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Full title: COVID-19 pandemic responses may impact the spread of antibiotic-resistant bacteria: a modelling study

Short title: COVID-19 pandemic responses and antibiotic resistance

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 (AK)

¶These authors contributed equally to this work.

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Abstract

COVID-19 pandemic responses have dramatically modified the global ecological and epidemiological landscape of many infectious diseases. However, the pandemic's impacts on antimicrobial resistance (AMR) are currently poorly understood and lack data. While surges in COVID-19 cases during the first wave of the pandemic may have exacerbated AMR, decreases in antibiotic use may have had the opposite effect. To disentangle how pandemic impacts such as lockdowns and modified antibiotic prescribing may affect AMR, we developed a mathematical model formalizing simultaneous transmission of SARS-CoV-2 and colonization with a bacterial pathogen across six pandemic scenarios. We used simulation to assess the effect of each scenario on the bacterial carriage prevalence, antibiotic resistance rate, and the invasive bacterial disease (IBD) incidence, using parameters based on the commensal community bacterium *Streptococcus pneumoniae*.

Pandemic scenarios without community-wide lockdowns all resulted in a decrease in carriage prevalence of antibiotic-sensitive bacteria and an increase in the prevalence of antibiotic-resistant bacteria, while the addition of a population-wide lockdown resulted in a large reduction in colonization prevalence and IBD incidence for both strains (>70%). This translated to an increase in the antibiotic resistance rate across all scenarios to varying degrees, with lingering effects after the cessation of COVID-19 response measures. In the absence of lockdown, a population-wide surge in antibiotic prescribing coincident with the peak in SARS-CoV-2 infection resulted in the greatest increases in resistance rate (23%) and resistant IBD incidence (6%). Within-host interactions, SARS-CoV-2 variants, and population immunity are found to further drive the magnitude of pandemic impacts on resistant IBD incidence. Sensitivity analyses suggest that the extent of such impacts likely varies across different bacterial species. Although real-life scenarios

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are significantly more complicated, our findings suggest that COVID-19 pandemic responses may significantly impact antibiotic resistance in the community and support the need for monitoring resistance during pandemic waves.

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Author Summary

Antimicrobial resistance (AMR) is a leading threat to global health. The ongoing COVID-19 pandemic has occurred during global efforts to combat AMR, and pandemic responses implemented to slow SARS-CoV-2 transmission have dramatically affected the incidence of common viral and bacterial respiratory infections at a global scale. However, impacts of the COVID-19 pandemic on AMR and the incidence of invasive bacterial disease (IBD) caused by antibiotic-resistant bacteria are still being uncovered. Here, we use mathematical modelling to explore how different pandemic scenarios accounting for variation in lockdown implementation and antibiotic use in the community may affect antibiotic-resistant bacteria. We found that lockdown implementation substantially reduces the number of annual cases of resistant IBD (over 70%), although the proportion of resistant bacteria among carriers is expected to increase when prophylactic antibiotics are prescribed in response to SARS-CoV-2 infection. We also found that a population-wide surge in antibiotic prescribing in the absence of lockdown may contribute to a large increase (6%) in the number of IBD cases caused by antibiotic-resistant bacteria, while the effect of reduced antibiotic use is negligible. However, such impacts likely vary depending on the bacterial species considered, within-host interactions, SARS-CoV-2 variants, and population immunization levels.

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Introduction

Responses to the COVID-19 pandemic have generated unprecedented changes in population mixing, care-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 COVID-19 on antimicrobial resistance (AMR) remain poorly understood.

AMR is one of the leading threats to global health. In 2019, AMR in clinically relevant bacteria was 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], the prevention and control of AMR are challenged by a wide range of biological, behavioural, 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 COVID-19 mitigation.

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 [8–10]. On the other hand, interventions implemented to control SARS-CoV-2 transmission –

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including lockdowns, physical distancing, travel restrictions, face mask use, and improved hygiene practices – may have concomitantly reduced the spread of antimicrobial-resistant pathogens [1,11]. 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 [8,12–14].

Mathematical models are useful tools for the simulation and quantification of transmission dynamics, particularly when data are limited or lacking [15]. 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 behaviour) [16–18]. Bacteria-virus interaction models have been used previously to disentangle the public health consequences of interactions between pathogens such as influenza and *Streptococcus pneumoniae* [19–21]. 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 S1.1).

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To disentangle how the COVID-19 pandemic has impacted the epidemiology of antibiotic-resistant bacteria, we propose a transmission model that simultaneously describes infection with SARS-CoV-2 and colonization with both sensitive and resistant bacteria, and which includes mechanistic impacts of SARS-CoV-2 infection burden on epidemiological parameters. Bacterial colonization is parameterized based on the commensal respiratory bacterium *S. pneumoniae*. This species was chosen because of its high rate of carriage in community settings, heterogenous levels of multidrug resistance across countries and demographic groups, and because its transmission was effectively – but inadvertently – controlled by COVID-19 lockdowns in 2020 [1]. We evaluate six different pandemic scenarios, each accounting for impacts of COVID-19 on antibiotic prescribing and inter-individual contact behaviour. Through simulation, we assess how these scenarios impact the prevalence of bacterial carriage, levels of antibiotic resistance, and incidence of the invasive bacterial disease (IBD) caused by antibiotic-resistant bacteria. Furthermore, we assess how IBD incidence may be additionally impacted by factors such as within-host viral interactions, emerging SARS-CoV-2 variants, and varying levels of population immunity.

Methods

Impacts of the COVID-19 pandemic – such as modified healthcare-seeking behaviour, administration of antibiotic prophylaxis to COVID-19 patients, and implementation of non-pharmaceutical interventions – may be expected to impact selection for the spread of antibiotic-resistant bacteria by modifying antibiotic prescribing and pathogen transmission (Fig 1A). To test these mechanisms, we developed an epidemiological, compartmental, deterministic transmission model describing infection with SARS-CoV-2 and colonization with commensal respiratory bacteria in a large, well-mixed human population. Using this model, we evaluated six pandemic

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scenarios by simulating disrupted antibiotic prescribing and the presence or absence of a population-wide lockdown over a 90-day period (Fig 1B and Supporting Information S2).

Model description

SARS-CoV-2 infection is modelled 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 (Fig S1, Supporting Information).

Individuals in the model can also 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 (Table S1, Supporting Information). 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 (C^S) colonization at a rate ω while having no direct impact on (C^R) colonization.

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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* [22,23].

We make two further assumptions about individuals with active SARS-CoV-2 infection. First, a certain proportion of infectious individuals receives antibiotic prophylaxis for COVID-19, resulting in an increased rate of antibiotic initiation by a factor A. Second, a certain proportion of infectious individuals undergoes quarantine, resulting in reduced transmission rates for SARS-CoV-2 and both strains of bacteria by a factor q. This model is illustrated and formalized through a system of ordinary differential equations (ODEs) detailed in Supporting Information S2.1 and S2.2.

Simulating different pandemic scenarios

Using this model, we explored how SARS-CoV-2 outbreaks impact bacterial carriage prevalence, antibiotic resistance rates, and IBD incidence in a simulated population of 100,000 individuals. First, assuming that the bacteria under study are endemic, ODEs were integrated numerically until endemic equilibria were found (see parameter values in Table S1, Supporting Information). Second, using equilibrium states as initial conditions, SARS-CoV-2 was introduced on day 0 (t=0), and ODEs were again integrated numerically, this time across six pandemic scenarios. Each scenario involves 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 S2, Supporting Information). Two such modifications were considered separately and in combination: changes in antibiotic initiation rate by a factor a (representing modified healthcare-

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seeking behaviour and/or prescribing behaviour), and changes in pathogen transmissibility by a factor θ_β (representing population-wide lockdowns).

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 (S2.4, Supporting Information). Finally, we estimated the relative change in cumulative IBD incidence (total incidence and incidence due to each strain) over 90 days and 365 days, as compared to the pre-pandemic period (i.e., over the same durations but assuming no SARS-CoV-2 circulation in the population).

Within-host interactions

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 favour bacterial disease (e.g., see impacts of influenza infection on invasive pneumococcal disease [24,25]), while increased antibiotic exposure in response to COVID-19 may also favour the within-host outgrowth of antibiotic-resistant bacteria [26,27]. To incorporate these mechanisms in our model, we included two within-host interaction terms: the co-infection 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

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antibiotic-resistant strain [28–31]. The equation 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 S2.5, Supporting Information.

Emerging SARS-CoV-2 variants and immunization

Impacts of SARS-CoV-2 on antibiotic-resistant IBD incidence may 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%).

Sensitivity analyses

Since there are more than 100 distinct serotypes of *S. pneumoniae* and the duration of pneumococcal carriage varies among different age groups, we conducted two separate sensitivity analyses. In the first one, we varied the duration of bacterial carriage [20, 30, and 50 days] and in the second one, we varied the fitness cost of resistance [0, 0.03, and 0.05] while maintaining the same R_0 value of bacterial colonization to see how changes in these parameters may impact IBD incidence and antibiotic resistance. Considering that this model could apply to any resistant bacterial pathogen that may interact with SARS-CoV-2 (and not only *S. pneumoniae*), we assessed changes in IBD incidence for different combinations of parameters by varying R_0 value of bacterial colonization [1.2, 1.3, and 1.4] and bacterial carriage duration [20, 30, and 50 days] simultaneously.

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Results

Pandemic waves increase resistance rates, although lockdowns limit bacterial colonization and disease

Pandemic scenarios not including lockdown (scenarios S0, S1, and S2) all resulted in a decrease in carriage of antibiotic-sensitive bacteria and an increase in antibiotic-resistant bacteria (Fig 2A-C, left panels). A population-wide surge in antibiotic prescribing coincident with the peak in SARS-CoV-2 infection (scenario S1) moderately decrease total bacterial carriage but result in the greatest increases in resistance rate (more than 22%) (Fig 2B, middle panel). While total and antibiotic-sensitive IBD incidence decrease, annual antibiotic-resistant IBD incidence increase up to 6% compared to pre-pandemic levels (Fig 2B, right panel). In scenario S2, reductions in overall community prescribing are counteracted by the surge in individuals receiving antibiotic prophylaxis for COVID-19, resulting in a limited overall impact on bacterial epidemiology (Fig 2C).

The addition of a population-wide lockdown (S3, S4, and S5) not only limits the transmission of SARS-CoV-2 but also results in a large reduction in colonization prevalence and IBD incidence for both strains of bacteria, regardless of the antibiotic use modification implemented. However, all scenarios were accompanied by an increase in the antibiotic resistance rate over the 90-day period with the magnitude of increase depending on antibiotic use in the community (Fig 2D-F). 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

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scenarios including lockdown, annual IBD incidence decreases substantially (up to 70%), with approximately 67% fewer annual cases of antibiotic-resistant IBD.

Within-host interactions favour the incidence of antibiotic-resistant invasive bacterial disease

On the one hand, when SARS-CoV-2 infection is assumed to favour progression from colonization to disease (ψ_c>1), surges in COVID-19 lead to substantial increases in the incidence of antibiotic-resistant IBD (Fig 3A and 3B). Indeed, a rate of disease progression increased by a factor ψ_c=10, in approximately 1.1 additional cases/100,000 over the course of one year in the absence of lockdown (scenarios S0, S1, and S2, Fig 3B). On the other hand, when antibiotic use is assumed to favour progression from antibiotic-resistant colonization to disease (ψ_a>1), surges in SARS-CoV-2 infection coincides with transient increases in incidence of antibiotic-resistant IBD, except when surges coincide with reduced antibiotic prescribing (e.g., scenarios S0, S1 vs. scenario S2, Fig 3C). An increased rate of disease progression by ψ_a=10, leads to an increase by approximately 1.6 annual additional cases/100,000 of the incidence of antibiotic-resistant bacterial disease in the absence of lockdown (scenario S1, Fig 3D).

Emerging SARS-CoV-2 variants and population immunity

Varying 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 increasing R_0 values of SARS-CoV-2 and decreases with the population immunity against SARS-CoV-2 infection (Fig 4).

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Sensitivity to the duration of bacterial carriage

Changing the duration of bacterial carriage while maintaining bacterial R_0 did not change the main trends observed. However, scenarios implemented over a 90-day period had a greater impact on both total and resistant IBD incidence when the duration of bacterial carriage was shorter (d = 20 days) (Fig S3A).

Sensitivity to the fitness cost of resistance

When assuming a lower fitness cost of resistance (c) but holding all other bacterial parameters equal, antibiotic-resistant bacteria were more prevalent in the population, as expected, but the relative impacts of pandemic scenarios on IBD incidence and antibiotic resistance rates were smaller (Fig S4). Moreover, in the absence of any resistance cost (c = 0) the antibiotic resistance rate decreased during the intervention period in scenario S5 (i.e., with lockdown and reduced community antibiotic prescribing), because resistant carriage prevalence decreased faster than sensitive carriage prevalence, before rising again due to rising antibiotic exposure and COVID-19 prophylaxis. Having a lower cost of resistance also meant that it took more time for resistant IBD incidence and resistance rate to return to the pre-pandemic levels (>3 years).

Other bacterial species

In all scenarios implementing lockdown (S3-S5), resistant IBD incidence did not experience a major change across different bacterial R_0 values during a 90-day period (Fig S6). However, the effect of lockdown was most beneficial in reducing the annual resistant IBD incidence for bacteria with shorter carriage duration and the lower R_0 values. Similar trends were observed for total IBD incidence across all lockdown scenarios (Fig S7). The opposite was true

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for bacteria with longer carriage durations and higher values of R_0. Bacteria with shorter carriage duration and higher R0 value experienced the greatest increase in annual resistant IBD incidence in the scenario with increased antibiotic use in the community (S1, Fig S6), although the total number of IBD cases was reduced (S1, Fig S7).

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 behavioural responses to the COVID-19 pandemic may 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 may have on epidemiological dynamics of antibiotic resistance. We found that IBD incidence may either increase or decrease, depending on how overall antibiotic prescribing in the community changes in response to COVID-19, and on implementation of measures to control viral transmission. Impacts of COVID-19 on IBD incidence and antibiotic resistance rate may linger long after extinction of SARS-CoV-2 outbreaks and the cessation of control measures, and the magnitude of such impacts for any particular bacterium may depend on its duration of carriage and the strength of potential fitness costs of resistance.

Impacts of the COVID-19 pandemic on epidemiological trends of antibiotic-resistant bacteria in community settings are still being uncovered. A 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 [32]. However, many studies have reported trends in the incidence of

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community-acquired bacterial infections since the onset of the pandemic. A comprehensive global analysis 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 the 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]. Across these studies, data on the relative impacts of COVID-19 on drug-sensitive versus drug-resistant isolates have been unavailable. However, data from France suggest a reduced proportion of extended spectrum-beta lactam producers among *Escherichia coli* urinary isolates in primary care patients and nursing home residents after the lockdown in March 2020 [37].

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 [38], with heterogeneity between countries and antibiotic classes. Similar temporal trends were observed in England [39], Canada [40], the United States [41], China [42], South Korea [43] and New Zealand [33]. These trends may largely be explained by reduced incidence of seasonal respiratory tract infections, and reduced primary care consultations [44,45]. 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 [46]. In a global analysis of antimicrobial sales, Khouja et al. found

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that antibiotic consumption initially increased by approximately 7% in March 2020, prior to subsequent declines through to August 2020 [47]. 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 [48–50]. Several studies have now characterized the wide range of antibiotics provided as prophylaxis to both mild and severe COVID-19 patients in 2020 [51,52], 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 shows that antibiotic resistance rates increase with surges in SARS-CoV-2 infections when there is a corresponding increase in antibiotic use due to COVID-19 prophylaxis, as expected, but that lockdowns can mitigate this increasing trend to some degree. To date, few studies have reported resistance rates in carriage from healthy patients during the COVID-19 waves. 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 of resistance genes against β-lactam antibiotics during the first wave of the pandemic compared to a pre-pandemic period [53]. One simulation study suggests that lockdowns and associated reductions in mobility and human contact (informed by Portuguese mobility data) may have led to

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reductions in the diversity of antibiotic resistance genes found in the human microbiome [54]. Such disruptions to human microbiota may have further downstream impacts on colonization resistance and the propensity for antibiotic-resistant bacterial symbionts to transmit [12,55].

One promising outcome of scenarios assuming a decrease in antibiotic use is that increases in antibiotic resistance were minor (Fig 2C and F), while changes in resistant IBD incidence were either negligible (Fig 2C) or negative (Fig 2F). However, for simplicity we simulated reduction of antibiotic use during a single 90-day period only. Real-life scenarios are significantly more complicated and may involve multiple alterations of these factors at different points in time. Over longer timescales, and in the context of successive COVID-19 outbreaks with heterogeneous public health responses and impacts on human behaviour, 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 [10,56,57], 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 [58], but antibiotic use may also favour progression to IBD for patients colonized with drug-resistant strains [59]. The results presented here (Fig 3) suggest that such overlapping within-host interactions could have important consequences for the IBD incidence during waves of COVID-19, but future studies are needed to better understand the magnitude of these interactions for *S. pneumoniae* and other commensal, facultatively pathogenic bacteria.

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Emerging SARS-CoV-2 variants, which often vary in their 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 $R_0 = 2.5$ [60,61] 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 [62], 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 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 4). 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 was structured and parameterized based upon *S. pneumoniae*, but other bacterial species might have been impacted by the COVID-19 outbreak in unique ways. Epidemiological and natural history characteristics of Enterobacterales, for example, strongly differ (e.g., longer

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bacterial colonization duration, greater carriage prevalence in the population) relative to respiratory bacteria. However, sensitivity analyses showed that our main conclusions still held across different pandemic scenarios when using different colonization durations but had impacts of different magnitude, suggesting that global trends predicted by our model might hold true for other bacterial species. A study by Zhu et al. showed that observed trends of bloodstream infections (BSI) greatly varied depending on the bacterial species considered, as well as settings: during the first wave, community-acquired *Escherichia coli* BSI felt below pre-pandemic levels whereas hospital-acquired methicillin-resistant Staphylococcus aureus BSI had a large increase in numbers compared to pre-pandemic [63].

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. 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. Ultimately, a lack of available data precluded us from accounting for such levels of complexity. Future work would benefit from integrating real-world data on AMR trends of different bacterial species during multiple COVID-19 waves. Although such data are currently lacking, especially in community settings, longitudinal microbiome sequencing may facilitate better understanding of the impacts of COVID-19 on the transmission of resistance throughout this period. This model can be applied to a wide variety of bacteria and epidemiological scenarios in the community, such as bacterial winter outbreaks as well as more endemic pathogens like ESBL-Enterobacterales.

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Our model and discussion have 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, a highly selective environment, favoured by extensive antibiotic use in COVID-19 patients and disruption of antibiotic stewardship programmes, may have predisposed patients and healthcare workers to increased antibiotic resistance carriage. In a meta-analysis conducted on studies published up to June 2020 [64], an estimated 68-81% of patients hospitalized with COVID-19, and 74-94% of patients in intensive care, were treated with antibiotics. In addition, workplace disorganization (e.g., low healthcare worker-patient ratios, overcrowded facilities, longer hospital stays for COVID-19 patients) may have led to decreased antibiotic resistance surveillance and detection, promoting the dissemination of resistant organisms through rooms and wards [8,65]. However, this increase has been mitigated or even absent in settings where antibiotic stewardship programs were implemented, as soon as March 2020, to lower antimicrobial use [66–68]. Increased hygiene through extensive personal protective equipment use and patient isolation also led to decreased antibiotic-resistant organisms in healthcare facilities [8,65]. Specific models dedicated to the analysis of such impact 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.

Conclusion

Using a mathematical modelling approach, we analysed how behavioural responses to the COVID-19 pandemic may differentially impact AMR in the community. In a context where data is still sorely lacking and more studies are required to evaluate the consequences of the pandemic

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on the global burden of AMR, this work demonstrates how mathematical modelling can help improve our understanding of the complex, overlapping links between COVID-19 and the epidemiology of antibiotic resistance.

Author Contributions

Conceptualization: LO, LT, AK, DRMS. Formal Analysis: AK, DRMS. Investigation: AK, DRMS, ER, SN, PH. Methodology: AK, DRMS, LO, LT. Supervision: LO, LT. Writing-Original Draft Preparation: AK, DRMS, ER, SN, PH. Writing- Review & Editing: AK, DRMS, ER, SN, PH, LT, LO.

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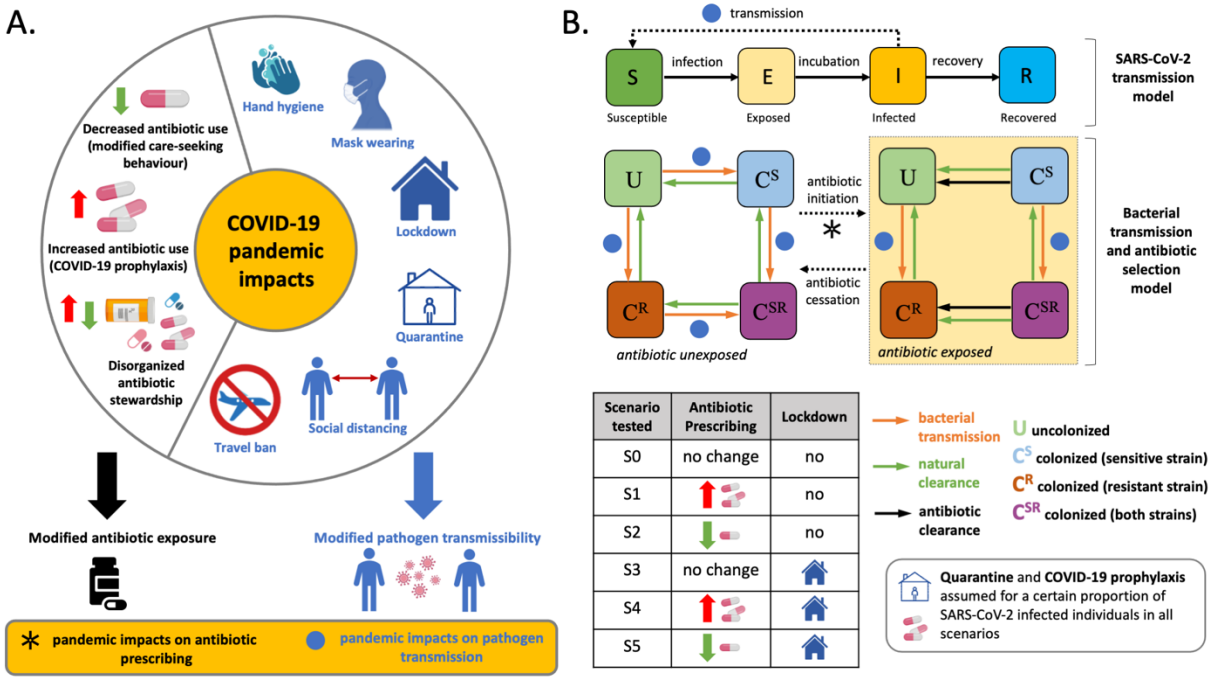
Figures



Scenario tested	Antibiotic Prescribing	Lockdown
S0	no change	no
S1	↑	no
S2	↓	no
S3	no change	⌂
S4	↑	⌂
S5	↓	⌂

Fig 1.

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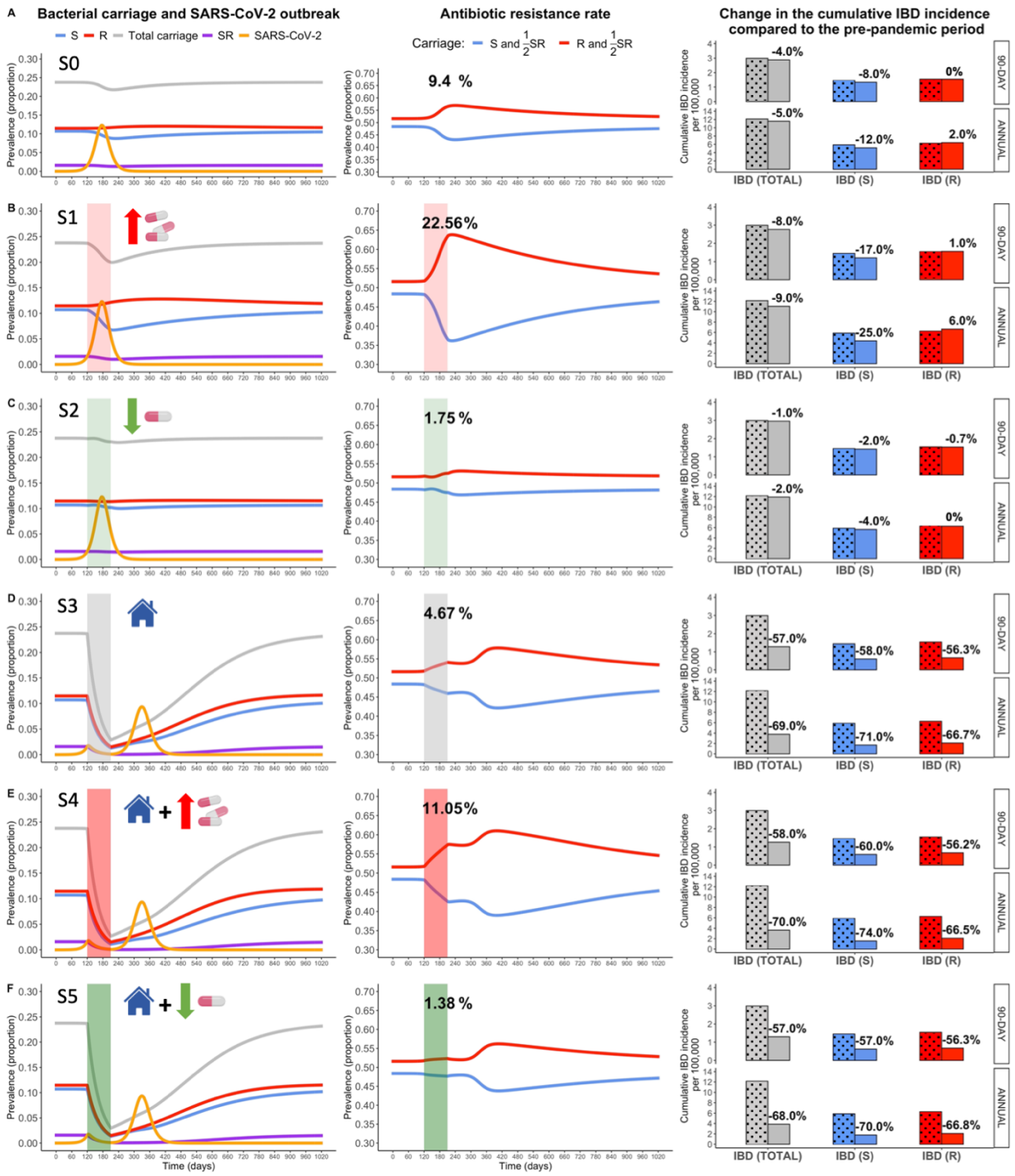

Fig 2.

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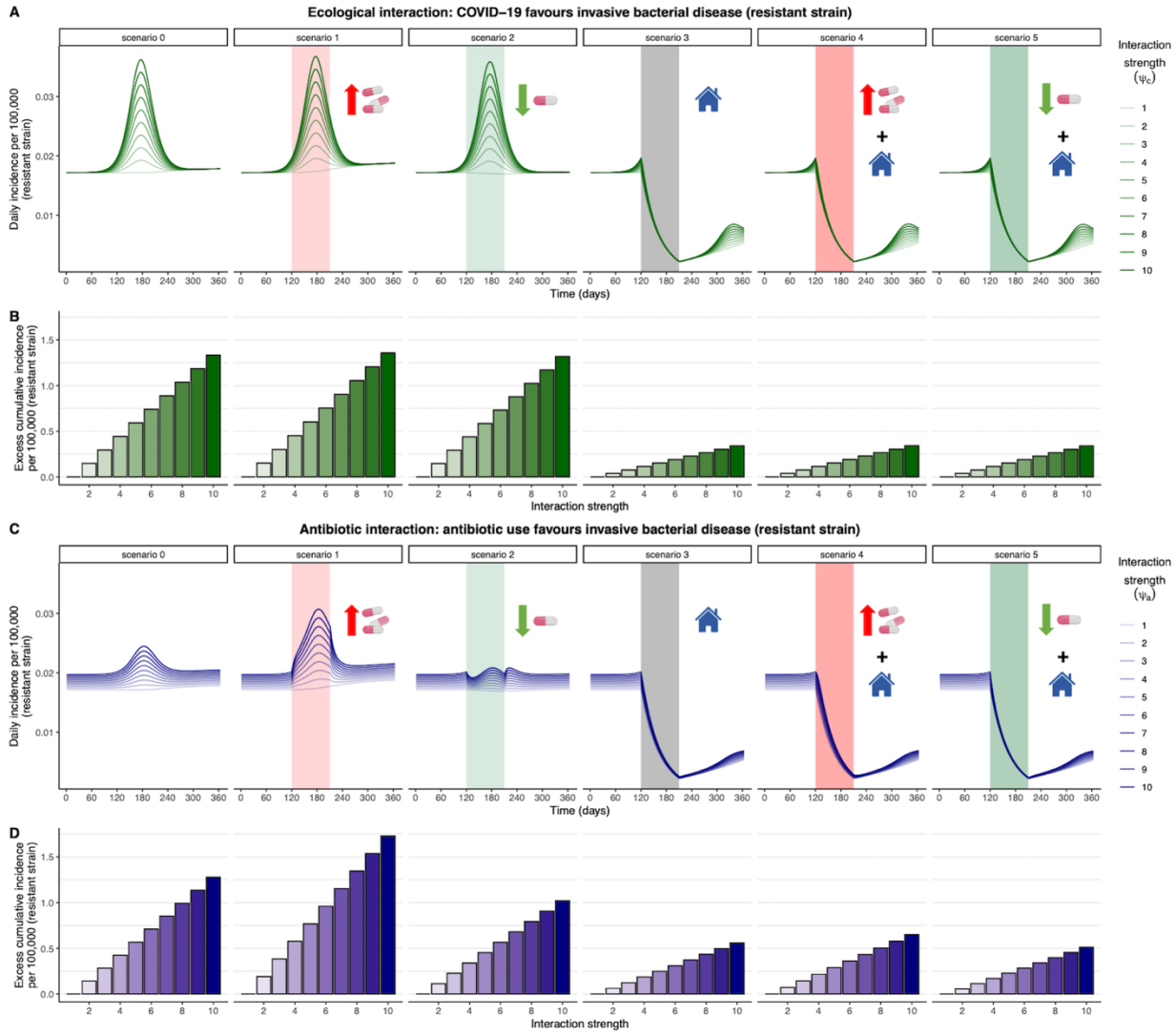

Fig 3.

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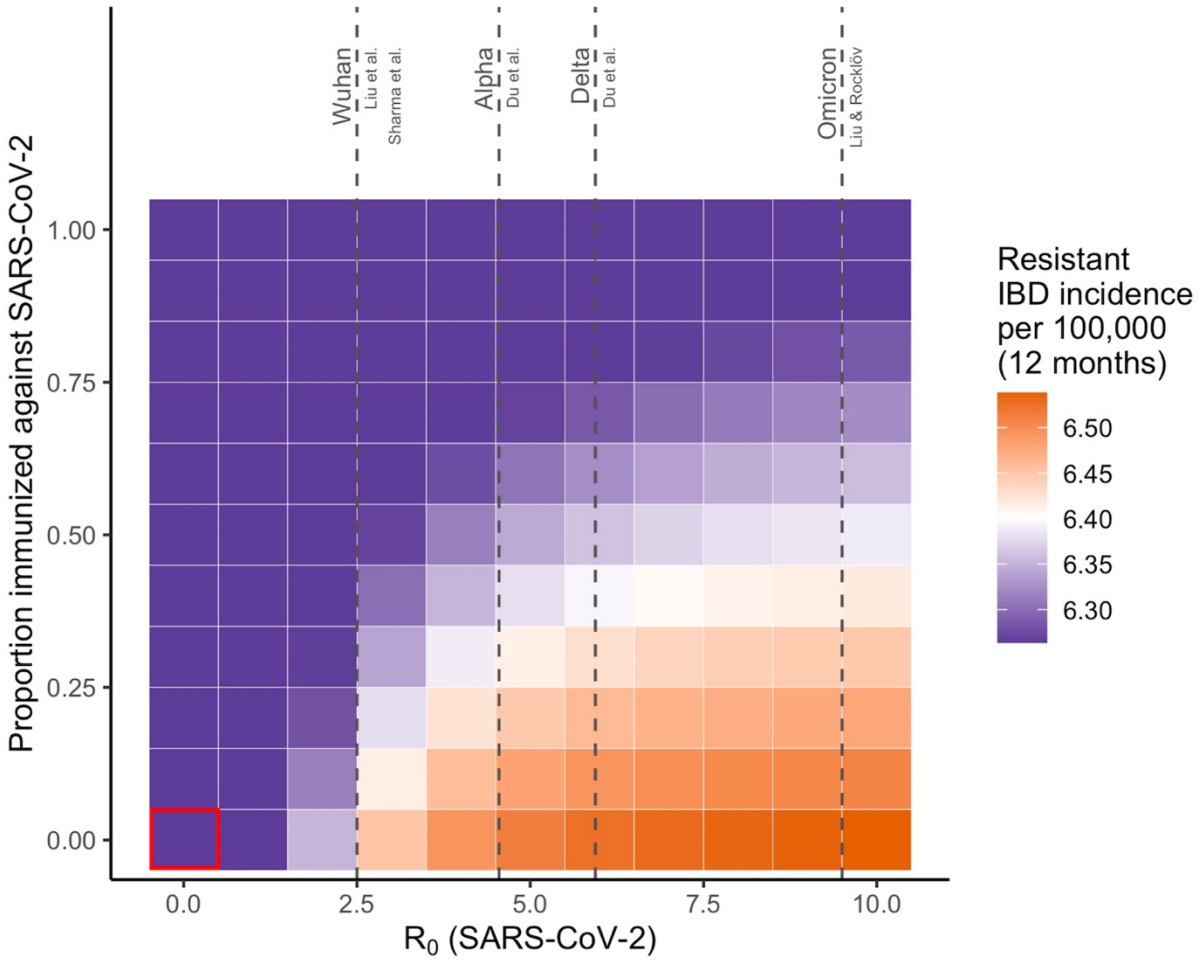

Fig 4.

Figure Legends

Fig 1. COVID-19 pandemic impacts, model schematic, and community scenarios of antibiotic prescribing and lockdown implementation.

A. COVID-19 pandemic impacts on antibiotic prescriptions and pathogen transmissibility B. Schematic of the model describing simultaneous co-circulation and transmission of SARS-CoV-2 infection and bacterial carriage. Scenarios implemented over a 90-day period combine factors leading to modifications in antibiotic prescribing in the community relative to the pre-pandemic

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period (no change/increase/decrease) and pathogen transmissibility (presence or absence of lockdown). Stars and blue circles represent parameters potentially impacted by COVID-19 burden due, respectively, to modified antibiotic exposure and modified pathogen transmissibility. Model equations, parameters, and a complete list of modelling assumptions are provided in S2, Supporting Information.

Fig 2. The effect of different community scenarios during the SARS-CoV-2 outbreak on the bacterial carriage, antibiotic resistance, and invasive bacterial disease (IBD) incidence over a period of 90 days and one year.

A. Scenario 0 (baseline scenario): no lockdown and no modification in the antibiotic use B. Scenario 1: no lockdown with increased antibiotic use C. Scenario 2: no lockdown with decreased antibiotic use D. Scenario 3: lockdown with no modification in the antibiotic use E. Scenario 4: lockdown with increased antibiotic use F. Scenario 5: lockdown with decreased antibiotic use. Highlighted time intervals represent a 90-day intervention period (days 120-210) of lockdown and antibiotic use modifications. SARS-CoV-2 is introduced at initial time t=0. Columns with dotted pattern represent pre-pandemic baseline - cumulative 90-day and annual IBD incidence (per 100,000).

Fig 3. Within-host interactions favour the incidence of antibiotic-resistant invasive bacterial disease (IBD) across different scenarios.

When SARS-CoV-2 infection leads to faster progression from bacterial colonization to disease (ψ_c>1), surges in COVID-19 lead to a greater daily incidence of disease (A) and a greater cumulative burden of disease (B). When antibiotic exposure leads to faster progression from

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antibiotic resistant bacterial colonization to disease (ψ_a>1), surges in COVID-19 can also lead to a greater daily incidence of disease (C) and a greater cumulative burden of disease (D). Here, simulations were truncated at time t=365 days to evaluate cumulative impacts of interactions after COVID-19 outbreak. Panels (B) and (D) show excess annual antibiotic-resistant IBD incidence (per 100,000) due to within-host interactions.

Fig 4. Annual cumulative incidence of antibiotic-resistant invasive bacterial disease (IBD) across different combinations of R_0 (SARS-CoV-2) values and levels of population immunity at SARS-CoV-2 introduction.

Assuming that there is no lockdown implementation and no change in the antibiotic prescribing in the community (except for COVID-19 prophylaxis in a certain proportion of infected individuals) – scenario S0 – the cumulative incidence of antibiotic-resistant IBD increases with the increasing R_0 values of SARS-CoV-2 (x-axis) and decreases with the increasing proportion of the population immunized against SARS-CoV-2 infection (y-axis). Square with the red border indicates baseline antibiotic-resistant IBD incidence when there is no SARS-CoV-2 circulating in the population and no immunization. R_0 estimates for different SARS-CoV-2 variants of concern (Wuhan, Alpha, Delta, and Omicron) are also depicted.