A modeling study on the impact of COVID-19 pandemic responses on the community transmission of antibiotic-resistant bacteria

Aleksandra Kovacevic, David Smith, Eve Rahbé, Sophie Novelli, Paul Henriot, Laura Temime, Lulla Opatowski

A modeling study on the impact of COVID-19 pandemic responses on the community transmission of antibiotic-resistant bacteria

Aleksandra Kovacevic[1,2¶] David R M Smith[1,2,3¶], Eve Rahbé[1,2], Sophie Novelli[2], Paul Henriot[3,4], Laura Temime[3,4], Lulla Opatowski[1,2]

1. Institut Pasteur, Université Paris Cité, Epidemiology and Modelling of Antibiotic Evasion (EMAE), Paris, France
2. Université Paris-Saclay, Université de Versailles Saint-Quentin-en-Yvelines, Inserm U1018, CESP, Anti-infective evasion and pharmacoepidemiology team, Montigny-Le-Bretonneux, France
3. Modélisation, épidémiologie et surveillance des risques sanitaires (MESuRS), Conservatoire national des arts et métiers, Paris, France
4. PACRI unit, Institut Pasteur, Conservatoire national des arts et métiers, Paris, France

*Corresponding author
E-mail: aleksandra.kovacevic@pasteur.fr

¶These authors contributed equally to this work.

Keywords: virus-bacteria interaction; pathogen interactions; SARS-CoV-2; COVID-19; *Streptococcus pneumoniae*; antibiotic resistance; invasive pneumococcal disease; carriage; bacterial co-infection

Abstract

Non-pharmaceutical COVID-19 interventions have dramatically modified the transmission dynamics of pathogens other than SARS-CoV-2. In many countries, reports have shown that implementation of population-wide lockdowns led to substantial reductions in invasive bacterial disease caused by respiratory bacteria such as *Streptococcus pneumoniae.* By contrast, most European countries reported increased antibiotic resistance among *S. pneumoniae* isolates from 2019 to 2020. To disentangle impacts of the COVID-19 pandemic responses on bacterial epidemiology in the community setting, we propose a mathematical model formalizing simultaneous transmission of SARS-CoV-2 and antibiotic-sensitive and -resistant strains of *S. pneumoniae*. The impacts of population-wide lockdowns, isolation of COVID-19 cases, changes in antibiotic consumption due to altered healthcare-seeking behavior and prophylactic use in the early pandemic were explored across six pandemic scenarios. Our model was able to reproduce the observed trends, showing how lockdowns substantially reduce invasive pneumococcal disease incidence, while surges in prophylactic antibiotic prescribing favor disease caused by resistant strains. Surges in COVID-19 cases were associated with increased antibiotic resistance rates across all pandemic scenarios. Introducing synergistic within-host SARS-CoV-2-pneumococcus interactions further exacerbates increasing incidence of resistant disease. When data availability is limited, mathematical modeling can help improve our understanding of the complex interactions between COVID-19 and antibiotic resistance.

Introduction

Responses to the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have generated unprecedented changes in population mixing, healthcare-seeking behavior, and infection prevention and control practices, which have dramatically modified the ecology and epidemiology of infectious diseases at a global scale. Collateral impacts of COVID-19 on epidemiological dynamics have been reported for common viral and bacterial respiratory infections, sexually transmitted infections like HIV, vector-borne infections like dengue, and even non-communicable diseases [1–4]. However, impacts of the COVID-19 pandemic on antimicrobial resistance (AMR) remain poorly understood, in part due to delayed or unavailable data.

AMR is one of the leading threats to global health. In 2019, AMR in clinically relevant bacteria were estimated to be associated with 4.95 million deaths, of which 1.27 million were directly attributable to resistance [5]. Although AMR continues to receive international attention through initiatives like the World Health Organization's Global Action Plan on AMR [6], AMR control is challenged by a wide range of biological, behavioral, and economic factors, from the evolution of novel multidrug-resistance genes, to pervasive inappropriate prescribing, to intensive prophylactic use in food-animal feedlots [7]. The ongoing COVID-19 pandemic has occurred during global efforts to combat AMR and has diverted considerable public health resources, redirecting them instead towards SARS-CoV-2 prevention and mitigation. According to The Centers for Disease Control and Prevention (CDC) report, repurposing of AMR surveillance infrastructure for COVID-19 surveillance led to substantial reductions in whole genome sequencing of bacterial isolates causing delay in AMR data reporting in the United States [8].

Several studies have raised concern about COVID-19-associated antimicrobial overuse or misuse exacerbating AMR, particularly during and following the first wave of the pandemic taking into consideration frequent administration of antibiotic prophylaxis, especially azithromycin, to COVID-19 patients [9–11]. On the other hand, non-pharmaceutical interventions (NPIs) implemented to control SARS-CoV-2 transmission – including lockdowns, physical distancing, travel restrictions, face mask use, and improved hygiene practices – may have had the opposite effect, concomitantly reducing the spread of antimicrobial-resistant pathogens [1,12]. A wide range of other pandemic impacts, such as reduced surveillance capacity, disrupted antimicrobial supply chains, and modified composition of the human microbiota, may have, and continue to influence the epidemiological dynamics of AMR in ways that are as-yet poorly understood [9,13–15].

Three years after the onset of the pandemic, data on global AMR trends remain relatively sparse. However, a joint 2022 report on antimicrobial resistance during 2020 from World Health Organization (WHO) and European Centre for Disease Prevention and Control (ECDC) has reported AMR trends across 29 European countries for eight antibiotic-resistant bacterial pathogens of concern, including *Streptococcus pneumoniae* [16]. *S. pneumoniae* has a high rate of carriage in community settings, heterogenous levels of multidrug resistance across countries and demographic groups, and its transmission was effectively – but inadvertently – controlled by COVID-19 lockdowns in 2020 [1]. In France, annual incidence of pneumococcal disease fell from 10.5 to 5.8 per 100,000 inhabitants from 2019 to 2020, representing a decline of 44.8% [17]. On

the other hand, most European countries, including France, reported an increase in pneumococcal resistance to penicillin and macrolides from 2019 to 2020 [16].

Mathematical models are useful tools for the simulation and quantification of infectious disease dynamics, particularly when data are limited or lacking [18]. When factors driving the transmission of one pathogen also impact another – as in the present context of the COVID-19 pandemic and its impacts on antibiotic use and antibiotic-resistant bacteria – a co-circulation model is necessary to better understand mechanistic links between coinciding pathogens. Such co-circulation models must be carefully tailored to the respective pathogens under study to accurately represent the biological mechanisms that drive their transmission across scales, including ecological dynamics within the host (e.g., competitive interactions with other organisms) and epidemiological drivers at the between-host level (e.g., inter-individual contact behavior) [19–21]. Bacteria-virus interaction models have been used previously to disentangle the public health consequences of interactions between pathogens such as influenza and *S. pneumoniae* [22-24]. However, in a systematic PubMed search conducted on 1 August 2022, we identified no epidemiological models describing the simultaneous transmission of SARS-CoV-2 and antibiotic-resistant bacteria (see Supporting Information, S1).

To disentangle how the COVID-19 pandemic has impacted the epidemiological dynamics of antibiotic resistance, we propose a mathematical model that formalizes simultaneous transmission of SARS-CoV-2 and both antibiotic-sensitive and -resistant strains of *S. pneumoniae* in the community setting, and which includes mechanistic impacts of SARS-CoV-2 infection burden on epidemiological parameters. We evaluate six different pandemic scenarios, each accounting for impacts of SARS-CoV-2 outbreak on healthcare-seeking, antibiotic prescribing and inter-individual contact behavior in the early months of the COVID-19 pandemic. Through simulation, we assess how these scenarios impact the prevalence of bacterial carriage, levels of antibiotic resistance in the community, and incidence of invasive bacterial disease (IBD) caused by both antibiotic-sensitive and -resistant bacteria. Furthermore, we assess how IBD incidence may be additionally impacted by other factors, such as within-host pathogen interactions, emerging SARS-CoV-2 variants with higher transmissibility, and varying levels of population immunity.

Results

Observed antibiotic resistance trends in *Streptococcus pneumoniae*

In routine surveillance data reported to the European Antimicrobial Resistance Surveillance Network (EARS-Net), most European countries reported an increase in antibiotic resistance in *S. pneumoniae* from 2019 to 2020, including increases in the proportion of invasive isolates with phenotypic resistance to both penicillin (Fig 1A) and macrolides (Fig 1B). At the same time, the total number of reported isolates decreased by 44.3% from 2019 to 2020 in the European Union/European Economic Area (EU/EEA) [16] (see Supporting Information, Table S1). Responses to the COVID-19 pandemic – such as implementation of NPIs, modified antibiotic prescribing due to changes in healthcare-seeking behavior, and prescription of prophylactic antibiotics to COVID-19 patients – are hypothesized to underlie these observed trends (Fig 2A).

A co-circulation model of SARS-CoV-2 infection and pneumococcal carriage transmission

To test mechanistic impacts of responses to the COVID-19 pandemic on bacterial epidemiology, we developed a compartmental, deterministic transmission model describing infection with SARS-CoV-2 and colonization with commensal respiratory bacteria in a large, well-mixed human population (Fig 2B). We assume that some individuals with symptomatic COVID-19 undergo isolation, reducing their transmission rates for SARS-CoV-2 and both strains of bacteria by a factor q, and also receive antibiotic prophylaxis for COVID-19, which increases their rate of antibiotic initiation by a factor A across simulation time (t = 365 days) (see Methods for more detail and Supporting Information S2). Parameterizing this model to *S. pneumoniae*, we then explored epidemiological impacts of six distinct pandemic scenarios in which, over a 90-day period coincident with the first wave of COVID-19, we simulated (i) population-wide increases or decreases in antibiotic prescribing and (i) the presence or absence of a population-wide lockdown (Fig 2C; see Supporting Information Table S3 for assumed parameter values).

Using model simulations, we assessed how SARS-CoV-2 outbreaks and corresponding pandemic scenarios may impact bacterial carriage prevalence, antibiotic resistance rates, and IBD incidence in a simulated population of 100,000 individuals. Several epidemiological outcomes were calculated from simulation outputs: (i) daily prevalence of bacterial colonization (the proportion of individuals in the population colonized with antibiotic-sensitive bacteria, antibiotic-resistant bacteria, or co-colonized with both), (ii) daily prevalence of SARS-CoV-2 infection (the proportion of infectious individuals), and (iii) the antibiotic resistance rate, defined as the number of individuals colonized with the resistant strain over the total number colonized (Supporting Information, S2.4). Finally, we estimated the relative change in cumulative IBD incidence (total incidence and incidence due to each strain) during the intervention period (90 days) and change in the annual IBD incidence, as compared to a pre-pandemic period (i.e., over the same durations but assuming no SARS-CoV-2 circulation in the population).

Model simulations of antibiotic resistance and IBD incidence in *Streptococcus pneumoniae*

Model simulations of the pandemic scenarios without lockdown implementation (scenarios S0, S1, and S2) all result in a decrease in carriage of antibiotic-sensitive bacteria and an increase in antibiotic-resistant bacteria (Fig 3A). Total bacterial colonization prevalence in the population generally declines during SARS-CoV-2 outbreaks. However, all scenarios are accompanied by an increase in the antibiotic resistance rate, with the magnitude of increase depending on the pandemic scenario (Fig 3B). A population-wide surge in antibiotic prescribing coincident with the peak in SARS-CoV-2 infection (scenario S1) moderately decreases total bacterial carriage but results in the greatest increase in the resistance rate (+ 22.6%). While total and antibiotic-sensitive IBD incidence both decrease in scenario S1 (Fig 3C), annual incidence of antibiotic-resistant disease increases (+3.2%) compared to the pre-pandemic levels (Fig 3C). In scenario S2, reductions in overall community antibiotic prescribing are counteracted by the surge in individuals receiving antibiotic prophylaxis for COVID-19, resulting in a limited overall impact on bacterial epidemiology (Fig 3A).

The addition of a population-wide lockdown (scenarios S3, S4, and S5) not only limits the transmission of SARS-CoV-2 but also results in a large reduction in colonization prevalence for

both strains of bacteria, regardless of a potential population-wide increase or decrease in antibiotic use. As a large share of the population remains susceptible to SARS-CoV-2 infection at the end of the lockdown, a second wave of COVID-19 follows several months later, which further increases the resistance rate due to COVID-19 prophylaxis. However, in all scenarios implementing a 90-day lockdown, total annual incidence of IBD decreases substantially (-57% during lockdown and -48% annually, on average) (Fig 3C). Outcomes of the scenarios that combine lockdown implementation along with the changes in community antibiotic prescribing, isolation and prophylactic antibiotic use in COVID-19 cases (S3, S4, or S5) are consistent with the IBD decrease reported in France, where annual incidence of pneumococcal disease (per 100,000 inhabitants) fell from 10.5 to 5.8 from 2019 to 2020, representing a decline of 44.8% [17], including the overall 44.3% reported decrease in invasive isolates in the European Union/European Economic Area (EU/EEA) [16].

Within-host interactions may favor incidence of antibiotic-resistant IBD during SARS-CoV-2 outbreaks

SARS-CoV-2 infection may impact progression from bacterial colonization to invasive bacterial disease at the within-host level. For instance, some respiratory viruses are known to favor bacterial disease (e.g., impacts of influenza infection on invasive pneumococcal disease [25,26]), while increased antibiotic exposure in response to COVID-19 may also favor the within-host outgrowth of antibiotic-resistant bacteria [27,28]. To incorporate these mechanisms in our model, we included two within-host interaction terms: the ecological interaction term (ψ_c) increases the rate of progression to invasive disease among colonized individuals who are also infected with SARS-CoV-2, while the antibiotic exposure interaction term (ψ_a) increases the rate of progression to invasive disease among individuals exposed to antibiotics and colonized with the antibiotic-resistant strain [29–32]. The equations for calculating daily IBD incidence assuming within-host interactions due to SARS-CoV-2 co-infection and antibiotic exposure with accompanying details can be found in Supporting Information, S2.5.

When SARS-CoV-2 infection is assumed to favor progression from colonization to disease ($\psi_c>1$), and there is no lockdown, surges in COVID-19 lead to substantial increases in the daily incidence of antibiotic-resistant IBD (Fig 4A). Indeed, a rate of disease progression increased by a factor $\psi_c=25$, results in approximately 3.8 additional cases/100,000 of resistant disease over the course of one year in the absence of lockdown (Fig 4C). Although lockdown implementation can successfully reduce annual resistant IBD incidence, if pathogen interaction strength is >85, lockdown may not be able to fully mitigate this effect, resulting in a rise in resistant disease despite reduced transmission. When antibiotic use is assumed to favor progression from antibiotic-resistant colonization to disease ($\psi_a>1$), surges in SARS-CoV-2 infection coincide with daily increases in incidence of antibiotic-resistant IBD, except when surges coincide with reduced antibiotic prescribing (e.g., scenarios S0, S1 vs. scenario S2, Fig 4B). However, even small increases in antibiotic use may contribute to an increase in annual resistant disease incidence, where an increased rate of disease progression by $\psi_a=12$ leads to an increase by approximately 2.3 additional cases/100,000 of the annual incidence of antibiotic-resistant bacterial disease in the absence of 90-day lockdown compared to the pre-pandemic period (Fig 4D).

Emerging SARS-CoV-2 variants and population immunization levels may impact AMR

Impacts of SARS-CoV-2 on antibiotic-resistant IBD incidence may also depend on the characteristics of locally circulating SARS-CoV-2 variants and their immune escape properties. To account for potential mediating impacts of SARS-CoV-2 transmissibility and population immunity, in simulations we varied (i) values of R_0 (basic reproduction number) for SARS-CoV-2 ($0 \leq R_0 \leq 10$) and (ii) the proportion of the population immunized against SARS-CoV-2 infection at simulation outset (from 0 % to 100 %).

Assuming different SARS-CoV-2 variant characteristics in the simplest scenario S0 (no lockdown, no community-level change in antibiotic prescribing, and no within-host interactions), we found that the annual cumulative incidence of antibiotic-resistant IBD increases with the higher R_0 values of SARS-CoV-2, which is led by antibiotic prophylaxis for COVID-19 and decreases with the population immunity against SARS-CoV-2 infection (Fig 5).

Discussion

We propose a novel co-circulation model describing the spread of SARS-CoV-2 and antibiotic-resistant bacteria in a community setting and show how behavioral responses to the COVID-19 pandemic can differentially impact AMR. By simulating a range of lockdown and antibiotic use scenarios, we highlight potential direct and indirect consequences that outbreaks of novel viral respiratory pathogens like SARS-CoV-2 can have on epidemiological dynamics of antibiotic resistance. We find that incidence of invasive bacterial disease may either increase or decrease, depending on how overall antibiotic prescribing in the community changes in response to COVID-19, on implementation of measures to control viral transmission, and on potential within-host interactions between co-circulating pathogens. Impacts of COVID-19 on disease incidence and antibiotic resistance rate may linger long after extinction of SARS-CoV-2 outbreaks and the cessation of control measures.

Many studies have reported trends on the incidence of community-acquired bacterial infections since the onset of the pandemic. A comprehensive global analysis by Brueggemann et al. using national surveillance data from 26 countries identified substantial and sustained reductions in *S. pneumoniae* incidence after the implementation of COVID-19 control measures such as lockdowns and travel restrictions [1]. Our model scenarios that most closely fit with early 2020 are scenarios including strict lockdown, with or without change in antibiotic use, which led to similar estimates of the relative (%) reduction in IBD incidence as observed in Brueggemann et al. [1]. Similar findings have been observed in the context of sentinel community-acquired infections in New Zealand [33], invasive pneumococcal disease (IPD) in Taiwan [34] and Hong Kong [35], and lower respiratory tract infection in China [36]. However, across these studies, data on the relative impacts of COVID-19 on drug-sensitive versus drug-resistant isolates have been unavailable.

Impacts of the COVID-19 pandemic on rates of antibiotic resistance among common bacterial pathogens in community settings are still being uncovered. European trends reported to EARS-Net (Fig 1) are perhaps the most comprehensive data available. An earlier study by Tomczyk et al. and the WHO AMR Surveillance Network from March 2021 highlighted that most

of the 73 countries surveyed had incomplete data on changing AMR rates due to the pandemic, lack of funding, or disruption of surveillance systems [37]. Similarly, a surveillance report from June 2022 from the Centers for Disease Control and Prevention (CDC) shows increases in AMR rates among hospital-onset infections due to diverse nosocomial pathogens but highlights inconclusive findings for community-associated bacteria like *S. pneumoniae* due to missing and delayed data [8]. Further, routinely collected AMR surveillance data are typically based upon invasive disease isolates collected in acute care settings and may thus be poorly representative of the bacteria actively circulating in the community.

Several studies have nonetheless reported resistance rates among colonizing bacteria from primary care and community settings since the onset of the COVID-19 pandemic. Data from primary care patients and nursing home residents in France have suggested a reduced proportion of extended spectrum-beta lactam producers among *Escherichia coli* urinary isolates after the national lockdown instated in March 2020 [38]. In community residents in Botswana, the percentage of Enterobacterales isolates resistant to carbapenems and extended-spectrum cephalosporins also reduced after lockdowns [39]. Conversely, using shotgun metagenomics on fecal samples, Peng et al. showed a decrease in Actinobacteria richness in the microbiota of healthy adults from Hong-Kong and an increase in resistance genes against β-lactam antibiotics during the first wave of the pandemic compared to a pre-pandemic period [40]. Regarding pandemic impacts on microbiome composition, one simulation study suggests that lockdowns and associated reductions in mobility and human contact (informed by Portuguese mobility data) may have led to reductions in the diversity of antibiotic resistance genes found in the human microbiome [41]. Such disruptions to human microbiota may have further downstream impacts on colonization resistance and the propensity for antibiotic-resistant bacterial symbionts to transmit [13,42].

Relative to data on AMR trends in the community since the emergence of COVID-19, data on antibiotic prescribing in primary care are more widely available. Globally, community antibiotic prescribing dropped during the first year of the COVID-19 pandemic compared to the pre-pandemic period. In Europe, antibiotic consumption decreased by almost 20% in 2020 compared to 2019 [43], with heterogeneity between countries and antibiotic classes. Similar temporal trends were observed in England [44], Canada [45], the United States [46], China [47], South Korea [48] and New Zealand [33]. These trends may largely be explained by reduced incidence of seasonal respiratory tract infections, and reduced primary care consultations [49,50]. On the other hand, the advent of telemedicine, pandemic-related patient stress, and antibiotic demand may have to a certain extent mitigated reductions in prescribing owing to reduced consultation [51]. In a global analysis of antimicrobial sales, Khouja et al. found that antibiotic consumption initially increased by approximately 7% in March 2020, prior to subsequent declines through to August 2020 [53]. Furthermore, while overall prescribing may have decreased, prescription of specific antibiotics has increased, particularly those associated with COVID-19 prophylaxis. For instance, community consumption of azithromycin increased during the first year of the pandemic in multiple countries [53–55]. Several studies have now characterized the wide range of antibiotics provided as prophylaxis to both mild and severe COVID-19 patients in 2020 [56,57], though it remains unclear to what extent prophylaxis is appropriate for prevention of bacterial coinfection in COVID-19 patients, particularly for mild cases treated in the community. Therefore, testing different scenarios with both increases and decreases in antibiotic use seems appropriate due to spatial and temporal heterogeneity in impacts of COVID-19 on antibiotic

exposure, especially considering that over time, many trends in antibiotic consumption observed early in the pandemic may have reversed or returned to the pre-pandemic baseline.

Our model simulations show that antibiotic resistance rates increase with surges in SARS-CoV-2 infections when there is a corresponding increase in prophylactic antibiotic use, as expected, but that lockdowns can mitigate this increasing trend to some degree. One promising outcome of scenarios that assume a decrease in antibiotic prescribing is that increases in antibiotic resistance were minor (Fig 3B, S2 and S5), while changes in resistant IBD incidence were either negligible or negative (Fig 3C). Conversely, surges in overall antibiotic prescribing during SARS-CoV-2 outbreaks, as reported in certain regions and pandemic periods, may cause substantial increases in resistance rates and the total incidence of disease due to antibiotic-resistant strains. In these analyses, for simplicity we simulated lockdowns and modifications of antibiotic prescribing lasting for a single 90-day period. Real-life scenarios are significantly more complicated and may involve multiple alterations of these factors at different points in time and heterogeneity across populations (e.g., prescribing increases in some demographic groups and decreases in others). Over longer timescales, and in the context of successive COVID-19 outbreaks with heterogeneous public health responses and impacts on human behavior, it is unclear exactly how levels of resistance and burden of disease may be expected to evolve.

SARS-CoV-2 bacterial coinfection has been reported relatively rarely over the course of the pandemic, suggesting that most COVID-19 patients probably do not require antibiotic therapy [11,58,59], although extensive antibiotic prophylaxis may have limited observed co-infection incidence. The inflammatory immune response resulting from COVID-19 likely predisposes patients to subsequent progression to IBD to some extent [60], but antibiotic use may also favor progression to IBD for patients colonized with drug-resistant strains [61]. The results presented here (Fig 4) suggest that such overlapping within-host interactions could have important consequences for the resistant IBD incidence during COVID-19 waves, especially in the elderly and high-risk groups. Future studies are needed to better understand the magnitude of these interactions for *S. pneumoniae* and other commensal, facultatively pathogenic bacteria [62].

Emerging SARS-CoV-2 variants, with varying transmissibility and severity, may be expected to have variant-specific impacts on AMR, especially in the context of the tightening and loosening of community control measures and their extensive heterogeneity both within and between countries. The highly heterogeneous distribution of diverse SARS-CoV-2 vaccines presents an additional mechanism that may further complexify interactions between antibiotic consumption, community control measures, circulating SARS-CoV-2 variants, and their cumulative impacts on antibiotic resistance. In our simulations, we used SARS-CoV-2 parameter values characteristic of the wild type or ancestral strain with $R_0 = 2.5$ [63,64] and in the absence of population immunity, best reflecting epidemiological dynamics from early in the pandemic. However, successive SARS-CoV-2 variants of concern, most notably Alpha, Delta, Omicron, and most recently Omicron sub-lineages BA.4 and BA.5 [65], are highly variable in their transmissibility, and evade to some degree the immune protection induced by prior infection and/or vaccination, especially if it has waned over time. Our analysis demonstrates that these viral parameters may affect how SARS-CoV-2 outbreaks impact antibiotic-resistant IBD incidence at the community level and shows how increasing SARS-CoV-2 R_0 values may exacerbate impacts of COVID-19 on antibiotic resistance, while increasing population immunity may mitigate them

(Fig 5). However, the overall impacts of COVID-19 on AMR are difficult to predict, likely vary over the short, medium, and long term, and depend on the specific organism and setting considered.

Our model has focused on the general community, yet COVID-19 has had distinct impacts on AMR in other settings, particularly in hospitals and long-term care facilities. In these settings, an extensive antibiotic use in COVID-19 patients and disruption of antibiotic stewardship programs may have predisposed patients and healthcare workers to increased antibiotic-resistant carriage. In a meta-analysis conducted on studies published up to June 2020 [67], an estimated 68-81% of patients hospitalized with COVID-19, and 74-94% of patients in intensive care, were treated with antibiotics. While hospital disorganization due to the COVID-19 pandemic may have led to decreased antibiotic resistance surveillance and detection promoting the dissemination of resistant organisms through rooms and wards, an implementation of antibiotic stewardship programs, as soon as March 2020, patient isolation, and an extensive use of personal protective equipment (PPE) have mitigated this increase [8,67–70]. Models dedicated to the analysis of such impacts in the hospital could bring a better understanding of the specificities of different settings on the contribution of COVID-19 to the antibiotic resistance burden [71].

We present here the first epidemiological model describing how the ongoing COVID-19 pandemic may have and may continue to influence the epidemiological dynamics of AMR in the community setting. Because this work was intended as a theoretical framework, we aimed at developing the simplest model possible. Nonetheless, an important limitation of our model is the lack of age structure, as SARS-CoV-2 infection risk, IBD risk, disease severity, bacterial carriage prevalence and antibiotic prescribing are all highly heterogeneous across age groups. Our model was also structured and parameterized based upon *S. pneumoniae*, limiting interpretation for other important community-associated bacteria such as *E. coli*, as their epidemiological and natural history characteristics differ substantially (e.g., differences in the within-host ecological niche, duration of colonization, baseline carriage prevalence). Nonetheless, by modulating model compartments and parameter values as necessary, our model could be applied to a wide variety of bacteria and epidemiological scenarios in the community (e.g., impacts of SARS-CoV-2-bacteria interactions in the context of seasonal outbreaks of endemic pathogens). Future work would benefit from fitting such a model to real-world data on AMR trends from different bacterial species. Although such data are currently lacking, especially in community settings, longitudinal microbiome sequencing in the context of ongoing SARS-CoV-2 outbreaks may facilitate better understanding of the impacts of COVID-19 on the transmission of antibiotic resistance into the future.

In conclusion, our work demonstrates how, in the case of delayed or limited data, a mathematical modeling approach can be useful to explain and anticipate how different COVID-19 pandemic responses may be expected to have impacted epidemiological dynamics of AMR in the community. Our model successfully captured the main trends of antibiotic resistance and IBD incidence observed in Europe in 2020 for *S. pneumoniae*. However, not all countries reported increases in AMR rates, and such inter-country heterogeneity may be attributed to other pandemic factors not directly implemented or assumed in model scenarios, such as different adherence to COVID-19 control measures, including impacts on disease surveillance and data reporting during the pandemic. In the current context where data remain limited and more studies are required to evaluate the consequences of the pandemic on the global burden of AMR, mathematical modeling

remains an indispensable tool in helping improve our understanding of the complex, overlapping links between COVID-19 and the epidemiology of antibiotic resistance.

Methods

Streptococcus pneumoniae surveillance data

For antibiotic resistance trends reported in 2019 and 2020, we used data from EARS-Net (European Antimicrobial Resistance Surveillance Network) acquired from a joint 2022 report on antimicrobial resistance during 2020 by World Health Organization (WHO) and European Centre for Disease Prevention and Control (ECDC) [16]. The annual incidence of *S. pneumoniae* invasive isolates for 2019 and 2020 was measured as the number of isolates from blood or cerebrospinal fluid. The proportion of resistant isolates represents the proportion of isolates with phenotypic resistance to penicillin and macrolides using standardized bacterial culture methods and EUCAST breakpoints. Out of 28 European countries that reported antibiotic resistance data, 24 countries had a sufficient number of samples to establish 2019-2020 resistance trends for penicillin and macrolides.

Developing a co-circulation model of SARS-CoV-2 infection and pneumococcal carriage

We developed a pathogen co-circulation model written using systems of ordinary differential equations (ODEs) (see Supplementary Information S2 for full model description and equations and R files available online at https://github.com/alekskovacevic/antibiotic_resistance). The model simultaneously describes potential infection with SARS-CoV-2 and colonization with antibiotic-sensitive and/or -resistant strains of a commensal respiratory bacterium in a well-mixed community population. SARS-CoV-2 infection is modeled by a Susceptible-Exposed-Infectious-Recovered (SEIR) process where individuals become infected with SARS-CoV-2 at rate β_C upon contact with other infectious individuals. Infection begins with a non-infectious exposed period lasting α^{-1} days and is followed by an infectious period lasting γ_c^{-1} days, eventually leading to recovery and immunization against future re-infection. Waning immunity and competitive multi-strain SARS-CoV-2 dynamics are not considered, since we are interested in the impact of a single COVID-19 wave on bacterial carriage and IBD disease dynamics (Supporting Information S2.1, Fig S1).

Individuals in S, E, I, and R compartments can be uncolonized with the focal bacterial species (U), colonized with either a drug-sensitive (C^S) or a drug-resistant strain (C^R), or co-colonized with both strains (C^{SR}). Colonization with each respective strain is acquired at rates β_S and β_R upon contact with other colonized individuals (Supporting Information, Table S2). We assume a metabolic cost of resistance c, whereby the drug-resistant strain has a reduced intrinsic transmission rate relative to the drug-sensitive strain, $\beta_R = \beta_S(1-c)$. Bacterial carriage is cleared naturally after an average duration of γ_b^{-1} days. We further assume that some share of the population is exposed to antibiotics at any given time, independently of bacterial carriage, with individuals initiating antibiotic therapy at rate τ, which lasts for an average duration of d days. Individuals exposed to antibiotics are unable to acquire the sensitive strain. Antibiotics are assumed to clear colonization with sensitive strains at a rate ω while having no direct impact on colonization with resistant strains. This bacterial colonization process results in antibiotic selection

for resistance via competition for limited hosts, facilitates epidemiological coexistence between strains and is adapted from previous models of *S. pneumoniae* [72,73]. We base both bacterial and antibiotic use model parameters on values estimated from prior studies using French data (Supporting Information, Table S2).

Simulating pandemic scenarios

First, assuming that the bacteria under study are endemic, ODEs were integrated numerically using the R package deSolve to simulate and quantify epidemiological dynamics [74]. Bacterial dynamics were simulated until endemic equilibrium was achieved. Second, using equilibrium states as initial conditions, two SARS-CoV-2 infected cases were introduced into the population on day 0 (t=0), simulation time was re-initialized to t=0, and ODEs were again integrated numerically to t=365 days across each pandemic scenario. Parameter values used for simulation were taken from prior studies prioritizing French data and are provided in Table S2, Supporting Information. Each scenario involved the modification of epidemiological parameters across the entire population for a 90-day period starting on day 120 in response to a surge in COVID-19 cases (see Table S3, Supporting Information). Two such modifications were considered separately and in combination: changes in population-wide antibiotic initiation rate by a factor a (representing modified healthcare-seeking behavior and/or prescribing behavior), and changes in pathogen transmissibility by a factor θ_β (representing population-wide lockdowns).

Acknowledgements

We thank Thomas Haschka for helpful comments.

Competing interests

Authors declare no competing interests.

Figures

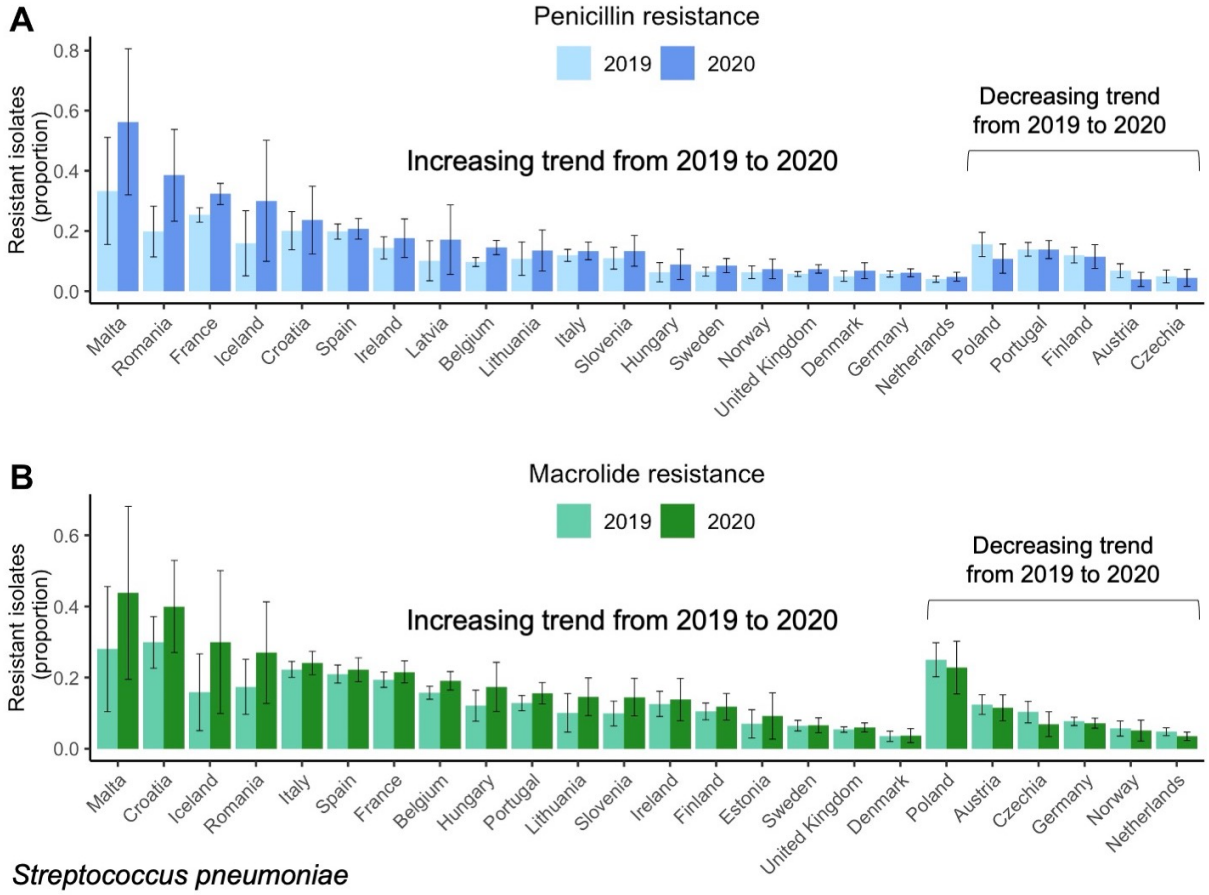
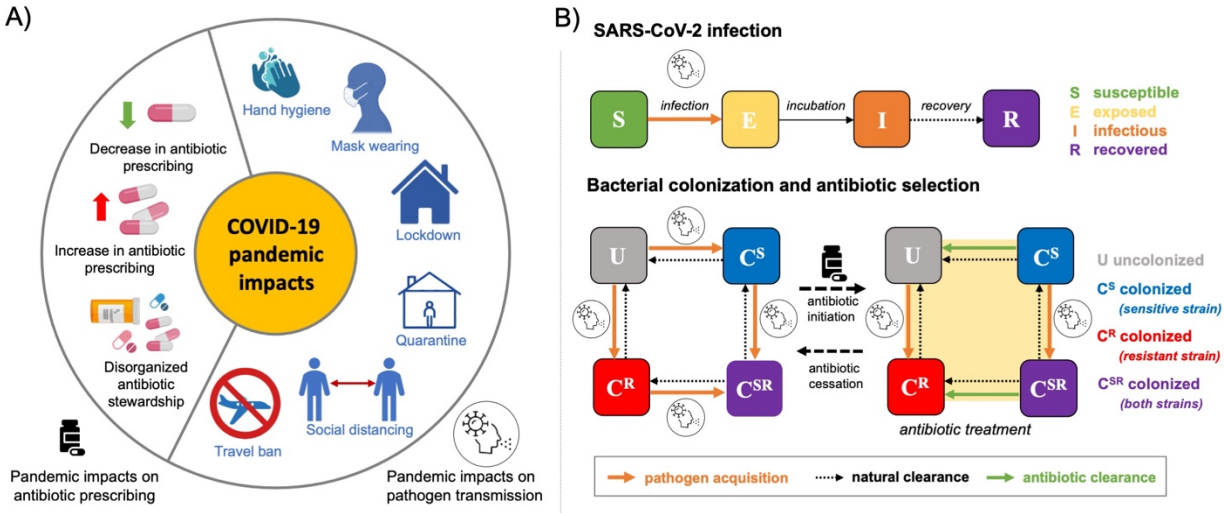


Figure 1. 2019-2020 antibiotic resistance trends in *Streptococcus pneumoniae* reported to EARS-Net (European Antimicrobial Resistance Surveillance Network) [16].
(A) Proportion of *S. pneumoniae* isolates resistant to penicillin across 24 European countries. **(B)** Proportion of *S. pneumoniae* isolates resistant to macrolides (azithromycin/ clarithromycin/ erythromycin) across 24 European countries. Error bars show 95% confidence intervals. Dataset available at https://github.com/alekskovacevic/antibiotic_resistance.



C)

Scenario:	S0	S1	S2	S3	S4	S5
Antibiotic prescribing (population-wide)	No change	↑	↓	No change	↑	↓
Lockdown (population-wide)	No lockdown	No lockdown	No lockdown	🏠	🏠	🏠

In all scenarios:
- quarantine of SARS-CoV-2 infected
- prophylactic antibiotic use among COVID-19 cases

Figure 2. A modeling framework for the selection and transmission of antibiotic-resistant bacteria in the community incorporating responses to the first wave of the COVID-19 pandemic. (A) The COVID-19 pandemic impacts modify community antibiotic prescribing and pathogen transmission. **(B)** Diagram depicting the main epidemiological processes included in the model, including SARS-CoV-2 infection, bacterial colonization, and antibiotic prescribing. Antibiotic initiation is assumed independent of bacterial carriage, reflecting widespread bystander selection for commensal bacteria like *S. pneumoniae*. **(C)** Pandemic scenarios (S0-S5) included in the model and implemented over a 90-day period combine factors leading to modifications in community antibiotic prescribing relative to the pre-pandemic period (no change/ increase/ decrease) and modifications in pathogen transmission due to presence or absence of lockdown. Quarantine and use of antibiotic prophylaxis assumed for a portion of symptomatic COVID-19 cases in all scenarios.

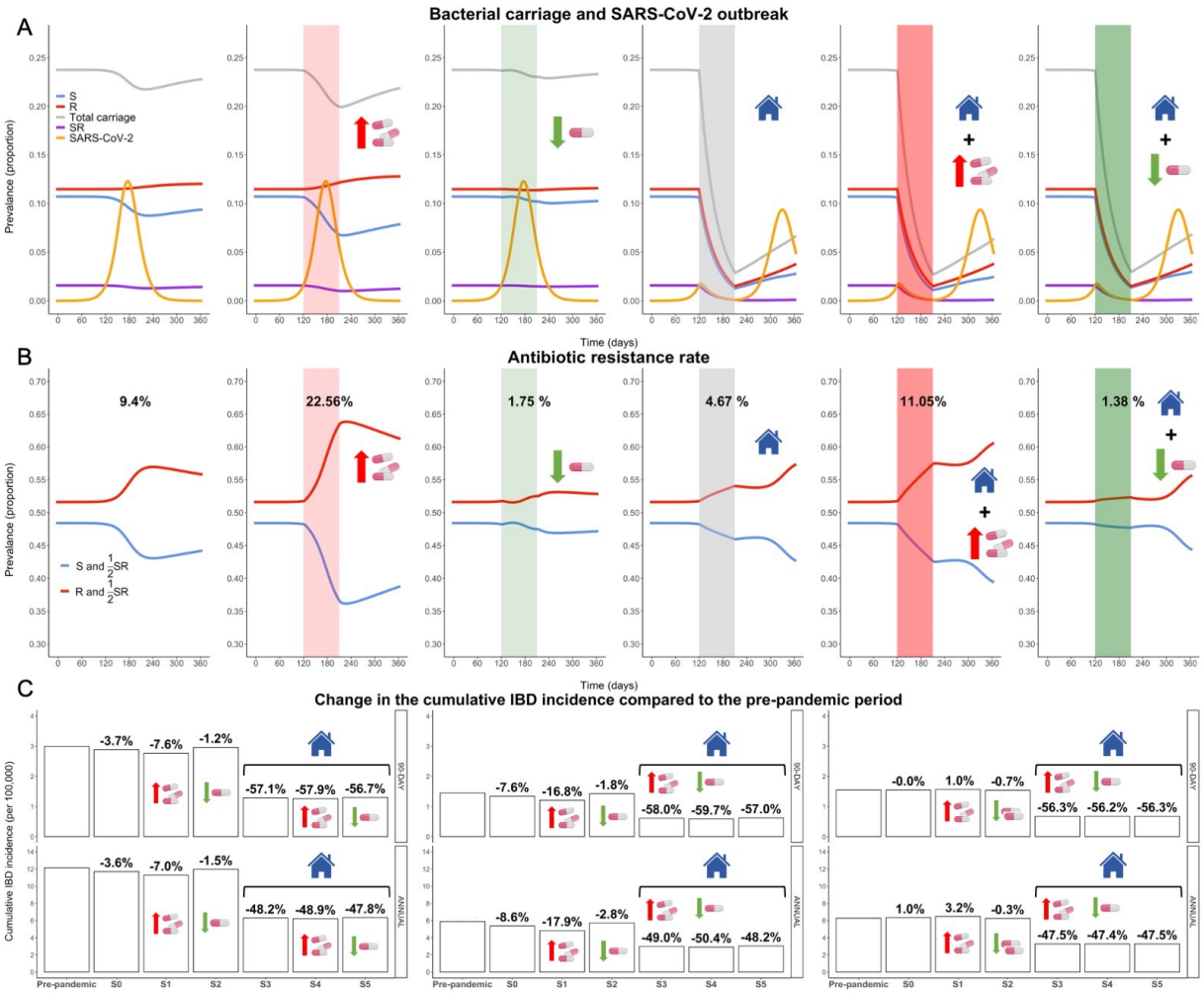


Figure 3. Impacts of pandemic scenarios on bacterial carriage, rates of antibiotic resistance, and incidence of invasive bacterial disease (IBD) in the community setting. **(A) Dynamics of bacterial carriage and SARS-CoV-2 infection.** Scenarios without lockdown implementation (S0, S1, S2) lead to a decrease in antibiotic-sensitive and an increase in antibiotic-resistant bacterial carriage. In scenario S2, reductions in overall community antibiotic prescribing are counteracted by the surge in individuals receiving antibiotic prophylaxis for COVID-19, resulting in a limited overall impact on bacterial epidemiology. Lockdown scenarios (S3, S4, S5) substantially reduce the prevalence of bacterial colonization. Highlighted time intervals (days 120-210) represent the 90-day period when lockdown and antibiotic use modifications were put in place. SARS-CoV-2 is introduced at initial time t=0. **(B) Rate of antibiotic resistance over time.** All scenarios are accompanied by an increase in the antibiotic resistance rate with a generally smaller magnitudes of increase in lockdown scenarios. A surge in community antibiotic prescribing coincident with the SARS-CoV-2 outbreak results in the greatest increase in antibiotic resistance rate (S1), which is somewhat controlled with lockdown implementation (S4). **(C) Change in the cumulative IBD incidence over 90 and 365 days.** Surge in the community antibiotic prescribing coincident with SARS-CoV-2 outbreak results in the greatest increases in the annual antibiotic-resistant IBD incidence (S1). Lockdown scenarios substantially reduce IBD incidence for both strains of bacteria. In the absence of lockdowns, all scenarios (S0, S1, S2) lead to reduced total IBD incidence, but increased antibiotic-resistant IBD incidence in some scenarios and decreased incidence in others. Bars labelled "pre-pandemic" represent cumulative 90-day and annual IBD incidence (per 100,000) assuming pre-pandemic scenario with no SARS-CoV-2 circulating in the population.

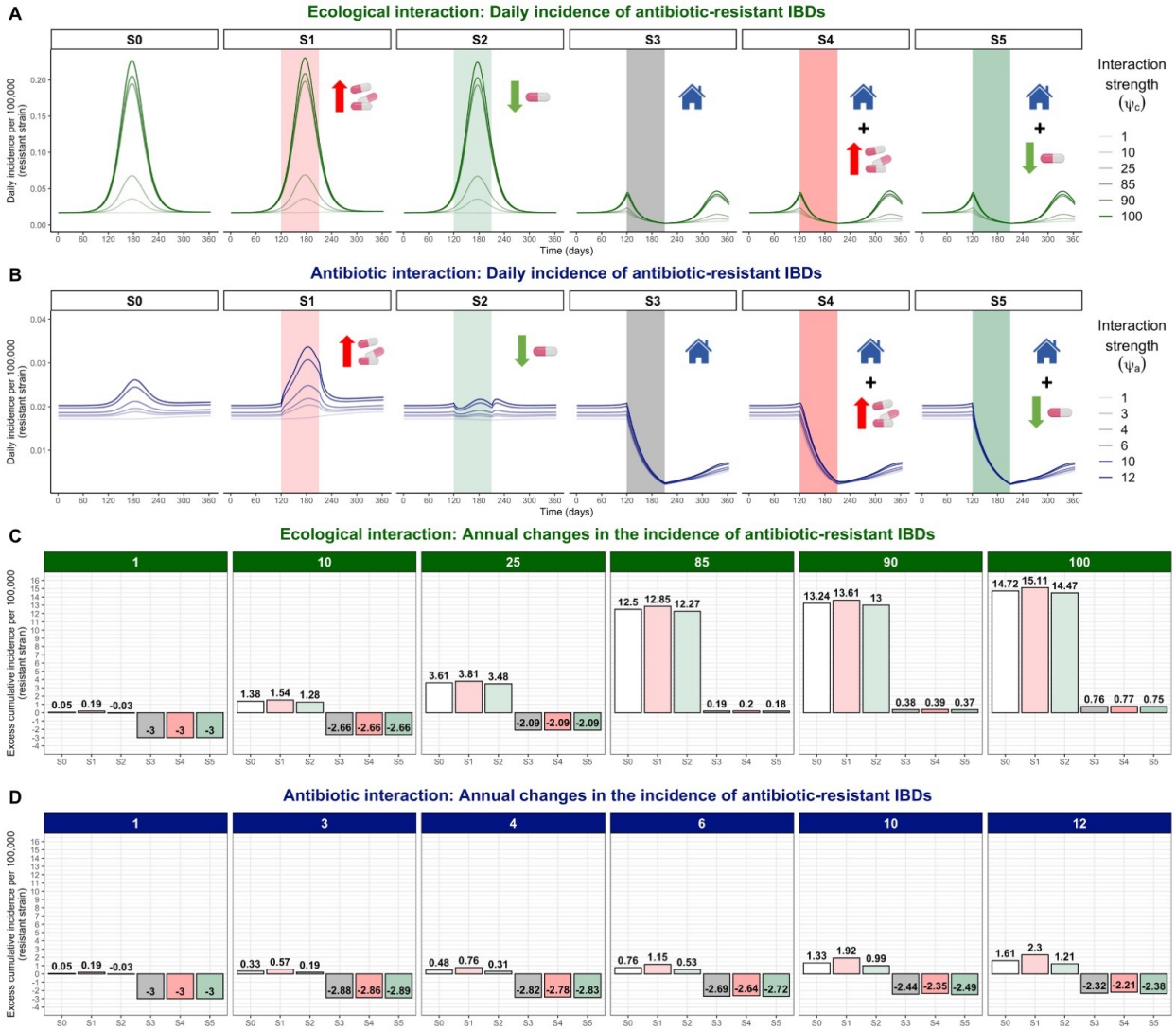


Figure 4. Within-host interactions favor the incidence of antibiotic-resistant invasive bacterial disease (IBD) across pandemic scenarios. (A) Impacts of ecological interactions. When SARS-CoV-2 infection leads to faster progression from bacterial colonization to disease (ψ_c>1), surges in COVID-19 cases lead to a greater daily incidence of antibiotic-resistant IBD, except in the context of lockdowns that dramatically reduce both the number of COVID-19 cases and bacterial colonization. **(B) Impacts of antibiotic interactions.** When antibiotic exposure leads to faster progression from antibiotic-resistant bacterial colonization to disease (ψ_a>1), surges in COVID-19 cases also lead to a greater daily incidence of antibiotic-resistant IBD, but to a smaller degree. Note different scales for y-axis in panels A and B. **(C) Annual change in cumulative IBD incidence due to synergistic within-host ecological interactions.** In the absence of lockdown (scenarios S0, S1, and S2), SARS-CoV-2 outbreaks increase annual antibiotic-resistant IBD incidence compared to the pre-pandemic period (6.26 cases per 100,000 inhabitants). If pathogen interaction strength is high (>85), total antibiotic-resistant IBD incidence increases even with lockdown implementation. **(D) Annual change in cumulative IBD incidence due to within-host antibiotic interactions.** Compared to the impacts of ecological interactions, impacts of within-host antibiotic interactions on annual change in antibiotic-resistant IBD incidence are smaller, but still noteworthy.

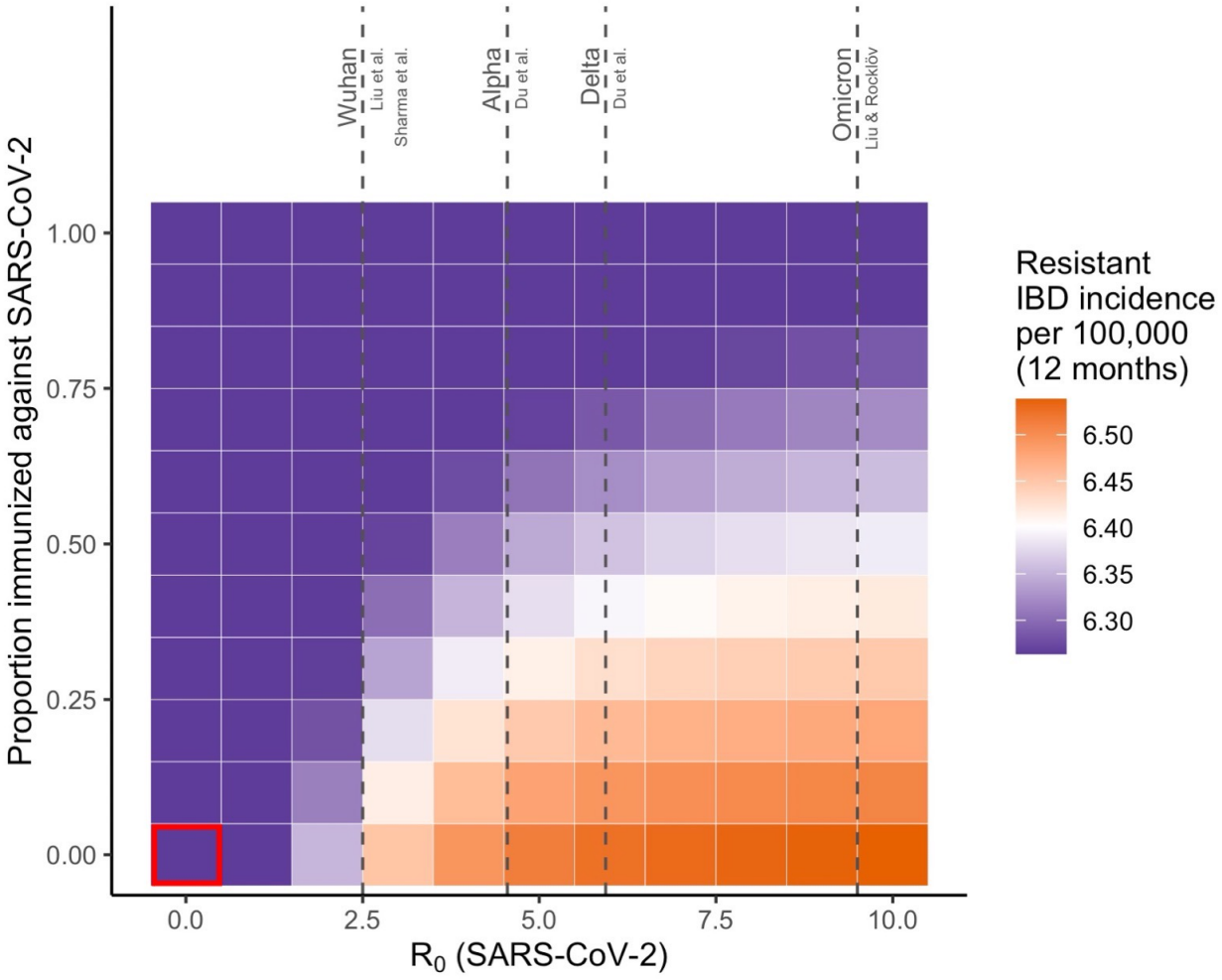


Figure 5. Annual cumulative incidence of antibiotic-resistant invasive bacterial disease (IBD) across different levels of R_0 for SARS-CoV-2 (x-axis) and population immunity against SARS-CoV-2 at simulation outset (y-axis) in scenario S0 (no lockdown, no changes in the antibiotic prescribing). The cumulative incidence of antibiotic-resistant IBD increases with the increasing values of R_0 for SARS-CoV-2 and decreases with the proportion of the population immunized against SARS-CoV-2 infection. The red square indicates baseline antibiotic-resistant IBD incidence when there is no SARS-CoV-2 circulating in the population and there is no immunity. R_0 estimates for different SARS-CoV-2 variants of concern (Wuhan, Alpha, Delta, and Omicron) are also depicted [63,64,75,76].

References

1. Brueggemann AB, Jansen van Rensburg MJ, Shaw D, McCarthy ND, Jolley KA, Maiden MCJ, et al. Changes in the incidence of invasive disease due to Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis during the COVID-19 pandemic in 26 countries and territories in the Invasive Respiratory Infection Surveillance Initiative: a prospective analysis of surveillance data. Lancet Digit Health. 2021;3: e360–e370. doi:10.1016/S2589-7500(21)00077-7
2. Palmer K, Monaco A, Kivipelto M, Onder G, Maggi S, Michel J-P, et al. The potential long-term impact of the COVID-19 outbreak on patients with non-communicable diseases in Europe: consequences for healthy ageing. Aging Clin Exp Res. 2020;32: 1189–1194. doi:10.1007/s40520-020-01601-4
3. Braunstein SL, Lazar R, Wahnich A, Daskalakis DC, Blackstock OJ. Coronavirus Disease 2019 (COVID-19) infection among people with human immunodeficiency virus in New York City: a population-level analysis of linked surveillance data. Clin Infect Dis. 2021;72: e1021–e1029. doi:10.1093/cid/ciaa1793
4. Chen Y, Li N, Lourenço J, Wang L, Cazelles B, Dong L, et al. Measuring the effects of COVID-19-related disruption on dengue transmission in southeast Asia and Latin America: a statistical modelling study. Lancet Infect Dis. 2022;22: 657–667. doi:10.1016/S1473-3099(22)00025-1
5. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399: 629–655. doi:10.1016/S0140-6736(21)02724-0
6. World Health Organization. Global action plan on antimicrobial resistance. World Health Organization. 2015 https://apps.who.int/iris/handle/10665/193736
7. Holmes AH, Moore LSP, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet. 2016;387: 176–187. doi:10.1016/S0140-6736(15)00473-0
8. CDC. COVID-19: U.S. Impact on antimicrobial resistance, special report 2022. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2022. https://www.cdc.gov/drugresistance/covid19.html
9. Knight GM, Glover RE, McQuaid CF, Olaru ID, Gallandat K, Leclerc QJ, et al. Antimicrobial resistance and COVID-19: intersections and implications. Elife. 2021;10. doi:10.7554/eLife.64139
10. Rusic D, Vilovic M, Bukic J, Leskur D, Seselja Perisin A, Kumric M, et al. Implications of COVID-19 pandemic on the emergence of antimicrobial resistance: adjusting the response to future outbreaks. Life (Basel). 2021;11. doi:10.3390/life11030220
11. Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect. 2020;26: 1622–1629. doi:10.1016/j.cmi.2020.07.016
12. Kadambari S, Goldacre R, Morris E, Goldacre MJ, Pollard AJ. Indirect effects of the covid-19 pandemic on childhood infection in England: population based observational study. BMJ. 2022;376: e067519. doi:10.1136/bmj-2021-067519
13. Finlay BB, Amato KR, Azad M, Blaser MJ, Bosch TCG, Chu H, et al. The hygiene hypothesis, the COVID pandemic, and consequences for the human microbiome. Proc Natl

Acad Sci USA. 2021;118. doi:10.1073/pnas.2010217118

14. Smith DRM, Opatowski L. COVID-19 containment measures and incidence of invasive bacterial disease. Lancet Digit Health. 2021;3: e331–e332. doi:10.1016/S2589-7500(21)00085-6

15. Årdal C, Baraldi E, Beyer P, Lacotte Y, Larsson DJ, Ploy M-C, et al. Supply chain transparency and the availability of essential medicines. Bull World Health Organ. 2021;99: 319–320. doi:10.2471/BLT.20.267724

16. WHO Regional Office for Europe/European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2022 – 2020 data. Copenhagen: WHO Regional Office for Europe; 2022.

17. Public Health France. EPIBAC public health bulletin: surveillance of invasive bacterial infections in 2020. https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infections-a-pneumocoque/documents/bulletin-national/bulletin-de-sante-publique-epibac-surveillance-des-infections-invasives-bacteriennes-en-2020. Accessed 1 Nov 2022.

18. Heesterbeek H, Anderson RM, Andreasen V, Bansal S, De Angelis D, Dye C, et al. Modeling infectious disease dynamics in the complex landscape of global health. Science. 2015;347: aaa4339. doi:10.1126/science.aaa4339

19. Opatowski L, Baguelin M, Eggo RM. Influenza interaction with cocirculating pathogens and its impact on surveillance, pathogenesis, and epidemic profile: A key role for mathematical modelling. PLoS Pathog. 2018;14: e1006770. doi:10.1371/journal.ppat.1006770

20. Birkegård AC, Halasa T, Toft N, Folkesson A, Græsbøll K. Send more data: a systematic review of mathematical models of antimicrobial resistance. Antimicrob Resist Infect Control. 2018;7: 117. doi:10.1186/s13756-018-0406-1

21. Ramsay DE, Invik J, Checkley SL, Gow SP, Osgood ND, Waldner CL. Application of dynamic modelling techniques to the problem of antibacterial use and resistance: a scoping review. Epidemiol Infect. 2018;146: 2014–2027. doi:10.1017/S0950268818002091

22. Domenech de Cellès M, Arduin H, Lévy-Bruhl D, Georges S, Souty C, Guillemot D, et al. Unraveling the seasonal epidemiology of pneumococcus. Proc Natl Acad Sci USA. 2019;116: 1802–1807. doi:10.1073/pnas.1812388116

23. Shrestha S, Foxman B, Dawid S, Aiello AE, Davis BM, Berus J, et al. Time and dose-dependent risk of pneumococcal pneumonia following influenza: a model for within-host interaction between influenza and Streptococcus pneumoniae. J R Soc Interface. 2013;10: 20130233. doi:10.1098/rsif.2013.0233

24. Arduin H, Domenech de Cellès M, Guillemot D, Watier L, Opatowski L. An agent-based model simulation of influenza interactions at the host level: insight into the influenza-related burden of pneumococcal infections. BMC Infect Dis. 2017;17: 382. doi:10.1186/s12879-017-2464-z

25. Fleming-Dutra KE, Taylor T, Link-Gelles R, Garg S, Jhung MA, Finelli L, et al. Effect of the 2009 influenza A(H1N1) pandemic on invasive pneumococcal pneumonia. J Infect Dis. 2013;207: 1135–1143. doi:10.1093/infdis/jit008

26. Weinberger DM, Simonsen L, Jordan R, Steiner C, Miller M, Viboud C. Impact of the 2009 influenza pandemic on pneumococcal pneumonia hospitalizations in the United States. J Infect Dis. 2012;205: 458–465. doi:10.1093/infdis/jir749

27. Jakobsson HE, Jernberg C, Andersson AF, Sjölund-Karlsson M, Jansson JK, Engstrand L.

Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. PLoS One. 2010;5: e9836. doi:10.1371/journal.pone.0009836

28. Stecher B, Maier L, Hardt W-D. "Blooming" in the gut: how dysbiosis might contribute to pathogen evolution. Nat Rev Microbiol. 2013;11: 277–284. doi:10.1038/nrmicro2989
29. Jenkins TC, Sakai J, Knepper BC, Swartwood CJ, Haukoos JS, Long JA, et al. Risk factors for drug-resistant *Streptococcus pneumoniae* and antibiotic prescribing practices in outpatient community-acquired pneumonia. Acad Emerg Med. 2012;19: 703–706. doi:10.1111/j.1553-2712.2012.01365.x
30. Bengoechea JA, Bamford CG. SARS-CoV-2, bacterial co-infections, and AMR: the deadly trio in COVID-19? EMBO Mol Med. 2020;12: e12560. doi:10.15252/emmm.202012560
31. Mirzaei R, Goodarzi P, Asadi M, Soltani A, Aljanabi HAA, Jeda AS, et al. Bacterial co-infections with SARS-CoV-2. IUBMB Life. 2020;72: 2097–2111. doi:10.1002/iub.2356
32. Aliberti S, Cook GS, Babu BL, Reyes LF, H Rodriguez A, Sanz F, et al. International prevalence and risk factors evaluation for drug-resistant *Streptococcus pneumoniae* pneumonia. J Infect. 2019;79: 300–311. doi:10.1016/j.jinf.2019.07.004
33. Duffy E, Thomas M, Hills T, Ritchie S. The impacts of New Zealand's COVID-19 epidemic response on community antibiotic use and hospitalisation for pneumonia, peritonsillar abscess and rheumatic fever. Lancet Reg Health West Pac. 2021;12: 100162. doi:10.1016/j.lanwpc.2021.100162
34. Chien Y-C, Lee Y-L, Liu P-Y, Lu M-C, Shao P-L, Lu P-L, et al. National surveillance of antimicrobial susceptibilities to dalbavancin, telavancin, tedizolid, eravacycline, omadacycline and other comparator antibiotics and serotype distribution of invasive Streptococcus pneumoniae isolates in adults: results from the Surveillance of Multicenter Antimicrobial Resistance in Taiwan (SMART) programme in 2017-2020. J Glob Antimicrob Resist. 2021;26: 308–316. doi:10.1016/j.jgar.2021.07.005
35. Teng JLL, Fok KMN, Lin KPK, Chan E, Ma Y, Lau SKP, et al. Substantial decline in invasive pneumococcal disease during coronavirus disease 2019 pandemic in Hong Kong. Clin Infect Dis. 2022;74: 335–338. doi:10.1093/cid/ciab382
36. Chen C, Zhu P, Zhang Y, Liu B. Effect of the "Normalized Epidemic Prevention and Control Requirements" on hospital-acquired and community-acquired infections in China. BMC Infect Dis. 2021;21: 1178. doi:10.1186/s12879-021-06886-y
37. Tomczyk S, Taylor A, Brown A, de Kraker MEA, El-Saed A, Alshamrani M, et al. Impact of the COVID-19 pandemic on the surveillance, prevention and control of antimicrobial resistance: a global survey. J Antimicrob Chemother. 2021;76: 3045–3058. doi:10.1093/jac/dkab300
38. Lemenand O, Coeffic T, Thibaut S, Colomb Cotinat M, Caillon J, Birgand G, et al. Decreasing proportion of extended-spectrum beta-lactamase among E. coli infections during the COVID-19 pandemic in France. J Infect. 2021; doi:10.1016/j.jinf.2021.09.016
39. Mannathoko N, Mosepele M, Gross R, Smith RM, Alby K, Glaser L, et al. Colonization with extended-spectrum cephalosporin-resistant Enterobacterales (ESCrE) and carbapenem-resistant Enterobacterales (CRE) in healthcare and community settings in Botswana: an antibiotic resistance in communities and hospitals (ARCH) study. Int J Infect Dis 2022;122:313–20. doi.org/10.1016/j.ijid.2022.06.004.
40. Peng Y, Zhang D, Chen T, Xia Y, Wu P, Seto W-K, et al. Gut microbiome and resistome changes during the first wave of the COVID-19 pandemic in comparison with pre-pandemic travel-related changes. J Travel Med. 2021;28. doi:10.1093/jtm/taab067

41. Rebelo JS, Domingues CPF, Dionisio F, Gomes MC, Botelho A, Nogueira T. COVID-19 lockdowns may reduce resistance genes diversity in the human microbiome and the need for antibiotics. Int J Mol Sci. 2021;22. doi:10.3390/ijms22136891
42. Smith DR, Temime L, Opatowski L. Microbiome-pathogen interactions drive epidemiological dynamics of antibiotic resistance: A modeling study applied to nosocomial pathogen control. Elife. 2021;10. doi:10.7554/eLife.68764
43. Högberg LD, Vlahović-Palčevski V, Pereira C, Weist K, Monnet DL, ESAC-Net study group, et al. Decrease in community antibiotic consumption during the COVID-19 pandemic, EU/EEA, 2020. Euro Surveill. 2021;26. doi:10.2807/1560-7917.ES.2021.26.46.2101020
44. Hussain AZ, Paudyal V, Hadi MA. Impact of the COVID-19 pandemic on the prescribing patterns of first-line antibiotics in English primary care: a longitudinal analysis of national prescribing dataset. Antibiotics (Basel). 2021;10. doi:10.3390/antibiotics10050591
45. Mamun AA, Saatchi A, Xie M, Lishman H, Blondel-Hill E, Marra F, et al. Community antibiotic use at the population level during the SARS-CoV-2 pandemic in British Columbia, Canada. Open Forum Infect Dis. 2021;8: ofab185. doi:10.1093/ofid/ofab185
46. Buehrle DJ, Wagener MM, Nguyen MH, Clancy CJ. Trends in outpatient antibiotic prescriptions in the United States during the COVID-19 pandemic in 2020. JAMA Netw Open. 2021;4: e2126114. doi:10.1001/jamanetworkopen.2021.26114
47. Zhang T, Shen X, Liu R, Zhao L, Wang D, Lambert H, et al. The impact of COVID-19 on primary health care and antibiotic prescribing in rural China: qualitative study. BMC Health Serv Res. 2021;21: 1048. doi:10.1186/s12913-021-07082-z
48. Ryu S, Hwang Y, Ali ST, Kim D-S, Klein EY, Lau EHY, et al. Decreased use of broad-spectrum antibiotics during COVID-19 epidemic in South Korea. J Infect Dis. 2021; doi:10.1093/infdis/jiab208
49. Andrews A, Bou-Antoun S, Guy R, Brown CS, Hopkins S, Gerver S. Respiratory antibacterial prescribing in primary care and the COVID-19 pandemic in England, winter season 2020-21. J Antimicrob Chemother. 2022;77: 799–802. doi:10.1093/jac/dkab443
50. Homeniuk R, Collins C. How COVID-19 has affected general practice consultations and income: general practitioner cross-sectional population survey evidence from Ireland. BMJ Open. 2021;11: e044685. doi:10.1136/bmjopen-2020-044685
51. Hsu J. How covid-19 is accelerating the threat of antimicrobial resistance. BMJ. 2020;369: m1983. doi:10.1136/bmj.m1983
52. Khouja T, Mitsantisuk K, Tadrous M, Suda KJ. Global consumption of antimicrobials: impact of the WHO Global Action Plan on antimicrobial resistance and 2019 coronavirus pandemic (COVID-19). J Antimicrob Chemother. 2022;77: 1491–1499. doi:10.1093/jac/dkac028
53. Alain Weill, Jérôme Drouin, David Desplas, Francois Cuenot, Rosemary Dray-Spira, Mahmoud Zureik. Usage des médicaments de ville en France durant l'épidémie de la Covid-19 –point de situation jusqu'au 25 avril 2021. EPI-PHARE - Groupement d'intérêt scientifique (GIS) ANSM-CNAM.
54. Parveen M, Molla MMA, Yeasmin M, Nafisa T, Barna AA, Ghosh AK. Evidences on irrational anti-microbial prescribing and consumption among COVID-19 positive patients and possible mitigation strategies: a descriptive cross sectional study. Bangladesh J Infect Dis. 2020; S3–S7. doi:10.3329/bjid.v7i00.50155
55. Bogdanić N, Močibob L, Vidović T, Soldo A, Begovac J. Azithromycin consumption

during the COVID-19 pandemic in Croatia, 2020. medRxiv. 2021; doi:10.1101/2021.10.31.21265714

56. Cong W, Poudel AN, Alhusein N, Wang H, Yao G, Lambert H. Antimicrobial Use in COVID-19 patients in the first phase of the SARS-CoV-2 pandemic: a scoping review. Antibiotics (Basel). 2021;10. doi:10.3390/antibiotics10060745
57. Adebisi YA, Jimoh ND, Ogunkola IO, Uwizeyimana T, Olayemi AH, Ukor NA, et al. The use of antibiotics in COVID-19 management: a rapid review of national treatment guidelines in 10 African countries. Trop Med Health. 2021;49: 51. doi:10.1186/s41182-021-00344-w
58. Garcia-Vidal C, Sanjuan G, Moreno-García E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect. 2021;27: 83–88. doi:10.1016/j.cmi.2020.07.041
59. Karami Z, Knoop BT, Dofferhoff ASM, Blaauw MJT, Janssen NA, van Apeldoorn M, et al. Few bacterial co-infections but frequent empiric antibiotic use in the early phase of hospitalized patients with COVID-19: results from a multicentre retrospective cohort study in The Netherlands. Infect Dis (Lond). 2021;53: 102–110. doi:10.1080/23744235.2020.1839672
60. Sender V, Hentrich K, Henriques-Normark B. Virus-induced changes of the respiratory tract environment promote secondary infections with Streptococcus pneumoniae. Front Cell Infect Microbiol. 2021;11: 643326. doi:10.3389/fcimb.2021.643326
61. Baggs J, Jernigan JA, Halpin AL, Epstein L, Hatfield KM, McDonald LC. Risk of subsequent sepsis within 90 days after a hospital stay by type of antibiotic exposure. Clin Infect Dis. 2018;66: 1004–1012. doi:10.1093/cid/cix947
62. Wong A, Barrero L, Goult E, Briga M, Kramer SC, Kovacevic A, et al. The interactions of SARS-CoV-2 with co-circulating pathogens: Epidemiological implications and current knowledge gaps. 2022. https://doi.org/10.48550/ARXIV.2205.07553.
63. Sharma V, Rai H, Gautam DNS, Prajapati PK, Sharma R. Emerging evidence on Omicron (B.1.1.529) SARS-CoV-2 variant. J Med Virol. 2022;94: 1876–1885. doi:10.1002/jmv.27626
64. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med. 2020;27. doi:10.1093/jtm/taaa021
65. ECDC. SARS-CoV-2 variants of concern as of 15 July 2022 [Internet]. 2022 [cited 15 Jul 2022]. Available: https://www.ecdc.europa.eu/en/covid-19/variants-concern
66. Langford BJ, So M, Raybardhan S, Leung V, Soucy J-PR, Westwood D, et al. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. Clin Microbiol Infect. 2021;27: 520–531. doi:10.1016/j.cmi.2020.12.018
67. Monnet DL, Harbarth S. Will coronavirus disease (COVID-19) have an impact on antimicrobial resistance? Euro Surveill. 2020;25. doi:10.2807/1560-7917.ES.2020.25.45.2001886
68. Henig O, Kehat O, Meijer SE, Chikly A, Weiss-Meilik A, Egoz E, et al. Antibiotic use during the COVID-19 pandemic in a tertiary hospital with an ongoing antibiotic stewardship program. Antibiotics (Basel). 2021;10. doi:10.3390/antibiotics10091056
69. Seaton RA, Gibbons CL, Cooper L, Malcolm W, McKinney R, Dundas S, et al. Survey of antibiotic and antifungal prescribing in patients with suspected and confirmed COVID-19 in Scottish hospitals. J Infect. 2020;81: 952–960. doi:10.1016/j.jinf.2020.09.024

70. Van Laethem J, Wuyts S, Van Laere S, Dirkx S, Seyler L, Mertens R, et al. Antibiotic prescriptions targeting bacterial respiratory infections in admitted patients with COVID-19: a prospective observational study. Infect Dis Ther. 2021;10: 2575–2591. doi:10.1007/s40121-021-00535-2
71. Smith DRM, Shirreff G, Temime L, Opatowski L. Collateral impacts of pandemic COVID-19 drive the nosocomial spread of antibiotic resistance. BioRxiv 2022. doi.org/10.1101/2022.08.15.503946.
72. Colijn C, Cohen T, Fraser C, Hanage W, Goldstein E, Givon-Lavi N, et al. What is the mechanism for persistent coexistence of drug-susceptible and drug-resistant strains of Streptococcus pneumoniae? J R Soc Interface. 2010;7: 905–919. doi:10.1098/rsif.2009.0400
73. Mulberry N, Rutherford A, Colijn C. Systematic comparison of coexistence in models of drug-sensitive and drug-resistant pathogen strains. Theor Popul Biol. 2020;133: 150–158. doi:10.1016/j.tpb.2019.12.001
74. Soetaert K, Petzoldt T, Setzer RW. Solving Differential Equations in R: Package deSolve. Journal of Statistical Software. 2010. doi:10.18637/jss.v033.i09+
75. Liu Y, Rocklöv J, The reproductive number of the Delta variant of SARS-CoV-2 is far higher compared to the ancestral SARS-CoV-2 virus, Journal of Travel Medicine. 2021; 28. doi.org/10.1093/jtm/taab124
76. Du Z, Liu C, Wang C, Xu L, Xu M, Wang L, Bai Y, Xu X, Lau EHY, Wu P, Cowling BJ. Reproduction numbers of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants: a systematic review and meta-analysis. Clin Infect Dis. 2022;75(1):e293-e295. doi: 10.1093/cid/ciac137