prescribing (Table 1) and SARS CoV2 incidence rates. The two more densely populated regions had higher COVID-19 incidences during the study period, specifically 93.0 cases per 1000 habitants in Lisbon and Tagus Valley and 110.8 in the North Region, with much lower values reported in the Central Region (53.5), Algarve (49.3) and Alentejo (42.2).

Regarding age, there was a reduction in prescribing in all age groups which was less pronounced in adolescents (0–10 years old −64.0% and >10 years −36.3%).

During the pandemic, consumption was lowest in infants (4.54DHD), and highest in teenagers aged 15<18 years old (9.17DHD), with other age groups with intermediate values. In the pre-pandemic period, the highest rates were among children aged 1<5 years (21.77DHD) and 5<10 years (13.95DHD). (Table 1)

**Discussion:**

A marked reduction in pediatric outpatient antibiotic prescribing was observed in Portugal during the COVID-19 pandemic, especially for Amoxicillin (with and without β-lactamase inhibitor) and macrolides, antibiotics mostly used in the management of respiratory-tract infections.

The observed reduction has been sustained for 12 months, but was much more pronounced during the two COVID-19 waves and respective lockdown periods, from March to the beginning of May/2020 and from November/2020 to February/2021. These results may be explained, at least partially, by the confinement and non-medical interventions adopted such as physical distancing, widespread use of masks, hygiene measures and closure of schools, resulting in lower incidence of some infections, in particular those of the respiratory tract.

An observation that also supports this explanation is the much greater reduction seen in younger children, particularly in pre-school age, a group with higher incidence of respiratory-tract infections. This represents a clear shift - before the pandemic, consumption was much higher in under 10's than in teenagers, while during the pandemic these values were similar, due to a much smaller reduction in teenagers.

The wish to avoid using limited resources, the fear of contracting COVID-19 by going to health care centers and the fact that COVID-19 in children is usually a mild self-limiting infection may also have
contributed to parents adopting a ‘watch and wait’ approach instead of seeking medical care. This may also have contributed to lower prescription rates.

On the other hand, antibiotics which are more commonly used to treat urinary tract infections (Co-Triomoxazol and Fosfomycin) had much less pronounced reductions. These infections generally do not result from human to human transmission and therefore should be less affected by the above mentioned non-medical interventions.

Despite the differences in the background rates of prescription, similar proportionate reductions in antibiotic use were observed in all regions of the country, suggesting a consistency in physicians’ behavior in the context of falling numbers of presentations with acute infections.

While some similar findings have been reported in recent studies from Scotland\(^6\), England\(^7\) and the Netherlands\(^8\), that also found a reduction in both incidence of infectious diseases and antibiotic consumption in the general population, particularly in respiratory-tract infections and prescription of penicillins, our study, limited to children and adolescents, adds more detail about different pediatric age groups and covers a longer period of time that spans 2 lockdowns and intervening non-lockdown period during the pandemic. It evaluates data on ambulatory prescribing by GPs and hospital emergency services in a country which, in contrast to those which have previously reported, is in the “middle band” for usage of antibiotics, and shows comparable decreases to those seen in these “low-use” countries.\(^7\text{–}^9\)

The strengths of this study are its sample size, the use of national data from a robust electronic system and the comparison of these data between pre- and per-pandemic time periods.

However, there are limitations - the data relates to prescriptions issued and we had no access to information as to whether they were dispensed and taken, nor on indication for prescription.

Further investigation is needed to ascertain whether there was any increase in complications of acute infectious diseases as a consequence of not seeking healthcare advice although others have found no evidence of any such increase \(^7\).

Further monitoring is necessary to see whether this reduction in community prescribing, a very high source of antibiotic use, persists and whether these changes will impact antimicrobial resistance. It will be interesting to observe the impact of the lessons learnt from this pandemic.

These observations advocate the importance of effective public health communication about non-medical interventions, not only in fighting the spread of SARS-CoV-2 but also of other infections and, additionally, for better and more rational use of health care services for some acute infections, with subsequent reductions in antibiotic prescribing.

In conclusion, our findings indicate that the COVID-19 pandemic has had a profound effect on antibiotic use in ambulatory care in children in Portugal.
List Of Abbreviations

AMR - Antimicrobial resistance
ATC – Anatomical Therapeutic Chemical
CFT – Classificação Farmaco-Terapêutica/Pharmaco-therapeutical classification
DDD - Defined Daily Dose
DGS – Direção Geral de Saúde/Directorate-General Health
DHD – DDD per 1000 per day
INE - Instituto Nacional de Estatística/National Institute of Statistics
GPs – General practitioners
SNS - Serviço Nacional de Saúde/National Health System
WHO – World Health Organization

Declarations

Author contributions:

José Alarcão conceptualized the idea and collected the data.

All authors contributed to the study design, analysis and manuscript draft.

Fernanda Rodrigues and Bárbara Oliveiros also critically revised the manuscript.

All authors read and approved the final manuscript.

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Figures
Figure 1

Monthly outpatient pediatric prescriptions by antibiotic class, overall reduction in prescribing and positive SARS-CoV-2 cases, from March 2020 to February 2021 in Portugal