Universidade de Lisboa

Faculdade de Farmácia

Impact of the COVID-19 pandemic on outpatient medicines use: antibiotics as an example

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Trabalho de Campo orientado pela Professora Doutora Carla de Matos Torre, Professora Auxiliar, e coorientado pelo Professor Doutor António Teixeira Rodrigues, Professor Auxiliar.

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Resumo

Contexto: A pandemia COVID-19 foi originada pelo novo coronavírus, SARS-CoV-2, que se propagou rapidamente por todo o mundo. As medidas de Saúde Pública que foram implementadas para reduzir a transmissão do vírus limitaram o acesso a prescrições médicas e poderão ter afetado a dispensa de medicamentos. O real impacto da pandemia e das medidas associadas no consumo de medicamentos em ambulatório não é conhecido.

Objetivo: Avaliar o impacto da pandemia COVID-19 nos padrões de utilização de antibióticos de uso sistémico na comunidade, em Portugal.

Método: Foi realizado um estudo descritivo e selecionados para análise, antibióticos de uso sistémico (classificação ATC J01). Uma análise de séries temporais, usando o modelo autorregressivo integrado de médias móveis (ARIMA), de indicadores de qualidade para o consumo de antibióticos na comunidade, em Portugal, foi realizada de 1 de janeiro de 2016 a 31 de dezembro de 2020.

Resultados: O consumo de antibióticos (J01) diminuiu acentuadamente nos primeiros três meses de pandemia em Portugal, tendo uma redução significativa de 3 DIDs por mês no efeito de curto prazo ($\rho = 0.0086$). Após o início da pandemia, melhorias foram obtidas apenas a curto prazo para o consumo de penicilinas ($\rho = 0.0247$) e cefalosporinas ($\rho = 0.0067$). Não foram encontradas alterações significativas no consumo de macrólidos, lincosamidas e estreptograminas, quinolonas e no consumo relativo de penicilinas sensíveis às ß-lactamases e cefalosporinas de 3ª e 4ª geração. O consumo relativo de fluoroquinolonas aumentou a longo prazo +0.160% ($\rho = 0.0199$). O consumo relativo de penicilinas com inibidores das ß-lactamases e a razão entre antibióticos de amplo e estreito espectro sofreu um aumento a curto prazo (0.768% e 9.6, respetivamente), mas uma diminuição a longo prazo (-0.343% e -1.7, respetivamente).

Conclusão: Existem alguns fatores relacionados à pandemia que levaram à diminuição do consumo de antibióticos de algumas classes, como o confinamento, a diminuição do número de consultas médicas presenciais realizadas e a redução da transmissão de outras infeções respiratórias. No geral, os nossos resultados mostram que a pandemia

COVID-19 levou a um decrescimento no consumo de antibióticos, o que no futuro pode significar uma diminuição de resistências bacterianas.

Palavras-chave: COVID-19; Antibióticos; Consumo de medicamentos; Análise de séries temporais; Farmácias.

Abstract

Background: The COVID-19 pandemic was generated by the new coronavirus, SARS-CoV-2, and spread rapidly throughout the world. Public-health measures that were implemented to reduce virus transmission have limited access to medical prescriptions, and it may have affected the dispensing of medicines. The real impact of the pandemic and associated measures on outpatient medicines use is unknown.

Objective: The aim of this study is to evaluate the impact of the COVID-19 pandemic on the patterns of use antibacterials for systemic use in the community, in Portugal.

Methods: A descriptive study was conducted and antibiotics for systemic use (ATC classification J01) were selected for analysis. An interrupted time series analysis using the autoregressive integrated moving average (ARIMA) model of quality indicators for antibiotic consumption in the community in Portugal was performed from January 1st, 2016, to December 31st, 2020.

Results: The consumption of antibiotics (J01) declined sharply in the first three months of the pandemic in Portugal, having a significant reduction of 3 DIDs per month in the short-term effect (ρ = 0.0086). After the beginning of the pandemic, improvements were obtained only in the short-term for the consumption of penicillins (ρ = 0.0247) and cephalosporins (ρ = 0.0067). No changes were found in the consumption of macrolides, lincosamides and streptogramins, quinolones, and in the relative consumption of penicillins sensitive to ß-lactamase and 3rd and 4th generation cephalosporins. The relative consumption of fluoroquinolones increased in the long-term +0.160% (ρ = 0.0199). The relative consumption of penicillins with ß-lactamase inhibitors and the ratio broad- to narrow-spectrum antibiotics suffered a short-term increase (0.768% and 9.6, respectively) but a long-term decrease (-0.343% and -1.7, respectively).

Conclusion: There are some factors related to the pandemic that might be related to the decrease in antibiotic consumption, such as lockdown, the decrease in the number of face-to-face medical consultations, the reduction in the transmission of other respiratory infections, enhanced by the use of face mask and hand sanitiser. In general, our results reveal that the COVID-19 pandemic led to a decrease in the consumption of antibiotics, which we hope a reduction in bacterial resistance in the future.

Keywords: COVID-19; Antibiotics; Medicines consumption; Time series analysis; Pharmacies.

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Um "Obrigada" nunca será suficiente.

Abbreviations

ACE	Angiotensin-converting enzyme
AMR	Antimicrobial resistance
API	Active pharmaceutical ingredient
ARB	Angiotensin II receptor blockers
ARIMA	Autoregressive integrated moving average
ATC	Anatomic therapeutic chemical
CEFAR	Centro de Estudos e Avaliação em Saúde
CHMP	EMA Committee for Medicinal Products for Human Use
COVID-19	Coronavirus Disease 2019
DDD	Defined daily dose
DGS	National Health Directorate
DID	DDD per 1000 inhabitants and per day
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
ESAC	European Surveillance of Antimicrobial Consumption
ESC	European Society of Cardiology
HMR	Health Market Research
INN	International nonproprietary name
ITS	Interrupted time series
RAAS	Blockers of the renin-angiotensin-aldosterone system
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization
URTI	Upper respiratory tract infection

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1 Introduction

The Coronavirus Disease 2019 (COVID-19) is an infectious respiratory disease caused by a newly discovered coronavirus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) declared this new virus on December 31st, 2019, after been reported cluster of cases of “viral pneumonia” in Wuhan, People’s Republic of China (1). On January 30th, 2020, WHO declared the outbreak as a public health emergency of international concern, and on March 11th, 2020, it designated COVID-19 as a pandemic (2).

COVID-19 is spread mainly by droplets produced when an infected individual exhales, coughs, or sneezes. Since these droplets are too dense to stay floating in the air, they easily land on surfaces and floors. Therefore, anyone may become infected by inhaling the virus when in proximity to someone infected with COVID-19 or by touching an infected surface and then touching their eyes, nose, or mouth (2).

COVID-19 affects each person in different ways. Most people infected with the disease have mild to moderate symptoms and recover without the need for hospitalisation. The most common symptoms are fever, dry cough, and tiredness. Still, symptoms such as muscle pain, sore throat, diarrhoea, conjunctivitis, headache, loss of taste or smell, and skin irritation or discoloration of the fingers or toes may also appear (2).

On August 17th 2021, the aetiologic agent SARS-CoV-2 has spread all over the world, leading to around 206 million confirmed cases and around 4.3 million deaths (3).

1.1 COVID-19 pandemic in Portugal

Since March 2020, Portugal has been experiencing the effects of the COVID-19 pandemic.

The Portuguese government, together with the National Health Directorate (DGS), declared a state of emergency and adopted interventive public health measures on March 18th, 2020, such as social distancing, lockdown, and adopting protective health policies, namely the usage of masks. Furthermore, the population was placed in lockdown in order to ensure compliance with the measures, except for the people that maintain essential services (4).

1.1.1 Cases of COVID-19 in Portugal

The number of new cases of COVID-19 in Portugal fluctuated considerably from March 2020 to July 2021. One year after the beginning of the COVID-19 pandemic in Portugal, the country registers more than 16.000 deaths and more than 800.000 confirmed cases. Portugal went through 4 phases with a large increase in the number of new confirmed daily cases, having registered a maximum value on January 28th, 2021, with 16432 new infections and 303 deaths.

The figure 1 shows the number of new daily cases in Portugal from March 2020 to July 2021 (5).

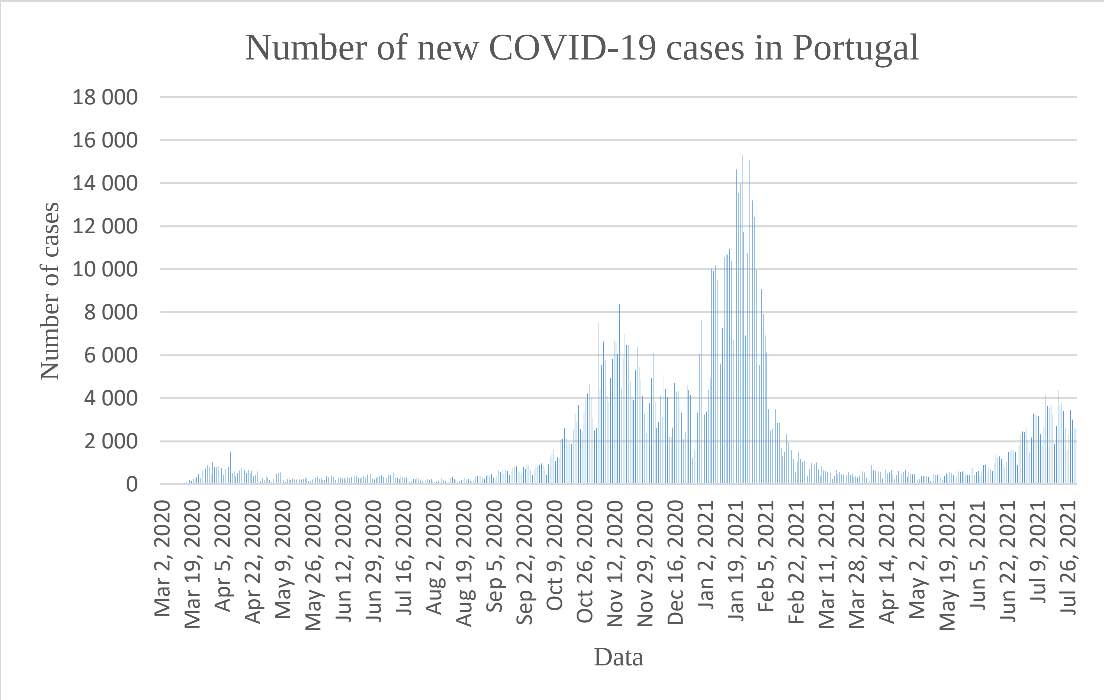

Figure 1: Number of new COVID-19 cases in Portugal from March 2020 to July 2021.

Adapted from Direção Geral de Saúde, *Ponto de Situação Atual em Portugal*, https://covid19.min-saude.pt/ponto-de-situacao-atual-em-portugal

The table below shows the chronology of the main events of a year and a half of COVID-19 in Portugal (5–7).

Table 1: Chronology of the main events of COVID-19 in Portugal

2020	
March 2nd	The first two cases of Portuguese people infected with the new coronavirus were announced. Public employees were on teleworking, if possible.
March 9th	Access to some public services were closed or conditioned and schools and universities suspended face-to-face classes.
March 11th	The WHO declared COVID-19 as a pandemic. The number of infections in Portugal increased to 59.
March 12th	Portuguese government decided that schools of all grades of education should suspend classroom activities.
March 16th	The first death in Portugal occurred (a 80-year-old man who had several associated pathologies). The number of infected people rose to 331.
March 18th	The President of the Republic decreed a state of emergency for a 15-day period, which included mandatory lockdown and restrictions on circulation.
March 19th	The Council of Ministers decided that public service establishments must close, and teleworking should be widespread.
April 2nd and 16th	The President of the Republic approved the extension of the state of emergency.
April 30th	A plan for the transition from a state of emergency to a state of calamity was approved. Cultural services started to open, teleworking was maintained, and the use of masks started to be mandatory in closed places with a high number of people.
May 2nd	The state of emergency ended, and the state of calamity began, the lockdown was suspended.
May 18th	Restaurants, cafes and daycare centers reopened and schools returned to face-to-face classes in the 11th and 12th years.
May 29th	The Government approved the extension of the calamity situation until June 14th.
August 3rd	Portugal registered the first day without deaths by COVID-19 since the beginning of the pandemic.
August 9th	Portugal had the highest number of daily new cases since April 20th (n=646). Health authorities justified this risen with the increased mobility.
September 14th	The basic and secondary levels of education returned with face-to-face classes. The use of masks in schools was mandatory and specific rules for circulation and use of spaces were implemented.

September 15th	Mainland Portugal entered on contingency situation until September 30th.
September 24th	The contingency situation in Portugal was prolonged until October 14th due to the increased number of cases.
October 14th	Portugal shifted from a contingency situation to a calamity situation.
October 28th	The use of masks in public spaces became mandatory.
November 2nd	The President of the Republic proposed to Parliament the declaration of a state of emergency in Portugal between 9 and 23 November, which allowed restrictions on freedom of movement.
November 7th	Portugal reached a new maximum of daily cases of COVID-19 by accounting for an additional 6,640 infections. 56 deaths were recorded, totalising 2,848 since the beginning of the pandemic.
November 20th	Parliament authorised the renewal of the state of emergency from November 24th until December 8th.
December 3rd	DGS stated that COVID-19 pandemic reached a peak on November 25th and started a downward trend afterwards.
December 17th	The President of the Republic decreed the renewal of the state of emergency for 15 days, until January 7th. New Year celebrations were completely cut off, but Christmas family gatherings were allowed.
December 20th	A new strain of COVID-19 originated from the United Kingdom, more transmissible, was detected.
December 27th	The national vaccination plan against COVID-19 started at the Hospital de São João, in Porto, structured by phases.
2021	
January 8th	Renewal of the state of emergency, until January15th. Portugal registered the higher COVID-19 numbers since the beginning of the pandemic: 118 deaths and 10,175 infections in a single day.
January 13th	Parliament approved the renewal of state of emergency until January 30th. Schools remained open, but the country returned to lockdown regimen in a similar way to March and April 2020.
January 16th	The number of COVID-19 cases continued to increase. Hospitals in the central region of the country were practically at the limit, close to rupture.
January 18th	Portugal became the country in the world with the highest number of new cases per million inhabitants.
January 21st	The Government announced the closure of schools at all levels of education.

January 27th	Detected a new strain of COVID-19 in Portugal originated from Brazil.
January 28th	Portugal registered the highest number of new cases, with 16 438 new daily cases of COVID-19 and 303 deaths, facing the worst phase since the beginning of the pandemic. Renewal of the state of emergency until February 14th.
February 8th	The numbers of new deaths and infections started to drop significantly, with 196 deaths and 2,505 new COVID-19 cases.
February 22nd	Portugal recorded 61 deaths related to COVID-19 and 549 new cases of infection, the lowest number since October 6th.
February 24th	DGS stated that close to 250 thousand Portuguese have already received two doses of the vaccine for COVID-19, which corresponds to 3% of the population.
April 25th	More than two million people have already received the first dose of the vaccine against COVID-19, which is equivalent to 20% of the Portuguese population. Around 800 thousand, representing 8% of the Portuguese population, have already been fully vaccinated against the disease.
July 21st	A new peak in the number of new COVID-19 cases was reached, with 4376 new cases.
July 25th	67% of the Portuguese population already has at least one dose of the vaccine, and 52% has full vaccination.
July 31st	The number of new cases of infection by COVID-19 has been decreasing, with 2590 new cases registered on this day.

1.1.2 COVID-19 – A landscape of potential strategies and unprecedent tales

1.1.2.1 Use of Renin–Angiotensin–Aldosterone System Blockers and the risk of COVID-19: Safety Signal

At the beginning of the pandemic, some researchers suggested (8,9) that patients with arterial hypertension, diabetes or heart disease, under treatment with or angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), would be at high risk of more severe disease progression, in case of infection by COVID-19. These opinions were based on the results of studies carried out in the China in patients infected with COVID-19, who had a more severe expression of disease and the prevalence of hypertension was very high (10,11).

As blockers of the renin-angiotensin-aldosterone system (RAAS), ACE-inhibitors and ARBs, are the most used drugs in the treatment of hypertension, those authors admitted that these drugs could have had a facilitating effect on viral invasion. ACE II is an enzyme with high kidney expression, endothelium, heart and lungs, which was identified as the functional receptor for coronaviruses - including SARS-CoV and SARS-CoV-2 - to enter the cells of the host and initiate viral replication (12). Thus, the authors of these studies admitted that the ACE inhibitors and ARBs, by increasing the expression of ACE II, would be facilitators of COVID-19 infection. However, the interactions of RAAS with this virus are not scientifically completely understood, and clinical evidence doesn’t support the hypothesis that ARBs treatment and ACE-inhibitors can make worse infections in COVID-19 context (13,14).

The European Medicines Agency (EMA) and the European Society of Cardiology (ESC) issued statements advising that it is important that patients do not interrupt their treatment with ACE inhibitors or ARBs, and there is no need to switch to other medicines (15).

1.1.2.2 Use of medicines which are potential COVID-19 treatments

1.1.2.2.1 Remdesivir

Remdesivir is a monophosphoramidate adenosine analogue prodrug that is metabolised to an active tri-phosphate form that inhibits viral RNA synthesis. This medicine has in vitro and in vivo antiviral activity against several viruses, including SARS-CoV2. Remdesivir is widely used in many countries, with several guidelines recommending its use in patients with severe or critical COVID-19 (16). In July 2020, EMA’s human medicines committee (CHMP) had recommended granting a conditional marketing authorisation to Veklury (remdesivir) for the treatment of COVID-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen. It is the first COVID-19 treatment recommended for European Union authorisation (17).

1.1.2.2.2 Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine have also been identified as potential therapies in the COVID-19. Both are indicated for the prevention and treatment of malaria and autoimmune diseases as chronic polyarthritis - rheumatoid arthritis and juvenile idiopathic arthritis, and lupus erythematosus. And it is based on this autoimmune activity that began to be thought of its use in the treatment of infections by the new coronavirus (18).

Chloroquine and hydroxychloroquine showed promising results in the laboratory when inhibiting SARS-COV-2 in vitro (19) and hydroxychloroquine appears to have a stronger antiviral effect. In Europe and, consequently, in Portugal, they were seen as a possible effective therapy in the treatment of patients with COVID-19 (18).

The dispense of these medicines in Portugal dramatically increased in March 2020 when compared to the same period of the previous year (more 200.6% in the second week of March). It is essential to guarantee the regular supply of patients already being treated with these medicines that are approved for the treatment of malaria and indication for rheumatoid arthritis and systemic lupus erythematosus. Noteworthy is the sharp growth registered at the end of the fourth week of March 2020, possibly related with the worldwide leaders advertising (*e.g*. US former President Donald Trump, Brazil President Jair Bolsonaro) to the use of hydroxychloroquine in the treatment of patients with COVID-19 (20).

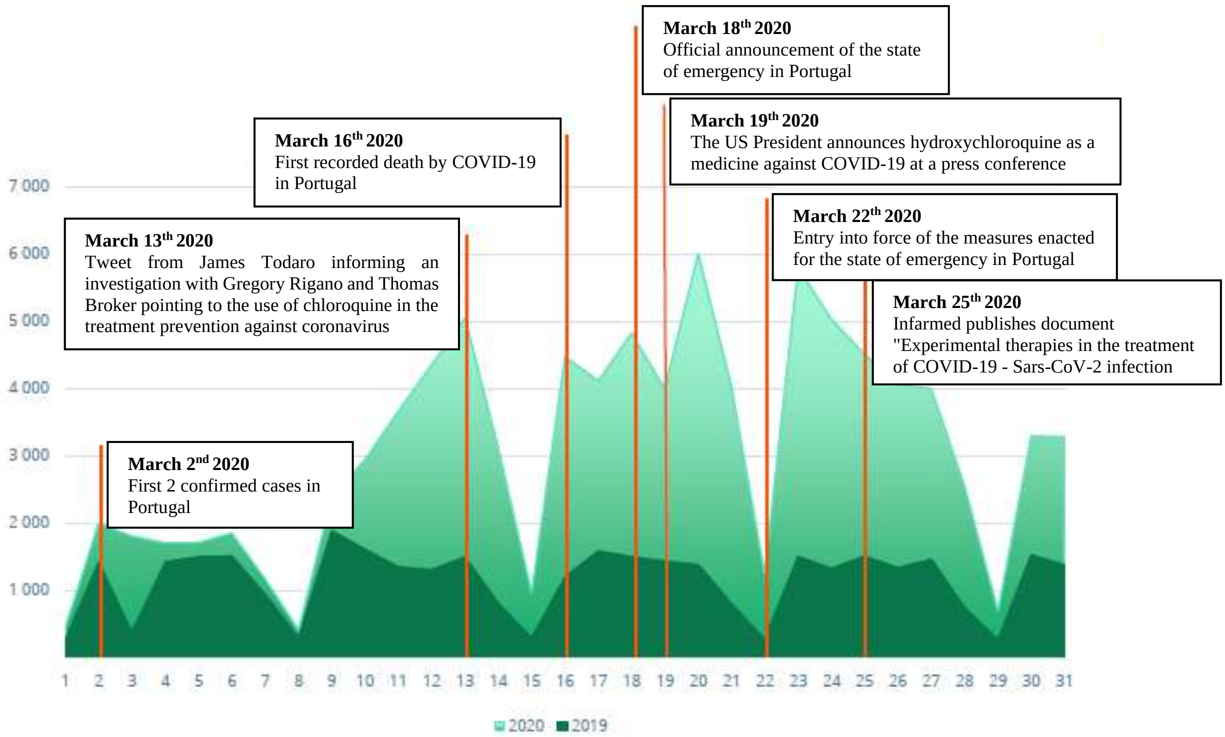

Figure 2: Daily evolution of sales of hydroxychloroquine and chloroquine in Portugal, in March 2019 vs March 2020.

From *Market Watch Portugal Março 2020*, Health Market Research, https://www.hmr.co.com/insights/market-watch-portugal-marco-2020/

On May 29th, 2020, Infarmed and the DGS recommended the suspension of treatment with hydroxychloroquine in patients with COVID-19, in line with the decision of the WHO, resulting from the publication of data that questioned the safety and efficacy of this potential therapy. Following a publication by *The Lancet* journal (21), on May 22nd, 2020, WHO decided to suspend the inclusion of new patients undergoing treatment with hydroxychloroquine from the global study Solidarity, which took place in several countries. The article published in this journal refers to a multinational observational study involving 96,032 patients, of whom 14,888 were treated with chloroquine or hydroxychloroquine, either alone or in combination with a macrolide class antibiotic such as azithromycin or clarithromycin. The study authors reported that they have not been able to confirm the benefit of hydroxychloroquine or chloroquine and point out an increased risk of mortality and new cases of ventricular arrhythmia during hospitalisation (22).

1.1.2.2.3 Ivermectin

Ivermectin is an antiparasitic drug used to treat several tropical diseases, including onchocerciasis, scabies and helminthiases (23).

Reports from in vitro studies suggested that ivermectin acts by inhibiting the host importin alpha/beta-1 nuclear transport proteins, which are part of an intracellular transport process that viruses bind to boost infection by suppressing the host's antiviral reaction. In addition, this medicine docking may interfere with the bidding of SARS-CoV-2 spike protein to the human cell membrane (24).

However, results from robust trials are needed to provide more evidence-based guidelines on the role of ivermectin in the treatment of COVID-19 (24). Furthermore, the effectiveness of ivermectin on mortality, hospital admission, duration of hospitalisation and viral clearance remain unclear because of the lack of quality of evidence addressing each of these outcomes. Infarmed, EMA and WHO does not recommend the use of ivermectin in the prophylaxis and treatment of COVID-19 (16,25,26).

Furthermore, some Portuguese doctors and pharmacists supported the use of ivermectin to treat early signs of COVID-19, a completely irresponsible measure (27).

1.1.2.2.4 Lopinavir/Ritonavir

The drug combination lopinavir–ritonavir has been suggested as an antiviral treatment for COVID-19. Lopinavir is an HIV-1 protease inhibitor, which is combined with ritonavir to increase its plasma half-life. Lopinavir is also an inhibitor of the SARS-CoV main protease, which is critical for replication and appears to be highly conserved in SARS-CoV-2 (28).

The pharmacodynamics of lopinavir/ritonavir increase concerns about whether it can achieve drug concentrations that can inhibit the SARS-CoV-2 proteases. Plus, lopinavir/ritonavir did not show efficacy in two large randomised controlled trials in hospitalised patients with COVID-19 (24).

There is no current data available on the use of lopinavir/ritonavir in nonhospitalised patients with COVID-19. In addition, the lack of evidence for a clinical benefit of hospitalised patients undermines confidence that lopinavir/ritonavir has any clinical benefit on SARS-CoV-2 infection. Therefore, WHO recommends against administering lopinavir/ritonavir for treatment of COVID-19 (16).

1.1.2.2.5 Anti-SARS-CoV-2 Monoclonal Antibodies

EMA is evaluating potential COVID-19 treatments with monoclonal antibodies, such as the combinations bamlanivimab plus etesevimab and casirivimab plus imdevimab, and also regdanvimab. These monoclonal antibodies attach the spike protein of SARS-CoV-2 at two different sites and reduce the ability of the virus to penetrate the body’s cells.

EMA started rolling reviews of these monoclonal antibodies and will continue until enough evidence is available to support formal marketing authorisation applications (29).

1.1.2.2.6 Baricitinib

Baricitinib is an immunosuppressant and is currently authorised for use in adults with moderate to severe rheumatoid arthritis or atopic dermatitis (eczema). EMA has started evaluating an application to extend the use of baricitinib to include treatment of COVID-19 in hospitalised patients from 10 years of age who require supplemental oxygen. The mechanism of action of baricitinib is blocking the action of Janus kinases that is important in immune processes that lead to inflammation. This could also help reduce tissue damage and the inflammation associated with severe COVID-19 infection (29).

1.1.2.2.7 Corticosteroids

Patients with severe COVID-19 might develop a systemic inflammatory response leading to multisystem organ dysfunction, more particularly lung injury. It has been proposed that the anti-inflammatory effect of corticosteroids might prevent or mitigate these effects. Dexamethasone, a corticosteroid, has improved survival in hospitalised patients who require supplemental oxygen, with the most significant benefit in patients who needs mechanical ventilation. Therefore, the use of dexamethasone is strongly recommended in this patient setting. The advantage of dexamethasone was observed in patients who were mechanically ventilated or required supplemental oxygen at enrolment. No benefit of dexamethasone was demonstrated in patients who did not require supplemental oxygen at enrolment. Therefore, WHO recommends the use of systemic corticosteroids rather than no corticosteroids for patients with severe or critical COVID-19-infection (16).

1.1.2.2.8 Vaccines for COVID-19

There are currently four vaccines for COVID-19 authorised for use in the European Union. Two of these vaccines are mRNA vaccines (nucleoside-modified) - Comirnaty and Spikevax, and the other two are made of another virus (adenovirus) that has been modified to contain the gene for making the SARS-CoV-2 spike protein - Vaxzevria and COVID-19 Vaccine Janssen (30).

1.2 Provision of healthcare during the COVID-19 pandemic

1.2.1 Medical Consultations in Portugal

In late March 2020, the Portuguese Government imposed lockdown across the country, making it illegal for citizens to leave home unless they had specific, essential reasons. During this period, it was increasingly difficult to get access to face-to-face medical consultations and the use of technology for remote consultations (telemedicine) was strongly encouraged by health authorities.

To analyse the impact of the COVID-19 pandemic on health care provision in Portugal, the available data from the number of medical consultations were compared with the 2019 homologous period, using the data from the SNS Transparency Portal (collected on February 10th, 2021).

As shown in figure 3, from January to December 2020, there were less 7 851 171 face-to-face medical consultations (a decrease of 38% of the total number of consultations) compared to the same period in 2019. On the other hand, the number of non-face-to-face medical contacts, like telephone and video consultations, doubled in 2020, compared to 2019. There was also a decrease in the number of medical consultations provided at home (31,32).

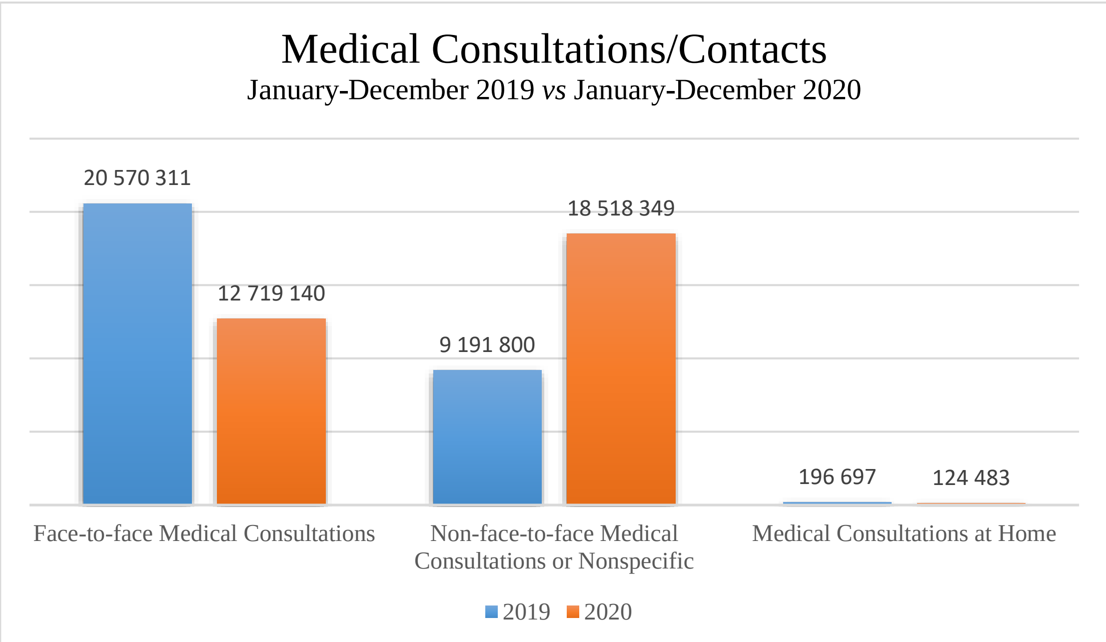

Figure 3: Number of face-to-face medical consultations, non-face-to-face or nonspecific and at home: January to December 2019 vs January to December 2020.

Adapted from Portal da Transparência, *Consultas Médicas nos Cuidados de Saúde Primários*, https://transparencia.sns.gov.pt/explore/dataset/evolucao-das-consultas-medicas-nos-csp/table/?sort=tempo

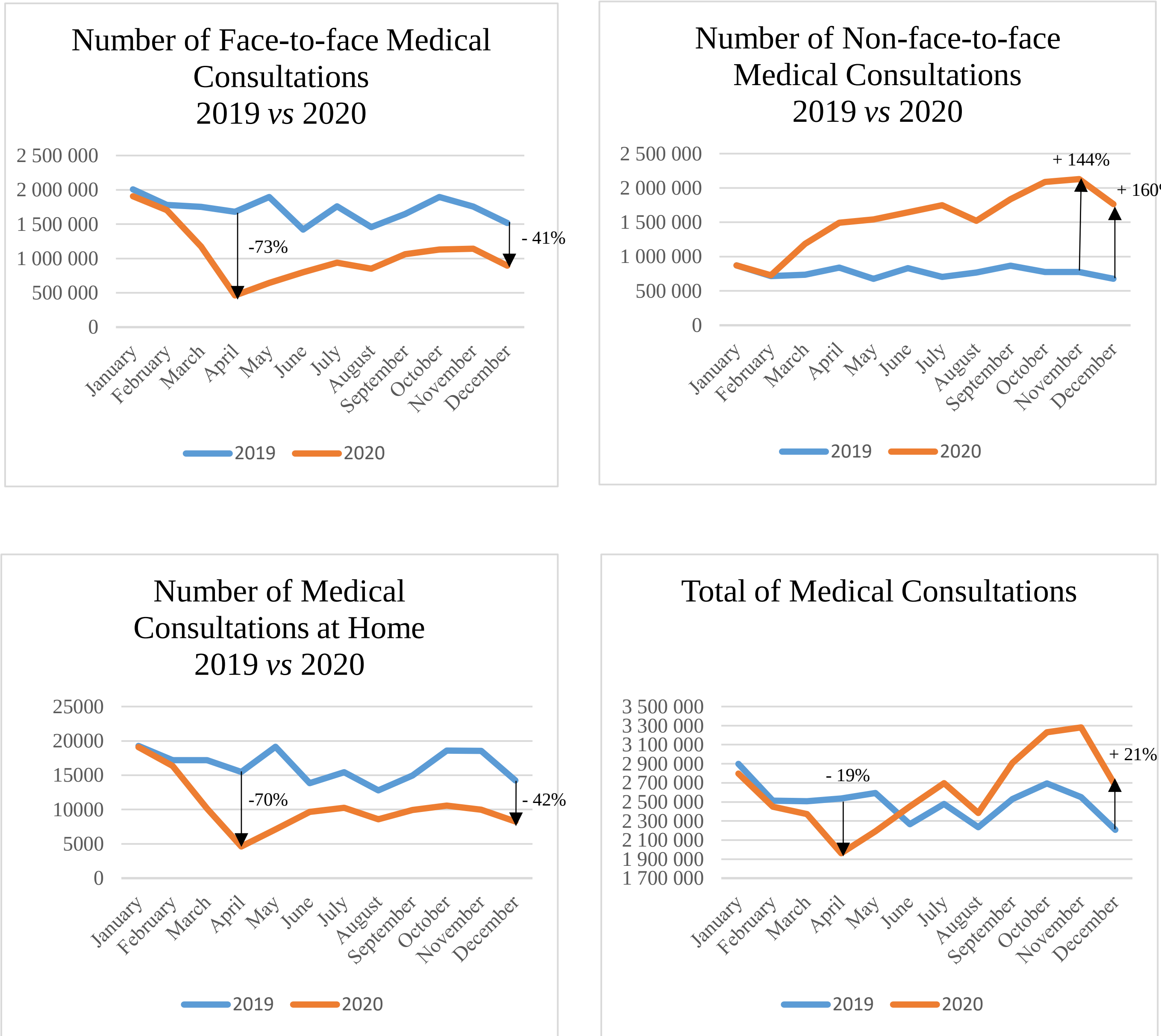

Figure 4: Medical consultations from January to December 2019 *vs* January to December 2020, per month.

Adapted from Portal da Transparência, *Consultas Médicas nos Cuidados de Saúde Primários*, https://transparencia.sns.gov.pt/explore/dataset/evolucao-das-consultas-medicas-nos-csp/table/?sort=tempo

As depicted in figure 4, in the first period of lockdown measures (April 2020), it is possible to observe a drastic decrease in the number of face-to-face medical consultations (-73%) and in the number of medical consultations at home (-70%). On the other hand, the number of non-face-to-face consultations has increased considerably since February 2020, remaining high until the end of that year, compared to 2019 (31,32).

Considering the total of medical consultations (face-to-face, non-face-to-face or non-specific and at home), it was found that in the first semester of 2020, the total number of consultations was lower than 2019, having reached a peak in April (-19%). From April onwards, the total number of consultations progressively increased until June that registered a higher frequency than in 2019, possibly compensating for consultations that were not carried out in the first period of national lockdown. In December 2020, there were more 21% of consultations when compared to the same period in 2019 (31,32).

The COVID-19 pandemic mirrored a rapid rise in the use of remote consultations by telephone and video. Remote consultations proved to be an important tool for supporting nonsevere COVID-19 patients, reducing pressure on inpatient care, and maintaining access to routine healthcare services. Although remote consultations cannot fully replace face-to-face consultations, it is a cost effective and efficient way of enabling access to healthcare (33).

1.2.2 Short- and long-term impacts of COVID-19 on the pharmaceutical sector

The COVID-19 pandemic affected world economics and societies as a whole, and the pharmaceutical sector was no exception. The pharmaceutical sector is struggling to maintain natural market flow, as the recent pandemic affected access to essential medicines at a reasonable price, which is the primary goal of every pharmaceutical system. The short-term impacts of COVID-19 on the health market includes demand change induced by panic-buying of home-medications, especially for chronic disease, which led to shortages caused by supply-chain inconsistencies. Studies reported that induced demand in the pharmaceutical market, mainly due to “panic-buying” of medicines for chronic disorders, was expected to be +8.9% by March 2020 (34).

In addition to the fear of becoming infected, many people prepared themselves for a possible quarantine period when the virus began to spread. Therefore, it is possible that people with chronic diseases stocked up on the medications they need for their diseases. The other possible reason for the increase in medicines stocking might be the fear of drugs shortages as many drugs are produced in countries where the pandemic took hold sooner, such as China and India. These countries are the world's main supplies of active pharmaceutical ingredients (APIs), and because of the disease, they are slowdown in production, which contributed to shortage and price increase in essential prescription medicines, including antibiotics (34).

As a result, people tried to buy their necessary medications in pharmacies while they were available. Finally, there is a possibility that consumers engaged in panic-buying out of a fear that all shops, pharmacies, and private medical practices would close (35).

In light of the initial increased demand for medicines and to prevent stockpiling, national authorities have taken several emergency responses. For example, it has been recommended that users should only buy one package of non-prescription medicines (36). For prescription medicines, guidelines and later national legislation imposed restrictions on the quantities that could be purchased. Medical prescriptions, valid for six months, whose validity period ended after the date of entry of the first state of emergency, were considered automatically renewed for the same period. Medical prescriptions that were valid for six months could not be fully dispensed at once, and pharmacies should only dispense the number of packages necessary for treatment up to two months in order to avoid inequities and ensure that all patients receive the medicines they need (37). Also, in line with recent EU guidelines, pharmacies were permitted to deliver prescription medicines to people's homes. This measure is intended to prevent patients from going to the pharmacy as frequently and be exposed to the coronavirus (36).

A change related to consumption and refilling prescriptions, especially in chronic disease therapeutic areas, might happen and may be further affected by the emerging telemedicine (34). Besides the need to guarantee the supply of critical medical and personal protective equipment to control the disease, there is a general concern regarding the preservation of the continued supply of medicines for the population. Therefore, it is essential to adopt preventive measures to safeguard access to medicines by all citizens, discouraging the acquisition of large quantities of packaging that do not correspond to real needs (38).

Regarding long-term impacts, there are delayed approvals for non-COVID-related pharmaceutical products: all countries are under pressure from the crisis and their priority is COVID-19 management. Coronavirus pandemic resulted in economic slowdown for many countries, and this will possibly lead to pharma industry growth slowdown, which are sensitive to country economic growth (34). One of the long-term effects is the use of poorly evidence COVID-19 treatments. Ethical issues should be considered in the use of these medicines as off-label (39). The long-term clinical benefits of the use of these pharmaceutical strategies in the coming years should be studied, and healthcare providers should make informed decisions on using off-label therapies in their clinical practice (34).

Identifying these impacts may guide policymakers informed to planning and decision-making to combat associated challenges. To avoid long-term complications, short-term impacts should be selected and further be measured with appropriate data analysis and outcomes (34).

1.3 Overall utilisation of medicines in Portugal

Some changes were observed in the use pattern of medicines dispensed in pharmacies due to the COVID-19 pandemic. In Portugal, in March 2020, the pharmacy market showed an atypical behaviour, *i.e.*, a strong growth in units sold compared to the same period in the previous year, clearly related to the pandemic. According to Health Market Research (HMR) reports, there was an increase of more than 35.0% in units sold compared to March 2019, especially in medicines used for chronic conditions, such as diabetes, cardiovascular and central nervous system therapy. An increase was also observed for medicines eventually used for the symptomatic treatment of COVID-19, such as antipyretics, analgesics, and immune system stimulants (40).

Studies showed that in the week of the first confirmed COVID-19 cases, the demand for medicines remained unchanged, as is depicted in figure 5. The highest growth in volume sales was registered just after WHO declared COVID-19 as a global pandemic.

On March 18th, the first emergency state was declared, and 4 days later Portugal entered in lockdown period. In this week, total sales dropped into a normal range (41).

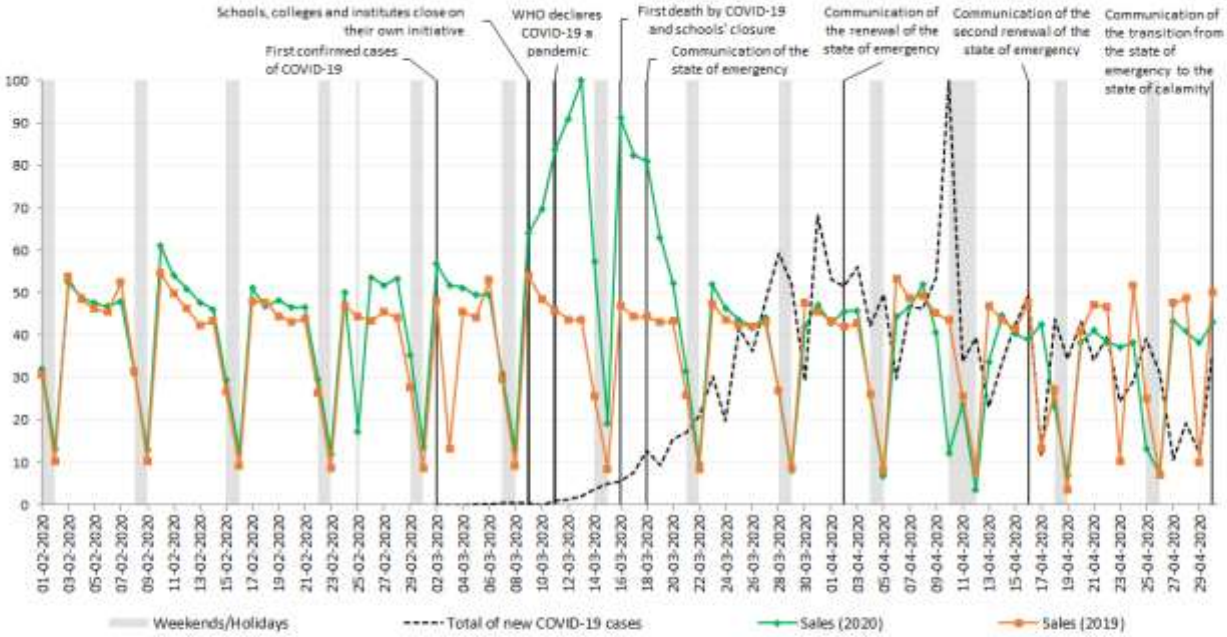

Figure 5: Normalised time series of community pharmacies' medicine sales in 2019 and 2020, new COVID-19 cases and major events regarding COVID-19 in Portugal.

From Romano, S. *et al* (2020).

In April 2020, the market showed an adjustment of the dynamics observed in March, with less 8.9% units sold compared to the same period in 2019, probably due to the patients' over-supply of medicines for chronic pathologies in the previous month (40).

Table 2 shows the therapeutic classes of medicines, with the respective ATC classification system (level 3), more frequently dispensed in 2020, according to HMR (40).

Table 2: Classes of drugs (ATC classification level 3) most sold in Portugal during 2020.

ATC classification (level 3)			Million units	Variation (2020 *vs* 2019)
1	N02B	**Other analgesics and antipyretics**	25.0	+3.47%
2	C10A	**Lipid modifying agents, plain**	13.2	+7.14%
3	N05B	**Anxiolytics**	11.1	+0.22%
4	N06A	**Antidepressants and mood stabilizers**	10.9	+6.54%
5	A02B	**Drugs for peptic ulcer and gastro-oesophageal reflux disease**	8.7	+1.26%

There was a remarkable growth of +3.5% of the class "N02B - Other analgesics and antipyretics", representing 9.6% of the pharmaceutical market volume. The most considerable absolute variation in units compared to 2019 are represented in table 3 (40).

Table 3: Classes of drugs (ATC classification level 3) with largest variation in units sold during 2020 compared to 2019.

ATC classification level 3			Absolute variation Million units	Variation (2020 *vs* 2019)
1	C10A	**Lipid modifying agents, plain**	0.88	+3.47%
2	N02B	**Other analgesics and antipyretics**	0.84	+7.14%
3	N06A	**Antidepressants**	0.67	+0.22%
(…)				
243	J01C	**Beta-lactam antibacterials, penicillins**	-1.04	-26.91%
244	R05C	**Expectorants, excl. combinations with cough suppressants**	-1.07	-34.69%
245	M01A	**Antiinflammatory and antirheumatic products, non-steroids**	-1.36	-14.59%

It is worth noting the sharp decrease in units sold in the class "J01C – Penicillins, beta-lactam antibacterials" *i.e.*, less 26.9% compared to 2019. When analysing the data of units sold by International Nonproprietary Name (INN), a decrease in the use of antibiotics is observed. Table 4 shows the pharmaceutical substances designated by the INN (40).

Table 4: **Pharmaceutical substances with largest variation in units sold during 2020 compared to 2019.**

INN		Absolute variation Million units	Variation (2020 *vs* 2019)
1	**Paracetamol**	0.70	+24.92%
2	**Atorvastatin**	0.59	+11.76%
3	**Quetiapine**	0.27	+16.66%
(…)			
243	**Amoxicillin + Clavulanic acid**	-0.25	-21.12%
244	**Ibuprofen**	-0.41	-17.18%

Paracetamol increased by 0,70 million units (+24.9%) during 2020 compared to 2019, which may be explained by the fact that it is used to treat fever, one of the most common symptoms of COVID-19 (42). The largest absolute changes in units were observed in the INNs for antibiotics azithromycin and amoxicillin + clavulanic acid (40).

1.3.1 The importance of analysing the consumption of antibiotics: Antibiotics resistance

Antibiotics were a landmark in pharmacological development and contributed to the improvement of public health worldwide by increasing the population's longevity (43). However, several studies have shown that the excessive and inadequate use of antibiotics is at the origin of the appearance of bacterial resistance and, consequently, of the therapeutic ineffectiveness of this class of drugs (44,45).

Antibiotic resistance occurs when bacteria change over time and no longer respond to medicines making infections harder to treat (46). From a worldwide perspective, antimicrobial resistance (AMR) has several clinical, economic, and social consequences is the cause of death of at least 150,000 persons a year, increase the difficulty to control infectious diseases, prolonging the illness period and increasing the probability of death, increase the costs of infections treatment and threatens several achievements in medicine and the return to a pre-antibiotic era (4. As a result, it is now considered as one of the top health challenges facing the 21st century, and WHO has declared that AMR is one of the top 10 global public health threats facing humanity (46).

Antibiotics are becoming increasingly ineffective as drug resistance spreads globally, leading to more difficult to treat infections. New antibiotics are urgently needed, but there are insufficient antibiotics in development - in 2019, WHO recognise 32 antibiotics in clinical development that integrate the WHO list of priority pathogens, of which only six were categorised as innovative. However, if people do not change how they use antibiotics, these new therapies will suffer the same destiny as the current ones and become ineffective (46).

Within the European context, Portugal remains one of the countries with high consumption of antibiotics in the community setting and a worrisome proportion of bacterial resistance, despite an evident decrease observed in the last years (47).

1.3.2 Antibiotics: General Concepts

Antibiotics are antimicrobial substances that can inhibit the growth of microorganisms or kill them and are intensely used to prevent and treat bacterial infections in humans and animals (48). Antibiotics are divided into several classes that are often grouped according to their mechanism of action, which can define the type of bacteria on which they will act: gram positive bacteria (gram +), gram negative (gram -) or both types.

Table 5 shows the different classes of antibiotics, their mechanisms of action, and some examples of antibiotics of these classes (49).

Table 5: Antibiotic classes and mechanisms of action

Classes	Mechanism of action	Antibiotic examples
Penicillins	Antibiotics that act on the bacterial wall	Amoxicillin, Ampicillin, Benzylpenicillin, Flucloxacillin, Piperacillin
β-lactamase inhibitors		Clavulanic acid
Cephalosporins		First-Generation: Cefazolin, Cephradine
		Second-Generation: Cefuroxime, Cefoxitin
		Third-Generation: Ceftriaxone, Cefotaxime
		Fourth-Generation: Cefepime
Monobactams		Aztreonam
Carbapenems		Meropenem, Ertapenem
Glycopeptides		Vancomycin
Tetracyclines	Antibiotics that interfere with bacterial ribosomes (30S subunit)	Doxycycline, Chlortetracycline
Aminoglycosides		Gentamycin, Amikacin, Neomycin
Chloramphenicol		Chloramphenicol

Macrolids	Antibiotics that interfere with bacterial ribosomes (50S subunit)	Erythromycin, Azithromycin, Clarithromycin
Lincosamides		Clindamycin
Streptogramins		Quinupristine Dalfopristin
Oxazolidinones	Other antibiotics that interfere with protein synthesis	Linezolid
Sulphonamides	Antibiotics that interfere with bacterial metabolism (Antimetabolites)	Sulfanilamide, Sulfadiazine
Trimethoprim		Trimethoprim
Quinolones	Antibiotics that interfere with nucleic acids	First-Generation: Nalidixic acid
		Second-Generation: Ciprofloxacin, Norfloxacin
		Third-Generation: Levofloxacin, Monifloxacin
		Fourth-Generation: Trovafloxacin
Imidazole derivatives		Metronidazole

2 Objective

The COVID-19 pandemic and related public-health mitigation measures substantially affected the provision of healthcare and services. These measures also potentially affected the transmission of infectious diseases commonly managed with antibiotics. The aim of this study is to evaluate the impact of the COVID-19 pandemic on the patterns of use antibacterials for systemic use in the community, in Portugal.

3 Methods

3.1 Study design and setting

A descriptive study was conducted and antibiotics for systemic use (ATC classification J01) were selected for analysis. An interrupted time series analysis using the autoregressive integrated moving average (ARIMA) model of quality indicators for antibiotic consumption in the community in Portugal was performed from January 1st, 2016, to December 31st, 2020. Antimicrobial utilisation was analysed quantitatively by calculating the defined daily doses (DDDs) per 1000 inhabitants per day. DDDs were obtained from the Anatomic Therapeutic Chemical/defined daily doses (ATC/DDD) Index of the WHO Collaborating Centre for Drugs Statistics.

3.2 Description of variables and data sources

3.2.1 Metrics to measure exposure to a medicine: ATC/DDD System

The ATC/DDD system is a comprehensive and logical classification system that was developed to categorise drug substances, which were divided into different groups according to the organ or system on which they act (anatomic), and then according to their specifications (50).

In this classification, the active substances are organised in a hierarchy with five different levels. The system has fourteen main anatomical/pharmacological groups or 1st levels. Each ATC main group is divided into 2nd levels, which could be either pharmacological or therapeutic groups. The 3rd and 4th levels are chemical, pharmacological, or therapeutic subgroups, and the 5th level is the chemical substance (50). Table 6 shows the groups of antibiotics according to the ATC classification.

Table 6: Classification of antibiotics by the ATC system

1st level	J	ANTIINFECTIVES FOR SYSTEMIC USE
2nd level	J01	ANTIBACTERIALS FOR SYSTEMIC USE
3rd level	J01A	TETRACYCLINES
	J01B	AMPHENICOLS
	J01C	BETA-LACTAM ANTIBACTERIALS, PENICILLINS
	J01D	OTHER BETA-LACTAM ANTIBACTERIALS
	J01E	SULFONAMIDES AND TRIMETHOPRIM
	J01F	MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS
	J01G	AMINOGLYCOSIDE ANTIBACTERIALS
	J01M	QUINOLONE ANTIBACTERIALS
	J01R	COMBINATIONS OF ANTIBACTERIALS
	J01X	OTHER ANTIBACTERIALS

Defined daily dose (DDD) is a technical unit of measurement based on the average dosage for the main indication in adults with normal organ function, with 70kg of weight, and related to the population analysed (51).

This metric is particularly useful when it is intended to compare consumption between countries or regions since it is independent of the way of dispensing medicines (*e.g.* through packaging or unidose), making it possible to standardise the measure for the comparison of consumption by DDD (50,52).

However, the DDD metric reports total consumption and is sensitive to the number of inhabitants. Consequently, if it is intended to compare two countries/regions with different population densities, the adjustment should be made using the calculation of the DDD per 1000 inhabitants per day (DID), according to the following (52):

$$DID = \frac{Total\ of\ DDDs\ consumed}{Population\ x\ 365\ days} x1000$$

Legend: DDD - Defined daily doses; DID - DDD per 10000 inhabitants per day

This way, it is possible to compare drug consumption between countries, and even between different regions, of the same country, with different population densities.

3.2.2 Variables: Quality indicators for antibiotic consumption in the community

Quality indicators for antibiotic prescribing have been validated and implemented by researchers worldwide, aiming to evaluate the prescription and consumption of antibiotics. Coenen *et al*. validated drug-specific quality indicators for outpatient antibiotic use in Europe derived from European Surveillance of Antimicrobial Consumption (ESAC) data (53).

The quality indicators for antibiotic consumption in the community, according to European Centre for Disease Prevention and Control (ECDC) methodology used in this study, expressed in DDD per 1000 inhabitants per day, are described in table 7 (54).

Table 7: **Quality indicators of antibiotic consumption defined by ESAC**

Quality Indicator		Description
J01_DID	Absolute consumption of antibiotics	Consumption of antibacterials for systemic use (J01) expressed in DID
J01C_DID	Absolute consumption of penicillins	Consumption of penicillins (J01C) expressed in DID
J01D_DID	Absolute consumption of cephalosporins	Consumption of cephalosporins (J01D) expressed in DID
J01F_DID	Absolute consumption of macrolides, lincosamides and streptogramins	Consumption of macrolides, lincosamides and streptogramins (J01F) expressed in DID
J01M_DID	Absolute consumption of quinolones	Consumption of quinolones (J01M) expressed in DID
J01CE_%	Relative consumption of penicillins sensitive to β-lactamases (%)	Consumption of beta-lactamase sensitive penicillins (J01CE) expressed as percentage of the total consumption of antibacterials for systemic use (J01)
J01CR_%	Relative consumption of combinations of penicillins with β-lactamases inhibitor (%)	Consumption of combination of penicillins, including beta-lactamase inhibitor (J01CR) expressed as percentage of the total consumption of antibacterials for systemic use (J01)
J01DD+DE_%	Relative consumption of 3^{rd} and 4^{th} generation cephalosporins (%)	Consumption of third- and fourth-generation cephalosporins (J01(DD+DE)) expressed as percentage of the total consumption of antibacterials for systemic use (J01)
J01MA_%	Relative consumption of fluoroquinolones (%)	Consumption of fluoroquinolones (J01MA) expressed as percentage of the total consumption of antibacterials for systemic use (J01) road/narrow
J01_B/N	Ratio of consumption of broad and narrow spectrum antibiotics	Ratio of the consumption of broad-spectrum (J01(CR+DC+DD+(F-FA01))) to the consumption of narrow-spectrum penicillins, cephalosporins and macrolides (J01(CE+DB+FA01))

Legend: DDD - Defined Daily Dose; DID - DDD per 1000 inhabitants and per day

This set of indicators were considered as being the most relevant to evaluate outpatient antibiotic use and were chosen because they are periodically published by ESAC and Portugal's national authorities, allowing the interpretation at a national and international level.

3.2.3 Data Sources

National antibiotics consumption were obtained through the HMR Information System, analysed by CEFAR (Centre for Health Evaluation and Research), which is a national database that provides representative national and regional estimates of drug dispensing data for all medicines (prescription and non-prescription), from 84% of all Portuguese community pharmacies (~2460 of 2920 pharmacies) (55).

Annual data on the size of the Portuguese population was obtained from the Portuguese Institute of National Statistics.

3.2.4 Data Analysis: Interrupted time series analysis using autoregressive integrated moving average (ARIMA) model

The interrupted time series (ITS) study design has been increasingly used to evaluate public-health interventions; it is particularly employed to analyse the effect of interventions implemented at a population level over a clearly defined time period (56). It also visually displays the dynamics of a population's response to an intervention by showing whether an effect is immediate or delayed, abrupt or gradual, and whether or not an effect persists or is solely temporary (57).

Interrupted time series analysis using autoregressive integrated moving average (ARIMA) model is a statistical method that allows an evaluation of how much an intervention changes an outcome of interest, immediately and in the long-term, allowing to generate hypothesis about the impact of that intervention. This approach is adequate even in a scenario where underlying trends, seasonality, or autocorrelation are present and allows flexible modelling of different impacts (58).

In time series of health data such as antibiotic consumption, the seasonality is present, which is due to natural causes (*i.e.*, weather patterns). In ARIMA modelling, the seasonality is usually dealt with by taking the seasonal difference (58).

In this analysis, the outcome measures for the time series are the quality indicators for antibiotic consumption in the community, before and after the month period when the WHO announced COVID-19 as a pandemic and when the first COVID-19 cases were reported in Portugal, *i.e.*, – March 2020. The interrupted time-series analysis used one timepoint: March 2020. Two time-periods were therefore considered: 50 months before March 2020 (January 1^{st}, 2016, to February 29^{th}, 2020) and 9 months afterwards (April 1^{st}, 2020, to December 31^{st}, 2020).

The temporal trends of the study outcomes were visualised using graphs of the change of quality indicators for antibiotic consumption in the community from January 1^{st}, 2016, to December 31^{st}, 2020.

4 Results

To assess the short-term and long-term impact of the COVID-19 pandemic on antibiotics use, the quality indicators for antibiotic consumption in the community were analysed, from January 2016 to December 2020, having as a point of intervention the month of March 2020, *i.e.*, when the first infections by SARS-CoV-2 were reported in Portugal and when the WHO announced COVID-19 as a worldwide pandemic.

As shown in figure 6, from 2016 to 2019, the consumption on antibacterials for systemic use (J01), the most generalised indicator for antibiotics, was broadly consistent over the years and similar seasonal patterns were observed. In January 2020, there was an ascending peak in antibiotic consumption, typical to previous years due to seasonality, followed by a usual decline in February. However, in March, April and May 2020, antibiotic consumption continued to decline sharply, contrary to what occurred in previous years; Thereafter, the consumption seems to return to the 2016–2019 rates, but still below the values recorded in recent years.

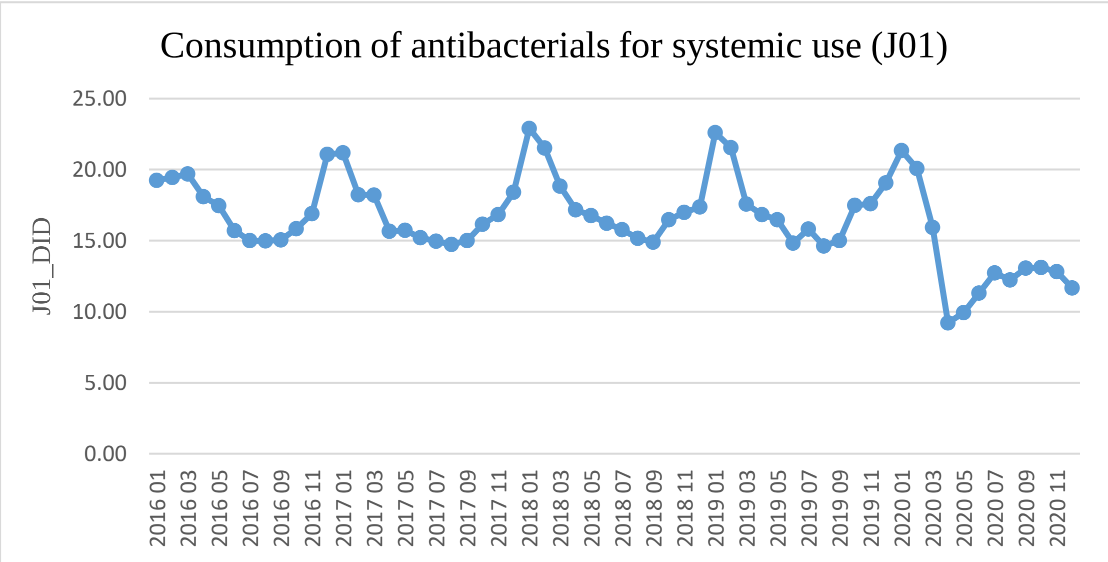

Figure 6: Consumption of antibacterials for systemic use (J01) (DID), 2016-2020.

Over the study period, the same pattern was observed for penicillins (J01C) (figure 7), cephalosporins (J01D) (figure 8), macrolides, lincosamides and streptogramins (J01F) (figure 9) consumption.

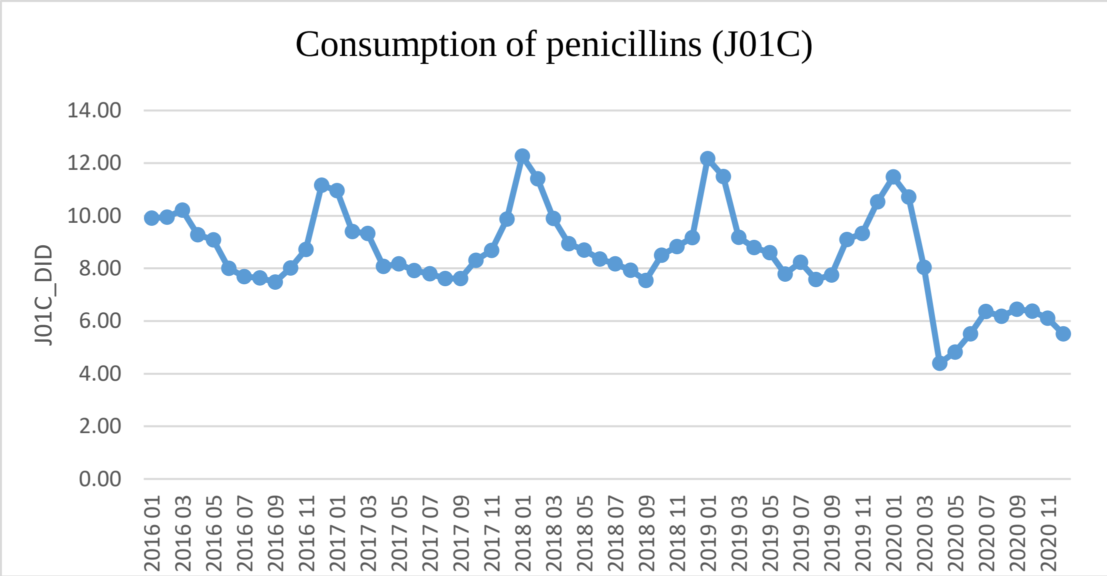

Figure 7: Consumption of penicillins (J01C) (DID), 2016-2020.

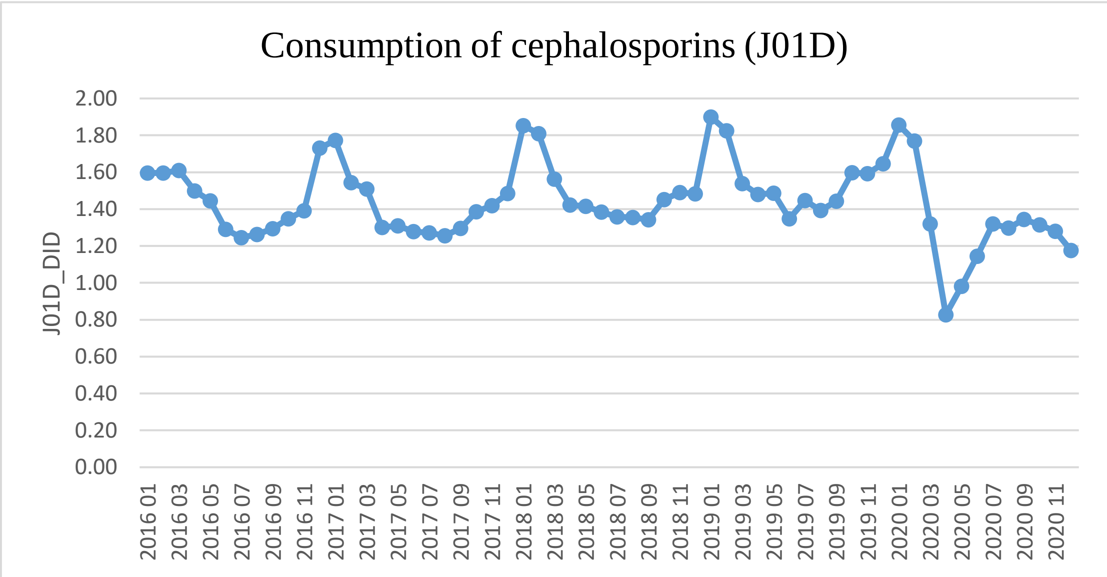

Figure 8: Consumption of cephalosporins (J01D) (DID), 2016-2020.

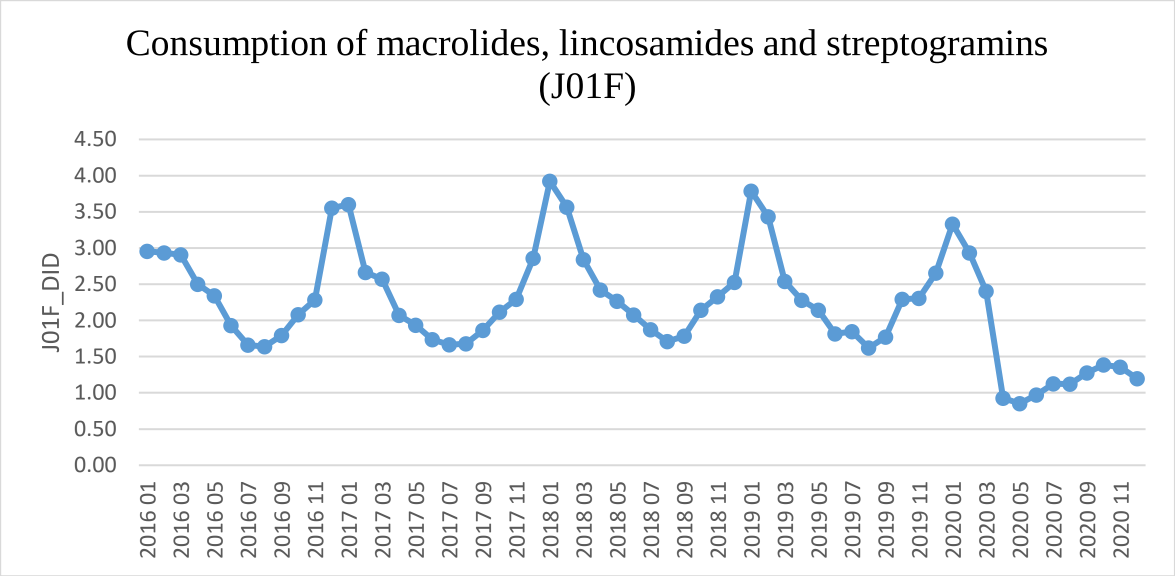

Figure 9: Consumption of macrolides, lincosamides and streptogramins (J01F) (DID), 2016-2020.

As depicted in Figure 10, a downward trend concerning quinolones consumption was observed since the beginning of the study period. A steep decline in quinolones consumption was registered in March 2020 (figure 10).

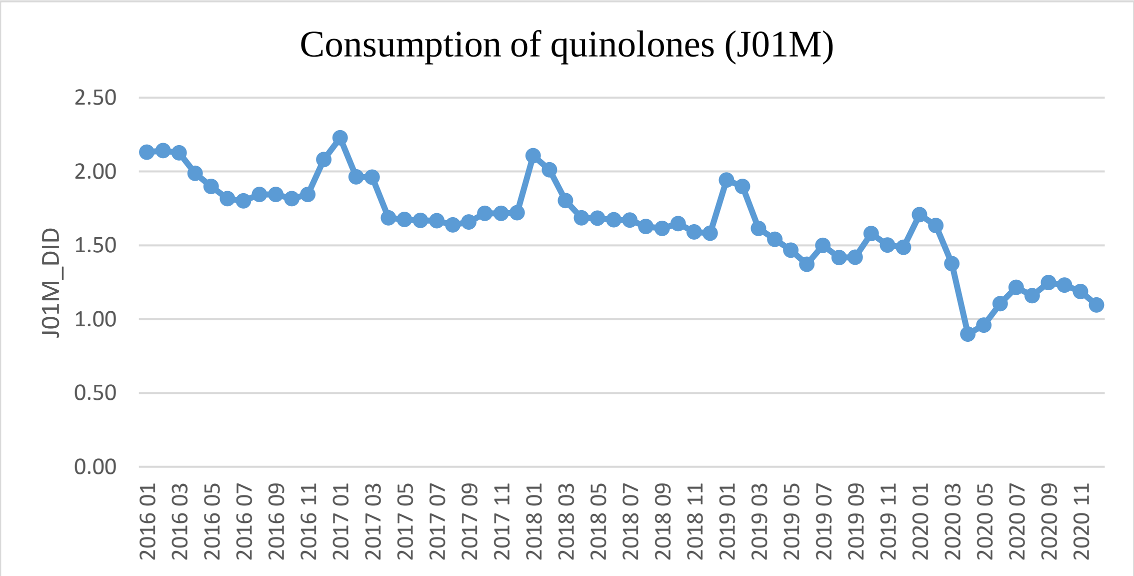

Figure 10: Consumption of quinolones (J01M) (DID), 2016-2020.

In relation to the relative consumption of penicillins sensitive to β-lactamases (J01CE_%), it's noticeable that from May 2020 to September 2020 there was no increase in penicillins sensitive to β-lactamases expressed as a percentage of the total consumption of antibacterials for systemic use, that generally occurred in previous years (figure 11).

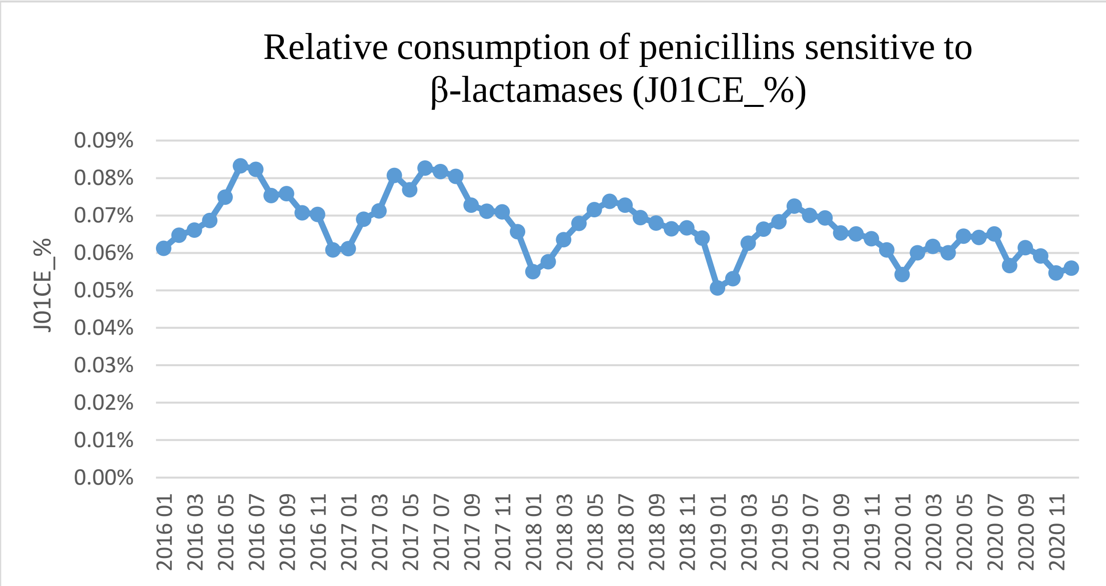

Figure 11: Consumption of beta-lactamase sensitive penicillins (J01CE) expressed as percentage of the total consumption of antibacterials for systemic use (J01), 2016-2020.

In relation to the other relative quality indicators [J01CR, J01(DD+DE)), J01MA] expressed as a percentage of the total consumption of antibacterials for systemic use, there were no considerable variations after March 2020 compared to previous years (figure 12,13,14, respectively).

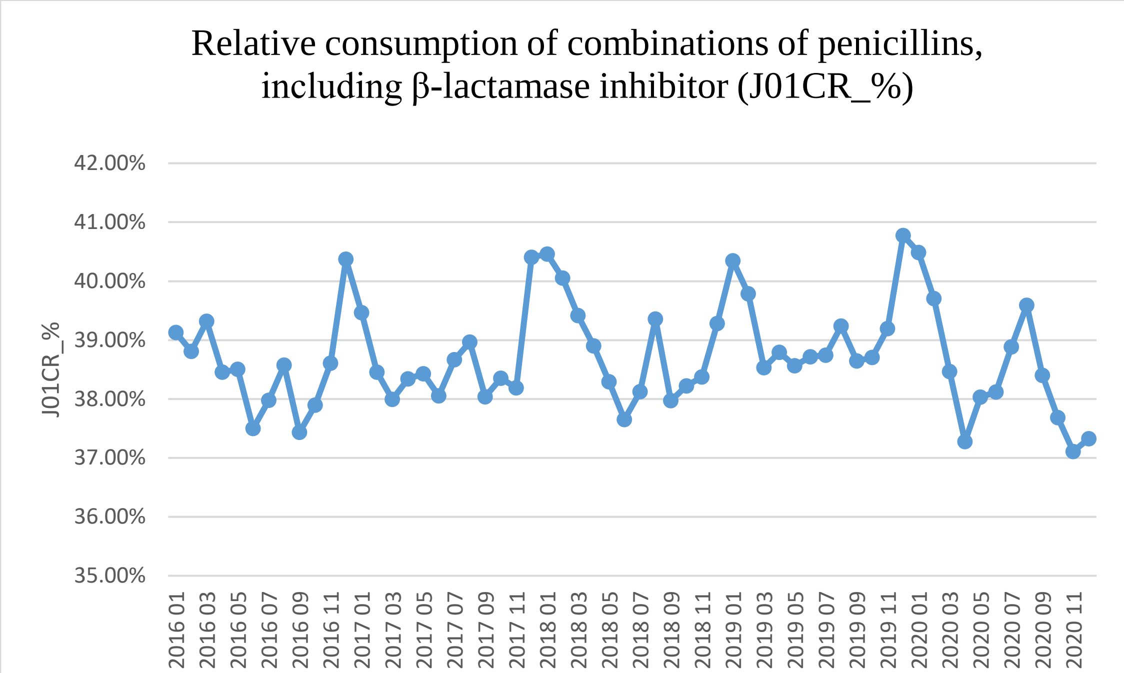

Figure 12: Consumption of combination of penicillins, including β-lactamase inhibitor (J01CR) expressed as percentage of the total consumption of antibacterials for systemic use (J01), 2016-2020.

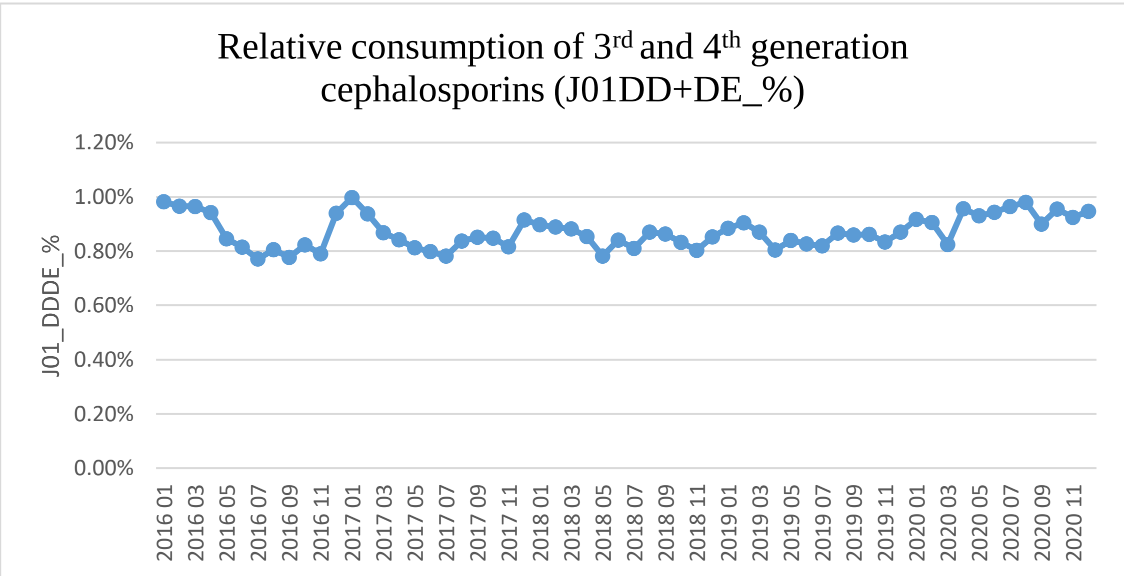

Figure 13: Consumption of third- and fourth-generation cephalosporins [J01(DD+DE)] expressed as percentage of the total consumption of antibacterials for systemic use (J01), 2016-2020.

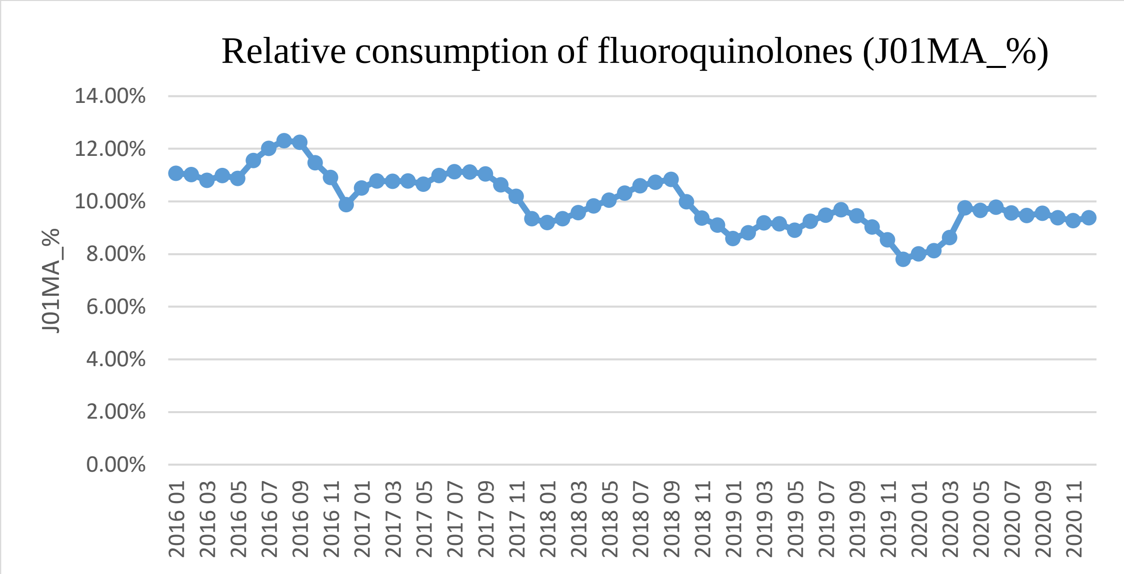

Figure 14: Consumption of fluoroquinolones (J01MA) expressed as percentage of the total consumption of antibacterials for systemic use (J01), 2016-2020.

The ratio of the consumption of broad-spectrum [J01(CR+DC+DD+(F-FA01))] to the consumption of narrow-spectrum penicillins, cephalosporins and macrolides [J01(CE+DB+FA01)] has increased over the years, reaching the highest peak in March 2020. This ratio has been decreasing since then, reaching in May 2020 values similar to September 2019.

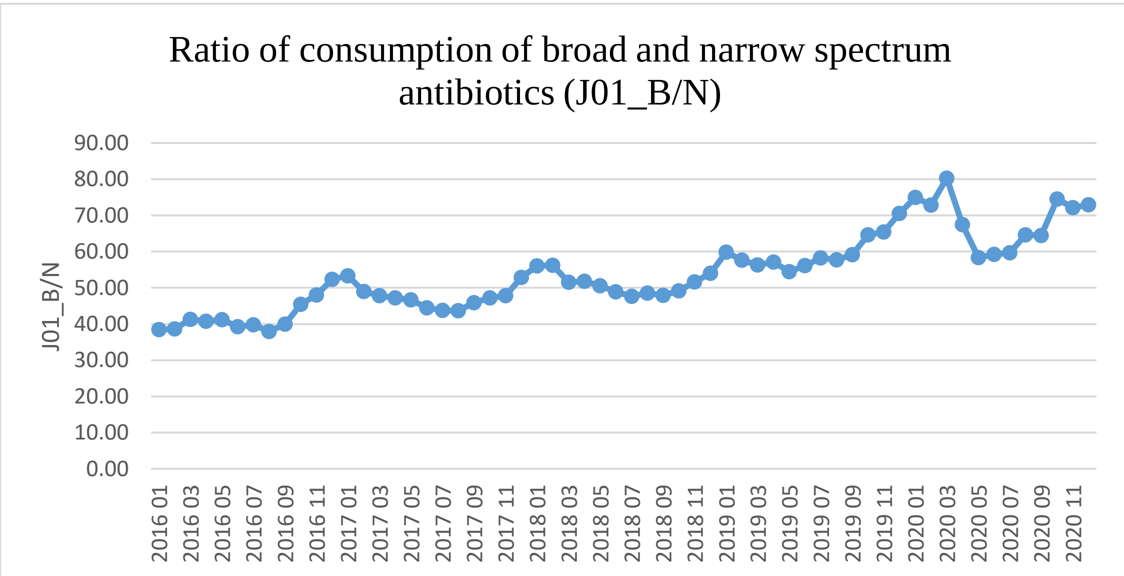

Figure 15: Ratio of the consumption of broad-spectrum [J01(CR+DC+DD+(F-FA01))] to the consumption of narrow-spectrum penicillins, cephalosporins and macrolides [J01(CE+DB+FA01)], 2016-2020.

To assess the impact of the COVID-19 pandemic on antibiotic consumption, an interrupted time series analysis using an autoregressive integrated moving average (ARIMA) model was performed, where variables such as the seasonality observed in antibiotic consumption were eliminated (Table 8).

Table 8: Short-term and long-term effects of the COVID-19 pandemic on quality indicators for antibiotic consumption in the community

Quality Indicator	Parameter	Estimate Effect per month	ρ
J01_DID	Short-term	-2.975	0.0086
	Long-term	-0.278	0.1868
J01C_DID	Short-term	-1.554	0.0247
	Long-term	-0.246	0.0577
J01D_DID	Short-term	-0.264	0.0067
	Long-term	-0.007	0.7120
J01F_DID	Short-term	-0.391	0.1533
	Long-term	-0.091	0.0659
J01M_DID	Short-term	-0.071	0.5536
	Long-term	-0.034	0.1371
J01CE_%	Short-term	-0.006%	0.1118
	Long-term	-4.43×10^{-5} %	0.9510
J01CR_%	Short-term	0,768%	0.0414
	Long-term	-0.343%	<0.0001
J01DD+DE_%	Short-term	0.05624%	0.0752
	Long-term	0.005%	0.3557
J01MA_%	Short-term	0.273%	0.3771
	Long-term	0.160%	0.0199
J01_B/N	Short-term	9.581	0.0033
	Long-term	-1.742	0.0466

In the quality indicator “Antibacterials for systemic use” (J01), there was a significant decrease, after March 2020, only in the short-term, of almost 3 DIDs per month (ρ = 0.0086). In the long-term it had a decrease of 0.28 DIDs, compared to the trend it was having before, but not significantly (ρ = 0.1868).

The consumption of penicillins (J01C) had a significant short-term effect (ρ = 0.0247), with a reduction of 1.554 DIDs per month compared to the previous trend. Although not significant (ρ = 0.0577), in the long-term it decreased 0.246 DIDs. This quality indicator had the highest consumption compared to indicators of other classes of antibiotics and followed the trend of J01: there was a sharp decrease in the short-term, but in the long-term there is no significant variation.

The consumption of cephalosporins (J01D) shows a significant reduction in the short-term of 0.26 DID per month (ρ = 0.0067). It also had a non-significant long-term reduction (ρ = 0.7120).

The consumption of macrolides, lincosamides and streptogramins (J01F) does not show a significant reduction after March 2020, both in the short-term and long-term.

The consumption of quinolones (J01M) decreased over the years and was even more pronounced from March 2020 onwards, however no statistically significant in the short- and long-term reduction.

The relative consumption of penicillins sensitive to β-lactamases (J01CE_%) has decreased over the study period and continues to decrease at the same rate. None of the parameters was significant.

The relative consumption of combinations of penicillins with β-lactamases inhibitors (J01CR_%) had significantly (ρ = 0.0414) increased 0.768% in the short-term, and in the long-term had significantly (ρ = <0.0001) decreased -0.343%.

The relative consumption of 3rd and 4th generation cephalosporins (J01DD+DE_%) did not show a significant variation in both parameters after March 2020.

The relative consumption of fluoroquinolones (J01MA_%) had a significant increase (ρ = 0.0199) of 0.160% in the long-term trend. On the other hand, no significant changes were observed in the short-term.

The ratio of consumption of broad- and narrow-spectrum antibiotics (J01_B/N) had a significant short-term ($\rho = 0.0033$) and long-term ($\rho = 0.0466$) effect. The ratio rose 9.6 with immediate effect but reduced 1.7 per month thereafter.

5 Discussion

The present study provides insights into the consumption of antibiotics and respective prescription quality indicators from the start of the COVID-19 pandemic in Portugal to December 2020.

In Portugal, in March 2020 (*i.e.*, when the first infections by SARS-CoV-2 were reported and when the WHO announced COVID-19 as a worldwide pandemic) there was an increase of more than 35.0% in units dispensed when compared to March 2019, especially in medicines used for chronic conditions and medicines eventually used for the symptomatic treatment of COVID-19, such as antipyretics, analgesics, and immune system stimulants. In April 2020, there were less 8.9% units of medicines sold compared to the same period in 2019, probably due to the patients' over-supply of medicines for chronic pathologies in the previous month, induced by panic buying. Overall, in 2020, there were 2.3% fewer units of medication dispensed when compared to 2019.

Contrary to what was observed with medicines utilisation in general, the outpatient consumption of antibiotics showed different behaviour. In fact, the consumption of antibiotics (J01) declined sharply in the first three months of the pandemic in Portugal. After this period, the consumption of outpatient antibiotics showed similar seasonal patterns when compared to the period 2016-19, however lower consumption rates were observed. It was also observed that the quality indicator "Antibacterials for systemic use (J01)" had only significantly reduced in the short-term but not in the long-term. Therefore, more evidence and data are needed to assess the long-term impact of the COVID-19 pandemic on outpatient antibiotic consumption.

On March 18th, 2020, it was declared the first state of emergency and adopted interventive public-health measures such as social distancing and lockdown to reduce the transmission of the virus. The use of face masks in closed spaces became mandatory on April 30th, 2020, and later, on October 28th, 2020, also in outdoor spaces.

It is acknowledged that the COVID-19 pandemic measures might also potentially affected the transmission of other infectious diseases commonly treated with antibiotics. Lockdown, social distancing, and compliance with respiratory etiquette proved to be good allies in slowing down the transmission of respiratory infections such as Influenza, as well as bacterial infections. The significant reduction in the prescription of antibiotics (penicillins and others) observed in 2020 seems to reflect hygiene and public health measures implemented in March 2020.

These interventive public health measures substantially reduced influenza activity at the latter end of the 2019-2020 northern hemisphere influenza season, an effect evident during the southern hemisphere 2020 winter season (59).

A study performed in Singapore (60) showed that estimated daily number of influenza cases decreased by 76% in epidemiologic weeks 5–9 of 2020 compared with the preceding years. In addition, the average number of visits per day to government primary care clinics for influenza-like illnesses also decreased substantially.

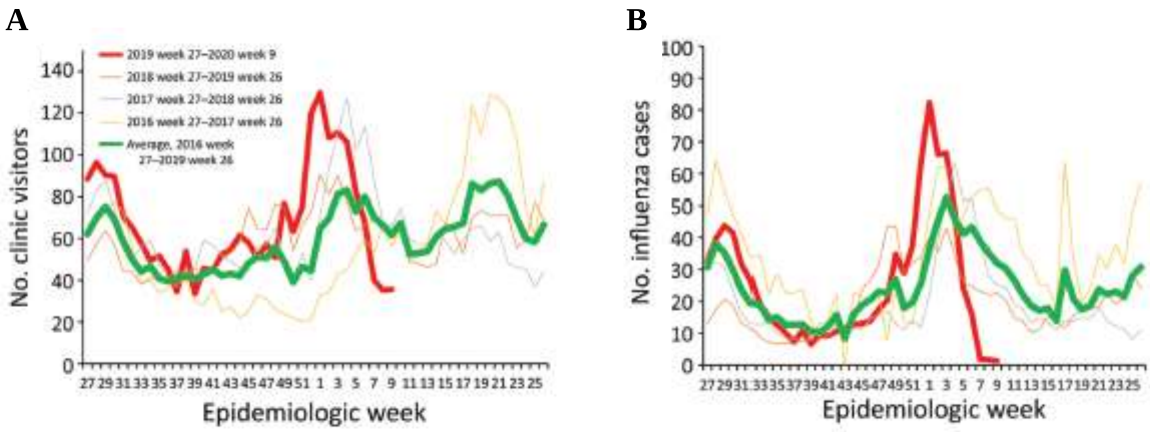

Figure 16: A) Average number of visits per day to government primary care clinics for influenza-like illnesses, 2016–2020. B) Estimated daily numbers of influenza cases, 2016–2020.

From Soo RJJ, Chiew CJ, Ma S, Pung R, Lee V, Lee VJ. Decreased influenza incidence under COVID-19 control measures, Singapore. Emerg Infect Dis. 2020;26(8):1933–5.

Another study performed in China (61) revealed that the number of reported influenza cases showed a decreasing trend from the beginning of 2020, while there were two growth waves in 2019 during the same period. However, we must consider that the observed reduction in influenza infections might be due to other factors, such as a diagnostic resources diversion from influenza to COVID-19 testing or fewer visits to primary healthcare centres due to COVID-19 public health restrictions (59).

Reports from National Institute of Health Doctor Ricardo Jorge (62) show that in Portugal, from March 2020 (week 10 of 2020) onwards, there were also significantly fewer cases of flu in Portugal compared to the same period in 2019.

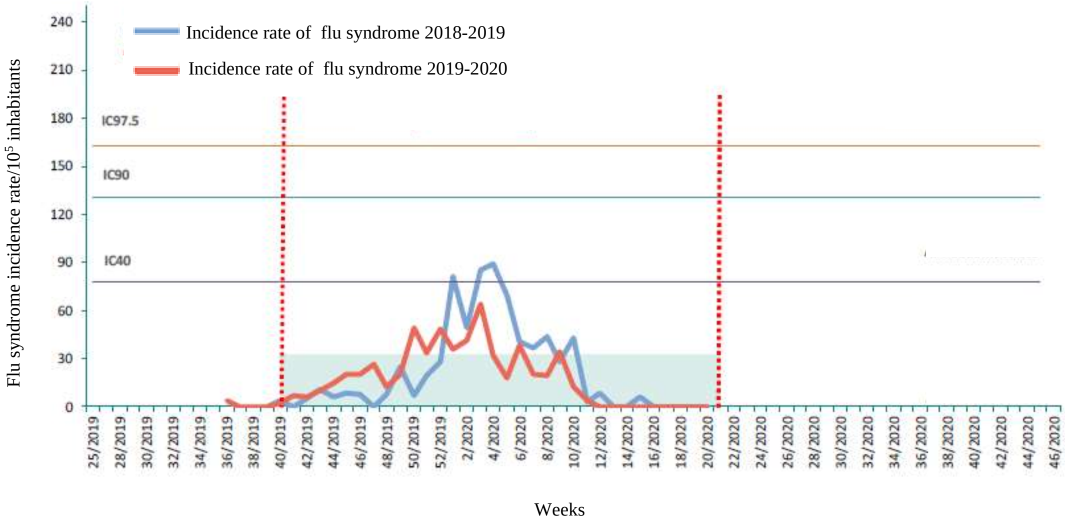

Figure 17: Evolution of the weekly incidence rate of flu syndrome in Portugal, 2018-2019 and 2019-2020.

Adapted from Instituto Nacional Ricardo Jorge. *Boletim de Vigilância Epidemiológica da Gripe*, 2020.

Antibiotics are sometimes wrongly prescribed to treat respiratory infections derived from the influenza virus (63). Against this background, we believe that the decrease in the number of influenza cases might be one of the potential reasons for the decrease in antibiotic consumption.

In Portugal, the change in the provision of health care was remarkable, with a 73% reduction in face-to-face consultations in the first period of lockdown measures (April 2020). On the other hand, the number of remote consultations has increased considerably since March 2020. Considering the total of medical consultations realised, in the first semester of 2020, the total number of consultations was lower than 2019, having reached a peak in April (-19%). From April onwards, the total number of consultations had progressively increased until June, where it registered a higher frequency than 2019, possibly to counterbalance for consultations that were not carried out in the first period of national lockdown. As a result of the decrease of face-to-face consultations, the reduction of prescription of medicines, such as antibiotics, was a reality. Even with the increase of remote consultations, it is acknowledged that telemedicine requires virtual examinations and sometimes, some diagnoses can be difficult to perform virtually (64). Possibly, more broad-spectrum than narrow-spectrum antibiotics may have been prescribed due to the increased difficulty in diagnosis.

Some studies have been published in the last year with an analysis of outpatient antibiotic consumption in various regions of the world before and after the onset of the pandemic.

In a study carried out in India (65), a significant increase in antibiotic sales, particularly azithromycin, was observed during the peak phase of the first COVID-19 epidemic wave. Azithromycin was repurposed for the treatment of COVID-19 based on its hypothetical anti-inflammatory and immunomodulatory properties (65). Although there is no robust evidence of the efficacy of azithromycin against SARS-CoV-2, a significant increase in the use of the antibiotic occurred (66).

As depicted in figure 18, antibiotic, including azithromycin sales, declined during the lockdown phase, i.e., between April and May 2020. However, a trend monthly increase was observed afterwards in all antibiotics, including azithromycin, from June to September 2020. After the epidemic peak in September 2020, a declining trend in sales was observed from October to December 2020, but it was significant, only for azithromycin (65).

The excess antibiotic sales observed between June and September 2020 likely resulted from the sudden flow in the number of patients seeking medical care for possible or confirmed COVID-19 both at community and hospital levels, as suggested by the abrupt increase in the use of azithromycin, which was often prescribed for this condition (65).

However, the data from this study concern the consumption of azithromycin in the community and the hospital, so we cannot thoroughly compare this data with our study that only have data on antibiotic consumption in the community. In fact, in our study, the consumption of macrolides (*e.g.*, azithromycin), lincosamides and streptogramins (J01F) does not show an abrupt increase after the lockdown period (figure 9).

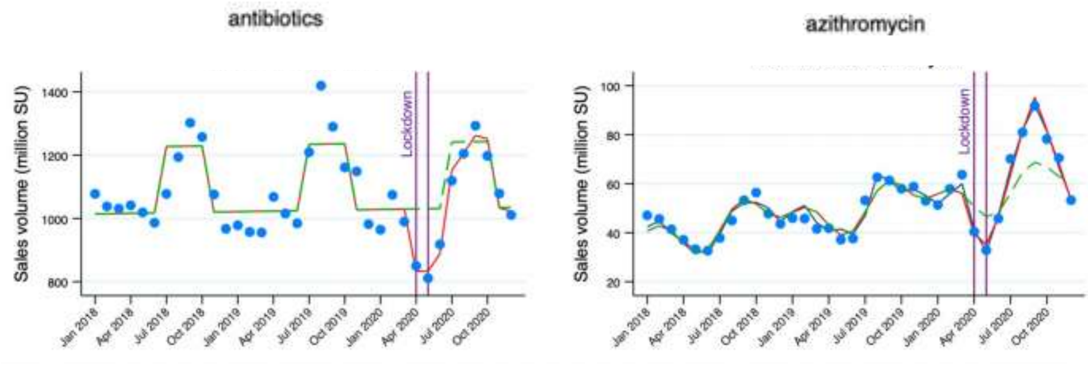

Figure 18: Segmented regression analysis for monthly sales volumes of total antibiotics and azithromycin in India, from January 2018 to December 2020 (65).

From Sulis G, Batomen B, Kotwani A, Pai M, Gandra S. Sales of antibiotics and hydroxychloroquine in India during the COVID-19 epidemic : An interrupted time series analysis. 2021;(March 2020):1–18.

According to another study carried out in the United States of America (67), from January to May 2020, the number of outpatients dispensed antibiotic prescriptions also decreased substantially more than seasonally expected, likely related to the COVID-19 pandemic. The number of patients dispensed antibiotic prescriptions decreased from 20.3 million to 9.9 million, 6.6 million fewer than seasonally expected, representing an additional decrease of 33% beyond the expected seasonal decline (January to May 2020 compared with January to May 2017-2019 average). This decrease was highest among children and substances frequently prescribed for respiratory infections, dentistry, and surgical prophylaxis (67).

The highest decrease was observed among the penicillin, macrolide, and cephalosporin classes. Amoxicillin accounted for 34% of the total beyond the seasonally expected decrease in patients dispensed antibiotic prescriptions, while azithromycin accounted for 21% of the total beyond the expected decrease. The largest additional percentage changes in patients dispensed antibiotic prescriptions were amoxicillin (-43%). While, overall, the number of patients dispensed azithromycin prescriptions decreased from January 2020 to May 2020, the number of patients dispensed azithromycin prescriptions increased by 5% from February 2020 to March 2020, followed by a 71% decrease from March 2020 to May 2020, as shown in figure 19 (67).

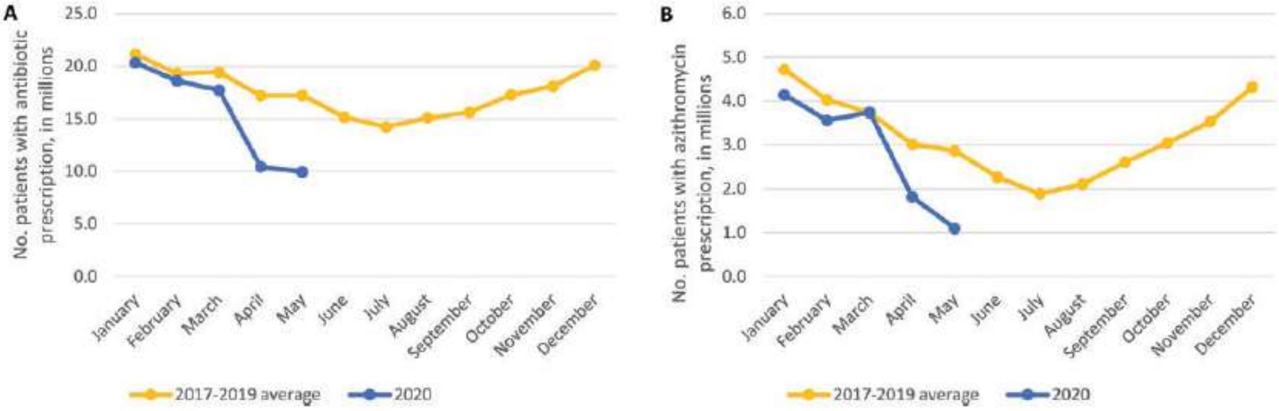

Figure 19: Estimated number of unique patients with prescriptions dispensed from retail pharmacies, by month for (A) all antibiotics and (B) azithromycin, 2017–2019 versus 2020, United States (67).

From King LM, Lovegrove MC, Shehab N, Tsay S, Budnitz DS, Geller AI, et al. Trends in US Outpatient Antibiotic Prescriptions During the Coronavirus Disease 2019 Pandemic. Clin Infect Dis. 2020;2:1–9.

Our study showed similar outpatient antibiotic use patterns as the study conducted in the USA by King *et al.*, where a decrease in the overall consumption of antibiotics, especially in penicillins and cephalosporins, was observed during the lockdown period.

Another research conducted in Australia (68) showed consistent results with our study (figure 20). It was also observed that reductions in antibiotics were not similar across therapeutic classes. Amoxicillin, which was the antibiotic most frequently prescribed, represented the largest reduction, with a 59% decrease at week 32 (August 5th, 2020).

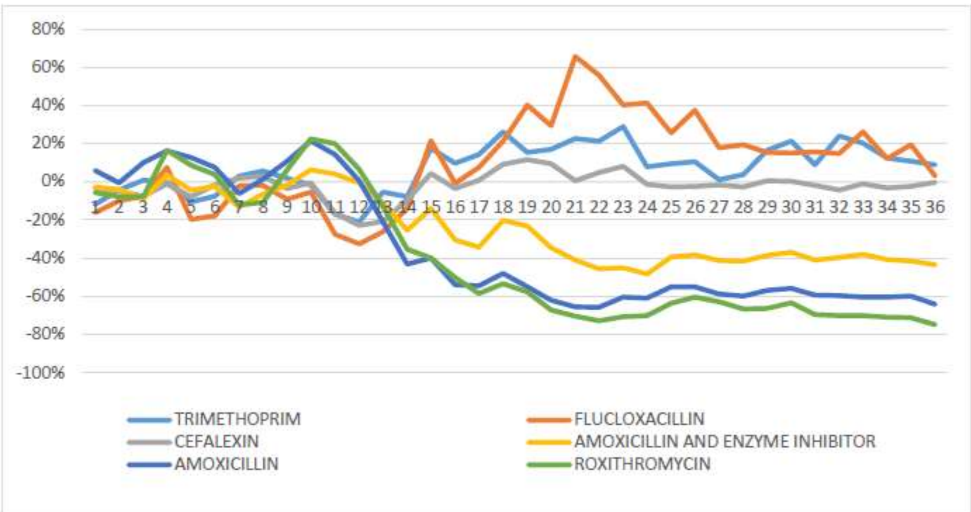

Figure 20: Estimated number of specific Antimicrobials prescribing by week, in Australia, 2020 (week 1 starts on January 1st) (68).

From Pearce C, McLeoad A, Gardner K, Supple J, Epstein D, Buttery J. Primary Care and SARS-CoV-2 : The first 40 weeks of the pandemic year. 2020;

Other antibiotics, such as flucloxacillin and trimethoprim, had increased in prescription rates, as shown in figure 20.

In this study, amoxicillin and enzyme inhibitor showed a pronounced decrease, which is in line with our study, where the consumption of penicillins (J01C) significantly decreased on average -1.554 DID per month. During the pandemic, no change in consumption patterns of cefalexin, a first-generation cephalosporin, was observed, except for a small reduction observed between weeks 10 and 12. Our study also showed a small reduction in the consumption of cephalosporins (J01D) in the short-term (0.26 DID).

The Australian study refers that the possible explanations are related to the therapeutic indication for these antibiotics. Amoxicillin and amoxicillin/clavulanic acid is primarily used in respiratory diseases. They are also widely used for viral upper respiratory tract infections (URTIs), ear infections and bronchitis, despite most clinical guidelines suggesting antimicrobials are only indicated for these conditions in limited circumstances.

It is possible that measures to contain the pandemic, such as the use of face mask and hand sanitisers, and reduction of personal contacts had decreased the contagion of respiratory infections, as mentioned above.

ESAC publishes periodic reports and online databases of the quality indicators for antibiotic consumption in the community in Europe. As shown in table 9 (54), Portugal remains one of the countries with higher rates of antibiotic use in the community, despite the decrease observed in the last years.

Our study results highlighted that the COVID-19 pandemic might have a significant impact only in the short-term for the general antibiotics quality indicator, J01, with a decrease of almost 3 DIDs per month (table 8).

Table 9: Quality indicators for antibiotic consumption in the community in Portugal and Europe: Data from 2011, 2015, 2019.

Quality Indicator	Portugal			Europe (Average)		
	2011	2015	2019	2011	2015	2019
J01	19.2	17.3	17.9	18.1	18.0	17.2
J01C	8.4	8.28	9.07	7.39	7.39	7.27
J01D	1.65	1,56	1.64	2.17	2.17	2.13
J01F	3.39	3.06	3.12	3.13	3.07	2.77
J01M	2.69	2.05	1.54	1.70	1.72	1.37
J01CE_%	0.20%	<0.10%	<0.10%	6.70%	5.97%	6.33%
J01CR_%	32.2%	35.7%	37,4%	17.6%	18.6%	19.2%
J01DD+DE_%	1.70%	1.10%	0.90%	2.50%	2.37%	2.67%
J01MA_%	14.0%	11.8%	8.60%	9.07%	9.24%	7.42%
J01_B/N	25.1	33.3	67,24	23.8	41.4	55.4

Regarding penicillins (J01C), Portugal is still consuming above the European average (table 9). Since the beginning of the pandemic, this quality indicator follows the trend of J01: there was a sharp decrease in the short-term (-1.554 DID per month) but in the long-term there was no significant variation (table 8). Penicillins are the most widely used class of antibiotics, so reducing their consumption demonstrates an improvement in the prescription quality (69).

In the case of cephalosporins (J01D) there was less consumption in Portugal in 2015 compared to 2011, but in 2019 there were again similar values to 2011 (table 9). Despite this increase, Portugal continues to have better consumption rates than Europe in general. The pandemic had a significant short-term impact on this quality indicator, of less 0.26 DID per month, but in the long-term it has no significant impact (table 8).

In the case of macrolides, lincosamides and streptogramins (J01F), Portugal improved consumption rates and in 2019 lower consumption was observed than in 2011 but remained above the European average (table 9). The pandemic had no impact on both short-term and long-term consumption (table 8).

In the case of quinolones (J01M), Portugal improved consumption rates over the years but continues to have worse results than the average of the European countries (table 9). In most situations, quinolones are not first-line therapy and are poorly prescribed. The pandemic did not significantly improve this indicator, in the short-term or long-term (table 8). The consumption decreased but has been decreasing over the years.

Regarding the relative quality indicators, Portugal reported lower rates of consumption of narrow-spectrum penicillins (J01CE_%) and, conversely, high consumption rates of broad-spectrum penicillins (J01CR_%) (table 9). A critical aspect to consider when evaluating the quality of antibiotic use is the relative use of broad- and narrow-spectrum penicillins in ambulatory care. The continuously increasing difference between the Portuguese and European average observed for broad-spectrum penicillins consumption is quite alarming. With the pandemic, the relative consumption of penicillins sensitive to β-lactamases (J01CE_%) has been decreasing over the years and continues to decrease at the same rate. None of the parameters were significant. The relative consumption of combinations of penicillins with β-lactamases inhibitors (J01CR_%) significantly increased 0.768% in the short-term, and in the long-term significantly decreased 0.343% (table 8). This recorded decrease in J01CR_% represents an improvement in prescription quality.

The consumption of 3rd and 4th generation cephalosporins in relation to the total number of antibiotics (J01DD+DE_%) has been decreasing in Portugal in the past years and is now below the European average (table 9), which proves that there has been an improvement in quality prescription. However, the pandemic had no impact on the consumption of these antibiotics (table 8).

In the relative consumption of fluoroquinolones (J01MA_%), Portugal has been declining its consumption but continues with values above the European average (table 9). With the pandemic, no significant changes were recorded in the short-term, but this indicator suffered a significant increase of 0.160% in the long-term trend (table 8). The increase in its consumption reflects a decrease in the quality of the prescription, but one of the possible explanations of the increase in long-term is the fact that the denominator consumption of antibiotics, in general, has decreased so much that even if the consumption of fluoroquinolones does not change, the indicator rises.

Finally, Portugal and the rest of the European countries are reporting progressively higher ratios between broad- and narrow-spectrum antibiotics consumed (table 9), which is quite alarming since the use of broad-spectrum antibiotics leads to increased antibiotic resistance. With the pandemic, the ratio of consumption of broad and narrow-spectrum antibiotics (J01_B/N) had a significant short-term and long-term effect. The ratio rises 9.6 significantly with immediate effect but reduces 1.7 per month thereafter (table 8). An exponential increase occurred soon after the onset of the pandemic but later began to decrease. The increase of the ratio can be explained by the increase in the consumption of broad-spectrum antibiotics, or by the decrease in the consumption of narrow-spectrum antibiotics, such as penicillins sensitive to β-lactamases, 1st generation cephalosporins and erythromycin, at the beginning of the pandemic, which led to an increase in the broad- and narrow-spectrum ratio, without actually having an increase in the consumption of broad-spectrum antibiotics.

Limitations

In this study, some limitations should be noted. In relation to data collection, there were only available data from 9 months after the beginning of the pandemic (April-December), which was not enough to show the significance of the results in the long-term in some quality indicators of antibiotic consumption in the community, such as the consumption of penicillins (J01C). If more data were available, we would probably see a long-term impact of the pandemic in the consumption of some classes of antibiotics.

6 Conclusion

The COVID-19 pandemic and related mitigation measures affected considerably healthcare services access and provision, as well as medicines utilisation patterns. In general, at the beginning of the pandemic (March 2020), the overall consumption of medicines used for chronic conditions and medicines eventually used for the symptomatic treatment of COVID-19 increased substantially. This was followed by a period where there was an abrupt decrease in consumption, mainly due to the lockdown.

In this study, we decided to analyse the impact of the COVID-19 pandemic on antibiotic consumption in the community in Portugal, using data collected from Portuguese pharmacies.

When analysing the quality indicators for antibiotic consumption in the community in Portugal, we concluded that, in general, the consumption of antibiotics (J01) declined sharply in the first three months of the COVID-19 pandemic. After this period, the consumption of outpatient antibiotics showed similar seasonal patterns when compared to the period 2016-19, however lower consumption rates were observed. It was also observed that the quality indicator “Antibacterials for systemic use” (J01) had only significantly reduced in the short-term (3 DIDs), but not in the long-term. More data would be needed to verify whether a significant long-term reduction would have occurred.

Improving antibiotic prescribing quality indicators is one of the main challenges to avoid the misuse of antibiotics. After the beginning of the pandemic, improvements in quality indicators were obtained only in the short-term for the consumption of penicillins and cephalosporins. No changes were found in the consumption of macrolides, lincosamides and streptogramins, quinolones as well as in the relative consumption of penicillins sensitive to ß-lactamase and 3rd and 4th generation cephalosporins. The relative consumption of penicillins with ß-lactamase inhibitors and the ratio broad- to narrow-spectrum antibiotics showed a short-term increase but a long-term decrease.

There are some factors related to the pandemic that might be related to the decrease in antibiotic consumption, such as lockdown, the decrease in the number of face-to-face medical consultations; the reduction in the transmission of other respiratory infections, such as the flu, enhanced by the use of face mask and hand sanitiser.

In general, our results reveal that the COVID-19 pandemic led to an improvement in the consumption of antibiotics, with a reduction of almost all classes, which we hope a decrease in bacterial resistance in the future.

Antimicrobial resistance is now considered as one of the top health challenges facing the 21st century, and WHO has declared that AMR is one of the top 10 global public health threats facing humanity. Antibiotics are becoming increasingly ineffective as drug resistance spreads globally, leading to more difficult to treat infections. Portugal remains one of the European countries with high consumption of antibiotics in the community setting and a worrisome proportion of bacterial resistance, despite an evident decrease observed in the last years.

It is important to continue monitoring the consumption of antibiotics since its inappropriate use can lead to bacterial resistance in the long-term.

7 References

1. Chauhan S. Comprehensive review of coronavirus disease 2019 (COVID-19). Biomed J [Internet]. 2020;43(4):334–40. Available from: https://doi.org/10.1016/j.bj.2020.05.023

2. World Health Organization. Coronavirus disease (COVID-19) pandemic [Internet]. [cited 2020 Mar 14]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019

3. World Health Organization. COVID-19 Weekly Epidemiological Update. World Heal Organ [Internet]. 2021;53(December):1–3. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/weekly_epidemiological_update_22.pdf

4. Pais RJ, Taveira N. Predicting the evolution and control of COVID-19 pandemic in Portugal. F1000 Res. 2020;1–16.

5. Direção Geral de Saúde. Current status point in Portugal [Internet]. 2021 [cited 2021 Aug 20]. Available from: https://covid19.min-saude.pt/ponto-de-situacao-atual-em-portugal/

6. Jornal de Notícias. Chronology of the main events of a year of COVID in Portugal [Internet]. 2021 [cited 2021 Apr 24]. Available from: https://www.jn.pt/nacional/cronologia-dos-principais-acontecimentos-de-um-ano-de-covid-em-portugal-13400044.html

7. Direção Geral de Saúde. Vaccination Report [Internet]. 2021 [cited 2021 Sep 3]. Available from: https://covid19.min-saude.pt/relatorio-de-vacinacao/

8. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? J Hypertens. 2020;38(5):781–2.

9. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med [Internet]. 2020;8(4):e21. Available from: http://dx.doi.org/10.1016/S2213-2600(20)30116-8

10. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in

Wuhan, China. JAMA - J Am Med Assoc. 2020;323(11):1061–9.

11. Zhang J jin, Dong X, Cao Y yuan, Yuan Y dong, Yang Y bin, Yan Y qin, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy Eur J Allergy Clin Immunol. 2020;75(7):1730–41.

12. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 2005;11(8):875–9.

13. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19. N Engl J Med. 2020;382(25):2431–40.

14. Danser AHJ, Epstein M, Batlle D. Renin-Angiotensin System Blockers and the COVID-19 Pandemic: At Present There Is No Evidence to Abandon Renin-Angiotensin System Blockers. Hypertension. 2020;75(6):1382–5.

15. European Society of Cardiology. Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers [Internet]. 2020 [cited 2021 May 1]. Available from: https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang

16. World Health Organization. Guideline Therapeutics and COVID-19: living guideline. 2021;

17. European Medicines Agency. First COVID-19 treatment recommended for EU authorisation. 2020 p. 1–2.

18. Infarmed. Guidelines for Access to Experimental Therapeutics in the treatment of COVID-19 - SARS-CoV-2 infection. 2020.

19. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269–71.

20. Health Market Research. Market Watch Portugal Março 2020. 2020; Available from: https://www.hmr.co.com/insights/market-watch-portugal-julho-2020-especial-covid-19-semana-13/

21. Mehra MR, Desai SS, Ruschitzka F, Patel AN. RETRACTED:Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet [Internet]. 2020; Available from: http://dx.doi.org/10.1016/S0140-6736(20)31180-6

22. Infarmed. Recommendation for precautionary suspension of the use of hydroxychloroquine in COVID-19 until evaluation by the WHO Safety Monitoring Committee of the Solidarity clinical trial. 2020.

23. Omura S, Crump A. Ivermectin: Panacea for resource-poor communities? Trends Parasitol. 2014;30(9):445–55.

24. National Institutes of Health. Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19. 2020;19:47–88.

25. Infarmed. Insufficient evidence for the use of ivermectin in COVID-19 [Internet]. [cited 2021 May 2]. Available from: https://www.infarmed.pt/web/infarmed/noticias/-/journal_content/56/15786/4262037

26. European Medicines Agency. EMA advises against use of ivermectin for the prevention or treatment of COVID-19 outside randomised clinical trials [Internet]. [cited 2021 May 2]. Available from: https://www.ema.europa.eu/en/news/ema-advises-against-use-ivermectin-prevention-treatment-covid-19-outside-randomised-clinical-trials

27. Donn N. Portuguese doctors support Ivermectin to treat early signs of Covid-19 [Internet]. Portugal Resident. 2021 [cited 2021 Sep 4]. Available from: https://www.portugalresident.com/portuguese-doctors-support-ivermectin-to-treat-early-signs-of-covid-19/

28. Horby PW, Mafham M, Bell JL, Linsell L, Staplin N, Emberson J, et al. Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2020;396(10259):1345–52.

29. European Medicines Agency. COVID-19 treatments: under evaluation [Internet]. 2021 [cited 2021 May 2]. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-

threats/coronavirus-disease-covid-19/treatments-vaccines/treatments-covid-19/covid-19-treatments-under-evaluation

30. European Medicines Agency. COVID-19 vaccines [Internet]. [cited 2021 May 2]. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines

31. Serviço Nacional de Saúde. Medical Appointments in Primary Health Care [Internet]. 2021 [cited 2021 Mar 20]. Available from: https://transparencia.sns.gov.pt/explore/dataset/evolucao-das-consultas-medicas-nos-csp/table/?sort=tempo

32. MOAI Consulting. Impact of the COVID-19 pandemic on healthcare provision in Portugal. 2021.

33. Richardson E, Aissat D, Williams GA, Fahy N. Keeping what works: remote consultations during the COVID-19 pandemic. Eurohealth (Lond). 2020;26(2):73–6.

34. Ayati N, Saiyarsarai P, Nikfar S. Short and long term impacts of COVID-19 on the pharmaceutical sector. DARU, J Pharm Sci. 2020;28(2):799–805.

35. Kostev K, Lauterbach S. Panic buying or good adherence? Increased pharmacy purchases of drugs from wholesalers in the last week prior to Covid-19 lockdown. 2020;(January):19–22.

36. European Comission. Communucation from the Comission. Guidelines on the optimal and rational supply of medicines to avoid shortages during the COVID-19 outbreak. Brussels; 2020.

37. Ministério da Saúde. Portaria n.º 90-A/2020 de 9 de abril. Diário da República, 1ª série, N.º 71 2020 p. 19-(2)-19-(3).

38. Infarmed. Guidelines for the Responsible Management of Medicines in the Current Context of the COVID-19 Pandemic. 2020.

39. Shojaei A, Salari P. COVID-19 and off label use of drugs: an ethical viewpoint. DARU, J Pharm Sci. 2020;28(2):789–93.

40. Health market research. Market Watch Portugal - December 2020 [Internet].

2020. Available from: www.hmr.co.com

41. Romano S, Galante H, Figueira D, Mendes Z, Rodrigues AT. Time-trend analysis of medicine sales and shortages during COVID-19 outbreak: Data from community pharmacies. 2020;(January).

42. Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the Clinical Characteristics of Coronavirus Disease 2019 (COVID-19). J Gen Intern Med. 2020;35(5):1545–9.

43. Sengupta S, Chattopadhyay MK, Grossart HP. The multifaceted roles of antibiotics and antibiotic resistance in nature. Front Microbiol. 2013;4(MAR):1–13.

44. Meyer E, Gastmeier P, Deja M, Schwab F. Antibiotic consumption and resistance: Data from Europe and Germany. Int J Med Microbiol [Internet]. 2013;303(6–7):388–95. Available from: http://dx.doi.org/10.1016/j.ijmm.2013.04.004

45. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infect Dis. 2014;14(1):1–25.

46. World Health Organization. Antimicrobial resistance [Internet]. 2020. [cited 2021 May 3]. Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance

47. Loureiro RJ, Roque F, Teixeira Rodrigues A, Herdeiro MT, Ramalheira E. Use of antibiotics and bacterial resistances: Brief notes on its evolution. Rev Port Saude Publica [Internet]. 2016;34(1):77–84. Available from: http://dx.doi.org/10.1016/j.rpsp.2015.11.003

48. Serwecinska L. Antimicrobials and Antibiotic-Resistant Bacteria : MPDI Water. 2020;12:1–17.

49. Gomes M. Relationship between Antibiotic Resistance and Antibiotic Consumption in Portugal [Internet]. Universidade de Lisboa; 2018. Available from: http://hdl.handle.net/10451/39441%0A

50. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2021. 2021;

51. Natsch S, Hekster YA, De Jong R, Heerdink ER, Herings RMC, Van Der Meer JWM. Application of the ATC/DDD methodology to monitor antibiotic drug use. Eur J Clin Microbiol Infect Dis. 1998;17(1):20–4.

52. Hutchinson JM, Patrick DM, Marra F, Ng H, Bowie WR, Heule L, et al. Measurement of antibiotic consumption: A practical guide to the use of the Anatomical Therapeutic Chemical classification and Defined Daily Dose system methodology in Canada. Can J Infect Dis. 2004;15(1):29–35.

53. Coenen S, Ferech M, Haaijer-Ruskamp FM, Butler CC, Vander Stichele RH, Verheij TJM, et al. European Surveillance of Antimicrobial Consumption (ESAC): Quality indicators for outpatient antibiotic use in Europe. Qual Saf Heal Care. 2007;16(6):440–5.

54. European Centre for Disesase Prevention and Control (ECDC). Quality indicators for antibiotic consumption in the community (primary care sector) in Europe 2017. [Internet]. 2019 [cited 2021 May 2]. Available from: https://www.ecdc.europa.eu/en/antimicrobial-consumption/database/quality-indicators

55. Torre C, Guerreiro J, De Oliveira Martins S, Raposo JF, Martins AP, Leufkens H. Patterns of glucose lowering drugs utilization in Portugal and in the Netherlands. Trends over time. Prim Care Diabetes [Internet]. 2015;9(6):482–9. Available from: http://dx.doi.org/10.1016/j.pcd.2015.03.009

56. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: A tutorial. Int J Epidemiol. 2017;46(1):348–55.

57. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002;27(4):299–309.

58. Schaffer AL, Dobbins TA, Pearson SA. Interrupted time series analysis using autoregressive integrated moving average (ARIMA) models: a guide for evaluating large-scale health interventions. BMC Med Res Methodol. 2021;21(1):1–12.

59. Chotpitayasunondh T, Fischer TK, Heraud JM, Hurt AC, Monto AS, Osterhaus

A, et al. Influenza and COVID-19: What does co-existence mean? Influenza Other Respi Viruses. 2021;15(3):407–12.

60. Soo RJJ, Chiew CJ, Ma S, Pung R, Lee V, Lee VJ. Decreased influenza incidence under COVID-19 control measures, Singapore. Emerg Infect Dis. 2020;26(8):1933–5.

61. Wu D, Lu J, Liu Y, Zhang Z, Luo L. Positive effects of COVID-19 control measures oninfluenza prevention. 2020;(January).

62. Instituto Nacional Ricardo Jorge. Influenza Epidemiological Surveillance Bulletin. 2020.

63. Imanpour S, Nwaiwu O, McMaughan DK, DeSalvo B, Bashir A. Factors associated with antibiotic prescriptions for the viral origin diseases in office-based practices, 2006–2012. JRSM Open. 2017;8(8):205427041771766.

64. Anthony Jnr B. Use of Telemedicine and Virtual Care for Remote Treatment in Response to COVID-19 Pandemic. J Med Syst [Internet]. 2020;44(7):J. Available from: http://link.springer.com/10.1007/s10916-020-01596-5

65. Sulis G, Batomen B, Kotwani A, Pai M, Gandra S. Sales of antibiotics and hydroxychloroquine in India during the COVID-19 epidemic : An interrupted time series analysis. 2021;(March 2020):1–18. Available from: http://dx.doi.org/10.1371/journal.pmed.1003682

66. Gonzalez-zorn B. Antibiotic use in the COVID-19 crisis in Spain. 2020;(January):2020–2.

67. King LM, Lovegrove MC, Shehab N, Tsay S, Budnitz DS, Geller AI, et al. Trends in US Outpatient Antibiotic Prescriptions During the Coronavirus Disease 2019 Pandemic. Clin Infect Dis. 2020;2:1–9.

68. Pearce C, McLeoad A, Gardner K, Supple J, Epstein D, Buttery J. Primary Care and SARS-CoV-2 : The first 40 weeks of the pandemic year. 2020;

69. Ferech M, Coenen S, Dvorakova K, Hendrickx E, Suetens C, Goossens H. European Surveillance of Antimicrobial Consumption (ESAC): Outpatient penicillin use in Europe. J Antimicrob Chemother. 2006;58(2):408–12.