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

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

## 47 **Abstract**

48  
49 Non-pharmaceutical COVID-19 interventions have dramatically modified the transmission  
50 dynamics of pathogens other than SARS-CoV-2. In many countries, reports have shown that  
51 implementation of population-wide lockdowns led to substantial reductions in invasive bacterial  
52 disease caused by respiratory bacteria such as *Streptococcus pneumoniae*. By contrast, most  
53 European countries reported increased antibiotic resistance among *S. pneumoniae* isolates from  
54 2019 to 2020. To disentangle impacts of the COVID-19 pandemic responses on bacterial  
55 epidemiology in the community setting, we propose a mathematical model formalizing  
56 simultaneous transmission of SARS-CoV-2 and antibiotic-sensitive and -resistant strains of *S.*  
57 *pneumoniae*. The impacts of population-wide lockdowns, isolation of COVID-19 cases, changes  
58 in antibiotic consumption due to altered healthcare-seeking behavior and prophylactic use in the  
59 early pandemic were explored across six pandemic scenarios. Our model was able to reproduce  
60 the observed trends, showing how lockdowns substantially reduce invasive pneumococcal disease  
61 incidence, while surges in prophylactic antibiotic prescribing favor disease caused by resistant  
62 strains. Surges in COVID-19 cases were associated with increased antibiotic resistance rates across  
63 all pandemic scenarios. Introducing synergistic within-host SARS-CoV-2-pneumococcus  
64 interactions further exacerbates increasing incidence of resistant disease. When data availability is  
65 limited, mathematical modeling can help improve our understanding of the complex interactions  
66 between COVID-19 and antibiotic resistance.

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## 93 Introduction

94  
95 Responses to the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute  
96 respiratory syndrome coronavirus 2 (SARS-CoV-2) have generated unprecedented changes in  
97 population mixing, healthcare-seeking behavior, and infection prevention and control practices,  
98 which have dramatically modified the ecology and epidemiology of infectious diseases at a global  
99 scale. Collateral impacts of COVID-19 on epidemiological dynamics have been reported for  
100 common viral and bacterial respiratory infections, sexually transmitted infections like HIV, vector-  
101 borne infections like dengue, and even non-communicable diseases [1–4]. However, impacts of  
102 the COVID-19 pandemic on antimicrobial resistance (AMR) remain poorly understood, in part  
103 due to delayed or unavailable data.

104  
105 AMR is one of the leading threats to global health. In 2019, AMR in clinically relevant  
106 bacteria were estimated to be associated with 4.95 million deaths, of which 1.27 million were  
107 directly attributable to resistance [5]. Although AMR continues to receive international attention  
108 through initiatives like the World Health Organization’s Global Action Plan on AMR [6], AMR  
109 control is challenged by a wide range of biological, behavioral, and economic factors, from the  
110 evolution of novel multidrug-resistance genes, to pervasive inappropriate prescribing, to intensive  
111 prophylactic use in food-animal feedlots [7]. The ongoing COVID-19 pandemic has occurred  
112 during global efforts to combat AMR and has diverted considerable public health resources,  
113 redirecting them instead towards SARS-CoV-2 prevention and mitigation. According to The  
114 Centers for Disease Control and Prevention (CDC) report, repurposing of AMR surveillance  
115 infrastructure for COVID-19 surveillance led to substantial reductions in whole genome  
116 sequencing of bacterial isolates causing delay in AMR data reporting in the United States [8].

117  
118 Several studies have raised concern about COVID-19-associated antimicrobial overuse or  
119 misuse exacerbating AMR, particularly during and following the first wave of the pandemic taking  
120 into consideration frequent administration of antibiotic prophylaxis, especially azithromycin, to  
121 COVID-19 patients [9–11]. On the other hand, non-pharmaceutical interventions (NPIs)  
122 implemented to control SARS-CoV-2 transmission – including lockdowns, physical distancing,  
123 travel restrictions, face mask use, and improved hygiene practices – may have had the opposite  
124 effect, concomitantly reducing the spread of antimicrobial-resistant pathogens [1,12]. A wide  
125 range of other pandemic impacts, such as reduced surveillance capacity, disrupted antimicrobial  
126 supply chains, and modified composition of the human microbiota, may have, and continue to  
127 influence the epidemiological dynamics of AMR in ways that are as-yet poorly understood [9,13–  
128 15].

129  
130 Three years after the onset of the pandemic, data on global AMR trends remain relatively  
131 sparse. However, a joint 2022 report on antimicrobial resistance during 2020 from World Health  
132 Organization (WHO) and European Centre for Disease Prevention and Control (ECDC) has  
133 reported AMR trends across 29 European countries for eight antibiotic-resistant bacterial  
134 pathogens of concern, including *Streptococcus pneumoniae* [16]. *S. pneumoniae* has a high rate of  
135 carriage in community settings, heterogenous levels of multidrug resistance across countries and  
136 demographic groups, and its transmission was effectively – but inadvertently – controlled by  
137 COVID-19 lockdowns in 2020 [1]. In France, annual incidence of pneumococcal disease fell from  
138 10.5 to 5.8 per 100,000 inhabitants from 2019 to 2020, representing a decline of 44.8% [17]. On

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

141  
142 Mathematical models are useful tools for the simulation and quantification of infectious  
143 disease dynamics, particularly when data are limited or lacking [18]. When factors driving the  
144 transmission of one pathogen also impact another – as in the present context of the COVID-19  
145 pandemic and its impacts on antibiotic use and antibiotic-resistant bacteria – a co-circulation model  
146 is necessary to better understand mechanistic links between coinciding pathogens. Such co-  
147 circulation models must be carefully tailored to the respective pathogens under study to accurately  
148 represent the biological mechanisms that drive their transmission across scales, including  
149 ecological dynamics within the host (e.g., competitive interactions with other organisms) and  
150 epidemiological drivers at the between-host level (e.g., inter-individual contact behavior) [19–21].  
151 Bacteria-virus interaction models have been used previously to disentangle the public health  
152 consequences of interactions between pathogens such as influenza and *S. pneumoniae* [22-24].  
153 However, in a systematic PubMed search conducted on 1 August 2022, we identified no  
154 epidemiological models describing the simultaneous transmission of SARS-CoV-2 and antibiotic-  
155 resistant bacteria (see Supporting Information, S1).

156  
157 To disentangle how the COVID-19 pandemic has impacted the epidemiological dynamics  
158 of antibiotic resistance, we propose a mathematical model that formalizes simultaneous  
159 transmission of SARS-CoV-2 and both antibiotic-sensitive and -resistant strains of *S. pneumoniae*  
160 in the community setting, and which includes mechanistic impacts of SARS-CoV-2 infection  
161 burden on epidemiological parameters. We evaluate six different pandemic scenarios, each  
162 accounting for impacts of SARS-CoV-2 outbreak on healthcare-seeking, antibiotic prescribing and  
163 inter-individual contact behavior in the early months of the COVID-19 pandemic. Through  
164 simulation, we assess how these scenarios impact the prevalence of bacterial carriage, levels of  
165 antibiotic resistance in the community, and incidence of invasive bacterial disease (IBD) caused  
166 by both antibiotic-sensitive and -resistant bacteria. Furthermore, we assess how IBD incidence  
167 may be additionally impacted by other factors, such as within-host pathogen interactions, emerging  
168 SARS-CoV-2 variants with higher transmissibility, and varying levels of population immunity.

## 169 170 **Results**

### 171 172 **Observed antibiotic resistance trends in *Streptococcus pneumoniae***

173  
174 In routine surveillance data reported to the European Antimicrobial Resistance Surveillance  
175 Network (EARS-Net), most European countries reported an increase in antibiotic resistance in *S.*  
176 *pneumoniae* from 2019 to 2020, including increases in the proportion of invasive isolates with  
177 phenotypic resistance to both penicillin (Fig 1A) and macrolides (Fig 1B). At the same time, the  
178 total number of reported isolates decreased by 44.3% from 2019 to 2020 in the European  
179 Union/European Economic Area (EU/EEA) [16] (see Supporting Information, Table S1).  
180 Responses to the COVID-19 pandemic – such as implementation of NPIs, modified antibiotic  
181 prescribing due to changes in healthcare-seeking behavior, and prescription of prophylactic  
182 antibiotics to COVID-19 patients – are hypothesized to underlie these observed trends (Fig 2A).

183  
184

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

186  
187 To test mechanistic impacts of responses to the COVID-19 pandemic on bacterial epidemiology,  
188 we developed a compartmental, deterministic transmission model describing infection with SARS-  
189 CoV-2 and colonization with commensal respiratory bacteria in a large, well-mixed human  
190 population (Fig 2B). We assume that some individuals with symptomatic COVID-19 undergo  
191 isolation, reducing their transmission rates for SARS-CoV-2 and both strains of bacteria by a factor  
192  $q$ , and also receive antibiotic prophylaxis for COVID-19, which increases their rate of antibiotic  
193 initiation by a factor  $A$  across simulation time ( $t = 365$  days) (see Methods for more detail and  
194 Supporting Information S2). Parameterizing this model to *S. pneumoniae*, we then explored  
195 epidemiological impacts of six distinct pandemic scenarios in which, over a 90-day period  
196 coincident with the first wave of COVID-19, we simulated (i) population-wide increases or  
197 decreases in antibiotic prescribing and (ii) the presence or absence of a population-wide lockdown  
198 (Fig 2C; see Supporting Information Table S3 for assumed parameter values).

199  
200 Using model simulations, we assessed how SARS-CoV-2 outbreaks and corresponding  
201 pandemic scenarios may impact bacterial carriage prevalence, antibiotic resistance rates, and IBD  
202 incidence in a simulated population of 100,000 individuals. Several epidemiological outcomes  
203 were calculated from simulation outputs: (i) daily prevalence of bacterial colonization (the  
204 proportion of individuals in the population colonized with antibiotic-sensitive bacteria, antibiotic-  
205 resistant bacteria, or co-colonized with both), (ii) daily prevalence of SARS-CoV-2 infection (the  
206 proportion of infectious individuals), and (iii) the antibiotic resistance rate, defined as the number  
207 of individuals colonized with the resistant strain over the total number colonized (Supporting  
208 Information, S2.4). Finally, we estimated the relative change in cumulative IBD incidence (total  
209 incidence and incidence due to each strain) during the intervention period (90 days) and change in  
210 the annual IBD incidence, as compared to a pre-pandemic period (i.e., over the same durations but  
211 assuming no SARS-CoV-2 circulation in the population).

### 212 213 **Model simulations of antibiotic resistance and IBD incidence in *Streptococcus pneumoniae***

214  
215 Model simulations of the pandemic scenarios without lockdown implementation (scenarios S0,  
216 S1, and S2) all result in a decrease in carriage of antibiotic-sensitive bacteria and an increase in  
217 antibiotic-resistant bacteria (Fig 3A). Total bacterial colonization prevalence in the population  
218 generally declines during SARS-CoV-2 outbreaks. However, all scenarios are accompanied by an  
219 increase in the antibiotic resistance rate, with the magnitude of increase depending on the pandemic  
220 scenario (Fig 3B). A population-wide surge in antibiotic prescribing coincident with the peak in  
221 SARS-CoV-2 infection (scenario S1) moderately decreases total bacterial carriage but results in  
222 the greatest increase in the resistance rate (+ 22.6%). While total and antibiotic-sensitive IBD  
223 incidence both decrease in scenario S1 (Fig 3C), annual incidence of antibiotic-resistant disease  
224 increases (+3.2%) compared to the pre-pandemic levels (Fig 3C). In scenario S2, reductions in  
225 overall community antibiotic prescribing are counteracted by the surge in individuals receiving  
226 antibiotic prophylaxis for COVID-19, resulting in a limited overall impact on bacterial  
227 epidemiology (Fig 3A).

228  
229 The addition of a population-wide lockdown (scenarios S3, S4, and S5) not only limits the  
230 transmission of SARS-CoV-2 but also results in a large reduction in colonization prevalence for

231 both strains of bacteria, regardless of a potential population-wide increase or decrease in antibiotic  
232 use. As a large share of the population remains susceptible to SARS-CoV-2 infection at the end of  
233 the lockdown, a second wave of COVID-19 follows several months later, which further increases  
234 the resistance rate due to COVID-19 prophylaxis. However, in all scenarios implementing a 90-  
235 day lockdown, total annual incidence of IBD decreases substantially (-57% during lockdown and  
236 -48% annually, on average) (Fig 3C). Outcomes of the scenarios that combine lockdown  
237 implementation along with the changes in community antibiotic prescribing, isolation and  
238 prophylactic antibiotic use in COVID-19 cases (S3, S4, or S5) are consistent with the IBD decrease  
239 reported in France, where annual incidence of pneumococcal disease (per 100,000 inhabitants) fell  
240 from 10.5 to 5.8 from 2019 to 2020, representing a decline of 44.8% [17], including the overall  
241 44.3% reported decrease in invasive isolates in the European Union/European Economic Area  
242 (EU/EEA) [16].

243

### 244 **Within-host interactions may favor incidence of antibiotic-resistant IBD during SARS-** 245 **CoV-2 outbreaks**

246

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

259

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

275

276

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

278  
279 Impacts of SARS-CoV-2 on antibiotic-resistant IBD incidence may also depend on the  
280 characteristics of locally circulating SARS-CoV-2 variants and their immune escape properties.  
281 To account for potential mediating impacts of SARS-CoV-2 transmissibility and population  
282 immunity, in simulations we varied (i) values of  $R_0$  (basic reproduction number) for SARS-CoV-  
283 2 ( $0 \leq R_0 \leq 10$ ) and (ii) the proportion of the population immunized against SARS-CoV-2  
284 infection at simulation outset (from 0 % to 100 %).

285  
286 Assuming different SARS-CoV-2 variant characteristics in the simplest scenario S0 (no  
287 lockdown, no community-level change in antibiotic prescribing, and no within-host interactions),  
288 we found that the annual cumulative incidence of antibiotic-resistant IBD increases with the higher  
289  $R_0$  values of SARS-CoV-2, which is led by antibiotic prophylaxis for COVID-19 and decreases  
290 with the population immunity against SARS-CoV-2 infection (Fig 5).

## 291 **Discussion**

292  
293  
294 We propose a novel co-circulation model describing the spread of SARS-CoV-2 and antibiotic-  
295 resistant bacteria in a community setting and show how behavioral responses to the COVID-19  
296 pandemic can differentially impact AMR. By simulating a range of lockdown and antibiotic use  
297 scenarios, we highlight potential direct and indirect consequences that outbreaks of novel viral  
298 respiratory pathogens like SARS-CoV-2 can have on epidemiological dynamics of antibiotic  
299 resistance. We find that incidence of invasive bacterial disease may either increase or decrease,  
300 depending on how overall antibiotic prescribing in the community changes in response to COVID-  
301 19, on implementation of measures to control viral transmission, and on potential within-host  
302 interactions between co-circulating pathogens. Impacts of COVID-19 on disease incidence and  
303 antibiotic resistance rate may linger long after extinction of SARS-CoV-2 outbreaks and the  
304 cessation of control measures.

305  
306 Many studies have reported trends on the incidence of community-acquired bacterial  
307 infections since the onset of the pandemic. A comprehensive global analysis by Brueggemann et  
308 al. using national surveillance data from 26 countries identified substantial and sustained  
309 reductions in *S. pneumoniae* incidence after the implementation of COVID-19 control measures  
310 such as lockdowns and travel restrictions [1]. Our model scenarios that most closely fit with early  
311 2020 are scenarios including strict lockdown, with or without change in antibiotic use, which led  
312 to similar estimates of the relative (%) reduction in IBD incidence as observed in Brueggemann et  
313 al. [1]. Similar findings have been observed in the context of sentinel community-acquired  
314 infections in New Zealand [33], invasive pneumococcal disease (IPD) in Taiwan [34] and Hong  
315 Kong [35], and lower respiratory tract infection in China [36]. However, across these studies, data  
316 on the relative impacts of COVID-19 on drug-sensitive versus drug-resistant isolates have been  
317 unavailable.

318  
319 Impacts of the COVID-19 pandemic on rates of antibiotic resistance among common  
320 bacterial pathogens in community settings are still being uncovered. European trends reported to  
321 EARS-Net (Fig 1) are perhaps the most comprehensive data available. An earlier study by  
322 Tomczyk et al. and the WHO AMR Surveillance Network from March 2021 highlighted that most



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

331  
332 Several studies have nonetheless reported resistance rates among colonizing bacteria from  
333 primary care and community settings since the onset of the COVID-19 pandemic. Data from  
334 primary care patients and nursing home residents in France have suggested a reduced proportion  
335 of extended spectrum-beta lactam producers among *Escherichia coli* urinary isolates after the  
336 national lockdown instated in March 2020 [38]. In community residents in Botswana, the  
337 percentage of Enterobacterales isolates resistant to carbapenems and extended-spectrum  
338 cephalosporins also reduced after lockdowns [39]. Conversely, using shotgun metagenomics on  
339 fecal samples, Peng et al. showed a decrease in Actinobacteria richness in the microbiota of healthy  
340 adults from Hong-Kong and an increase in resistance genes against  $\beta$ -lactam antibiotics during the  
341 first wave of the pandemic compared to a pre-pandemic period [40]. Regarding pandemic impacts  
342 on microbiome composition, one simulation study suggests that lockdowns and associated  
343 reductions in mobility and human contact (informed by Portuguese mobility data) may have led to  
344 reductions in the diversity of antibiotic resistance genes found in the human microbiome [41].  
345 Such disruptions to human microbiota may have further downstream impacts on colonization  
346 resistance and the propensity for antibiotic-resistant bacterial symbionts to transmit [13,42].

347  
348 Relative to data on AMR trends in the community since the emergence of COVID-19, data  
349 on antibiotic prescribing in primary care are more widely available. Globally, community  
350 antibiotic prescribing dropped during the first year of the COVID-19 pandemic compared to the  
351 pre-pandemic period. In Europe, antibiotic consumption decreased by almost 20% in 2020  
352 compared to 2019 [43], with heterogeneity between countries and antibiotic classes. Similar  
353 temporal trends were observed in England [44], Canada [45], the United States [46], China [47],  
354 South Korea [48] and New Zealand [33]. These trends may largely be explained by reduced  
355 incidence of seasonal respiratory tract infections, and reduced primary care consultations [49,50].  
356 On the other hand, the advent of telemedicine, pandemic-related patient stress, and antibiotic  
357 demand may have to a certain extent mitigated reductions in prescribing owing to reduced  
358 consultation [51]. In a global analysis of antimicrobial sales, Khouja et al. found that antibiotic  
359 consumption initially increased by approximately 7% in March 2020, prior to subsequent declines  
360 through to August 2020 [53]. Furthermore, while overall prescribing may have decreased,  
361 prescription of specific antibiotics has increased, particularly those associated with COVID-19  
362 prophylaxis. For instance, community consumption of azithromycin increased during the first year  
363 of the pandemic in multiple countries [53–55]. Several studies have now characterized the wide  
364 range of antibiotics provided as prophylaxis to both mild and severe COVID-19 patients in 2020  
365 [56,57], though it remains unclear to what extent prophylaxis is appropriate for prevention of  
366 bacterial coinfection in COVID-19 patients, particularly for mild cases treated in the community.  
367 Therefore, testing different scenarios with both increases and decreases in antibiotic use seems  
368 appropriate due to spatial and temporal heterogeneity in impacts of COVID-19 on antibiotic

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

371  
372 Our model simulations show that antibiotic resistance rates increase with surges in SARS-  
373 CoV-2 infections when there is a corresponding increase in prophylactic antibiotic use, as  
374 expected, but that lockdowns can mitigate this increasing trend to some degree. One promising  
375 outcome of scenarios that assume a decrease in antibiotic prescribing is that increases in antibiotic  
376 resistance were minor (Fig 3B, S2 and S5), while changes in resistant IBD incidence were either  
377 negligible or negative (Fig 3C). Conversely, surges in overall antibiotic prescribing during SARS-  
378 CoV-2 outbreaks, as reported in certain regions and pandemic periods, may cause substantial  
379 increases in resistance rates and the total incidence of disease due to antibiotic-resistant strains. In  
380 these analyses, for simplicity we simulated lockdowns and modifications of antibiotic prescribing  
381 lasting for a single 90-day period. Real-life scenarios are significantly more complicated and may  
382 involve multiple alterations of these factors at different points in time and heterogeneity across  
383 populations (e.g., prescribing increases in some demographic groups and decreases in others).  
384 Over longer timescales, and in the context of successive COVID-19 outbreaks with heterogeneous  
385 public health responses and impacts on human behavior, it is unclear exactly how levels of  
386 resistance and burden of disease may be expected to evolve.

387  
388 SARS-CoV-2 bacterial coinfection has been reported relatively rarely over the course of  
389 the pandemic, suggesting that most COVID-19 patients probably do not require antibiotic therapy  
390 [11,58,59], although extensive antibiotic prophylaxis may have limited observed co-infection  
391 incidence. The inflammatory immune response resulting from COVID-19 likely predisposes  
392 patients to subsequent progression to IBD to some extent [60], but antibiotic use may also favor  
393 progression to IBD for patients colonized with drug-resistant strains [61]. The results presented  
394 here (Fig 4) suggest that such overlapping within-host interactions could have important  
395 consequences for the resistant IBD incidence during COVID-19 waves, especially in the elderly  
396 and high-risk groups. Future studies are needed to better understand the magnitude of these  
397 interactions for *S. pneumoniae* and other commensal, facultatively pathogenic bacteria [62].

398  
399 Emerging SARS-CoV-2 variants, with varying transmissibility and severity, may be  
400 expected to have variant-specific impacts on AMR, especially in the context of the tightening and  
401 loosening of community control measures and their extensive heterogeneity both within and  
402 between countries. The highly heterogeneous distribution of diverse SARS-CoV-2 vaccines  
403 presents an additional mechanism that may further complexify interactions between antibiotic  
404 consumption, community control measures, circulating SARS-CoV-2 variants, and their  
405 cumulative impacts on antibiotic resistance. In our simulations, we used SARS-CoV-2 parameter  
406 values characteristic of the wild type or ancestral strain with  $R_0 = 2.5$  [63,64] and in the absence  
407 of population immunity, best reflecting epidemiological dynamics from early in the pandemic.  
408 However, successive SARS-CoV-2 variants of concern, most notably Alpha, Delta, Omicron, and  
409 most recently Omicron sub-lineages BA.4 and BA.5 [65], are highly variable in their  
410 transmissibility, and evade to some degree the immune protection induced by prior infection and/or  
411 vaccination, especially if it has waned over time. Our analysis demonstrates that these viral  
412 parameters may affect how SARS-CoV-2 outbreaks impact antibiotic-resistant IBD incidence at  
413 the community level and shows how increasing SARS-CoV-2  $R_0$  values may exacerbate impacts  
414 of COVID-19 on antibiotic resistance, while increasing population immunity may mitigate them

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

417  
418 Our model has focused on the general community, yet COVID-19 has had distinct impacts  
419 on AMR in other settings, particularly in hospitals and long-term care facilities. In these settings,  
420 an extensive antibiotic use in COVID-19 patients and disruption of antibiotic stewardship  
421 programs may have predisposed patients and healthcare workers to increased antibiotic-resistant  
422 carriage. In a meta-analysis conducted on studies published up to June 2020 [67], an estimated 68-  
423 81% of patients hospitalized with COVID-19, and 74-94% of patients in intensive care, were  
424 treated with antibiotics. While hospital disorganization due to the COVID-19 pandemic may have  
425 led to decreased antibiotic resistance surveillance and detection promoting the dissemination of  
426 resistant organisms through rooms and wards, an implementation of antibiotic stewardship  
427 programs, as soon as March 2020, patient isolation, and an extensive use of personal protective  
428 equipment (PPE) have mitigated this increase [8,67–70]. Models dedicated to the analysis of such  
429 impacts in the hospital could bring a better understanding of the specificities of different settings  
430 on the contribution of COVID-19 to the antibiotic resistance burden [71].

431  
432 We present here the first epidemiological model describing how the ongoing COVID-19  
433 pandemic may have and may continue to influence the epidemiological dynamics of AMR in the  
434 community setting. Because this work was intended as a theoretical framework, we aimed at  
435 developing the simplest model possible. Nonetheless, an important limitation of our model is the  
436 lack of age structure, as SARS-CoV-2 infection risk, IBD risk, disease severity, bacterial carriage  
437 prevalence and antibiotic prescribing are all highly heterogeneous across age groups. Our model  
438 was also structured and parameterized based upon *S. pneumoniae*, limiting interpretation for other  
439 important community-associated bacteria such as *E. coli*, as their epidemiological and natural  
440 history characteristics differ substantially (e.g., differences in the within-host ecological niche,  
441 duration of colonization, baseline carriage prevalence). Nonetheless, by modulating model  
442 compartments and parameter values as necessary, our model could be applied to a wide variety of  
443 bacteria and epidemiological scenarios in the community (e.g., impacts of SARS-CoV-2-bacteria  
444 interactions in the context of seasonal outbreaks of endemic pathogens). Future work would benefit  
445 from fitting such a model to real-world data on AMR trends from different bacterial species.  
446 Although such data are currently lacking, especially in community settings, longitudinal  
447 microbiome sequencing in the context of ongoing SARS-CoV-2 outbreaks may facilitate better  
448 understanding of the impacts of COVID-19 on the transmission of antibiotic resistance into the  
449 future.

450  
451 In conclusion, our work demonstrates how, in the case of delayed or limited data, a  
452 mathematical modeling approach can be useful to explain and anticipate how different COVID-19  
453 pandemic responses may be expected to have impacted epidemiological dynamics of AMR in the  
454 community. Our model successfully captured the main trends of antibiotic resistance and IBD  
455 incidence observed in Europe in 2020 for *S. pneumoniae*. However, not all countries reported  
456 increases in AMR rates, and such inter-country heterogeneity may be attributed to other pandemic  
457 factors not directly implemented or assumed in model scenarios, such as different adherence to  
458 COVID-19 control measures, including impacts on disease surveillance and data reporting during  
459 the pandemic. In the current context where data remain limited and more studies are required to  
460 evaluate the consequences of the pandemic on the global burden of AMR, mathematical modeling

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

463

## 464 **Methods**

465

### 466 ***Streptococcus pneumoniae* surveillance data**

467

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

478

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

480

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

494

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

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

511

### 512 **Simulating pandemic scenarios**

513

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

527

### 528 **Acknowledgements**

529

530 We thank Thomas Haschka for helpful comments.

531

### 532 **Competing interests**

533

534 Authors declare no competing interests.

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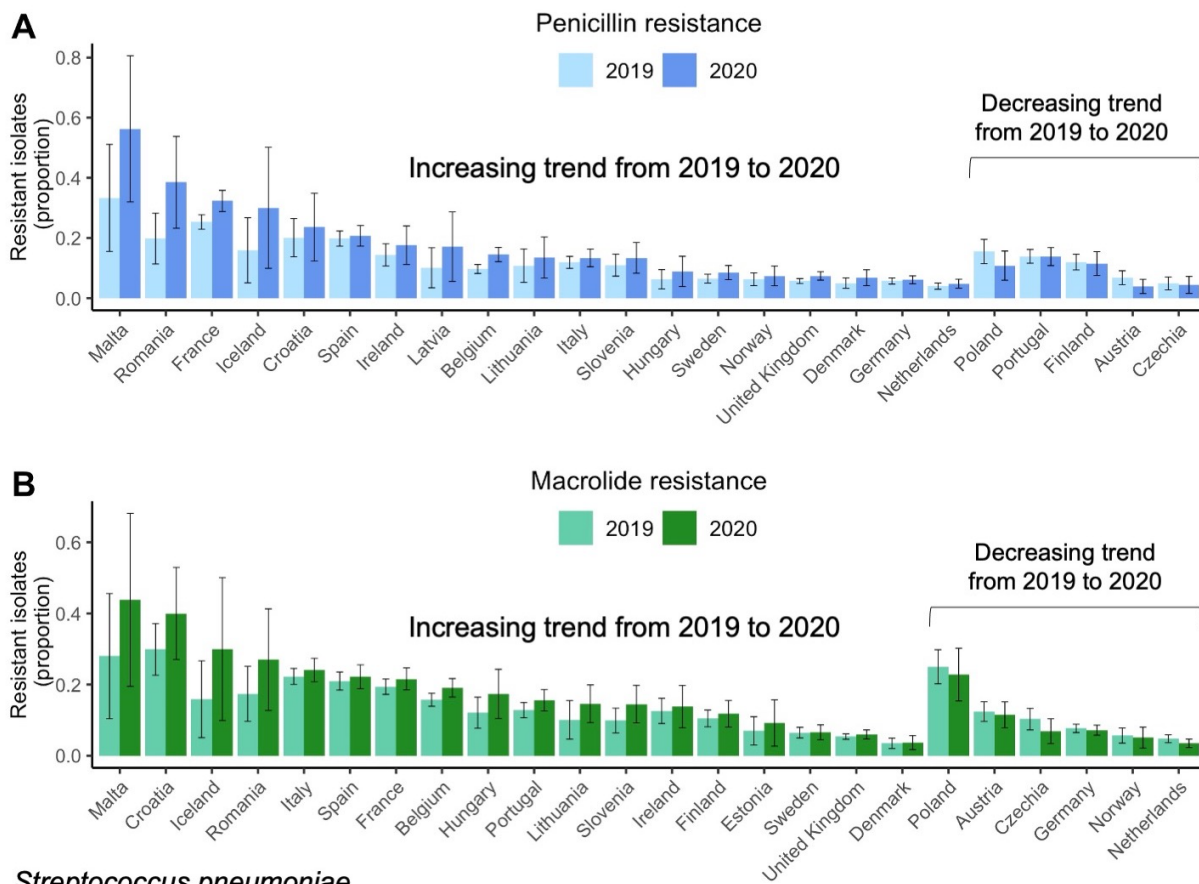
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553 **Figures**

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*Streptococcus pneumoniae*

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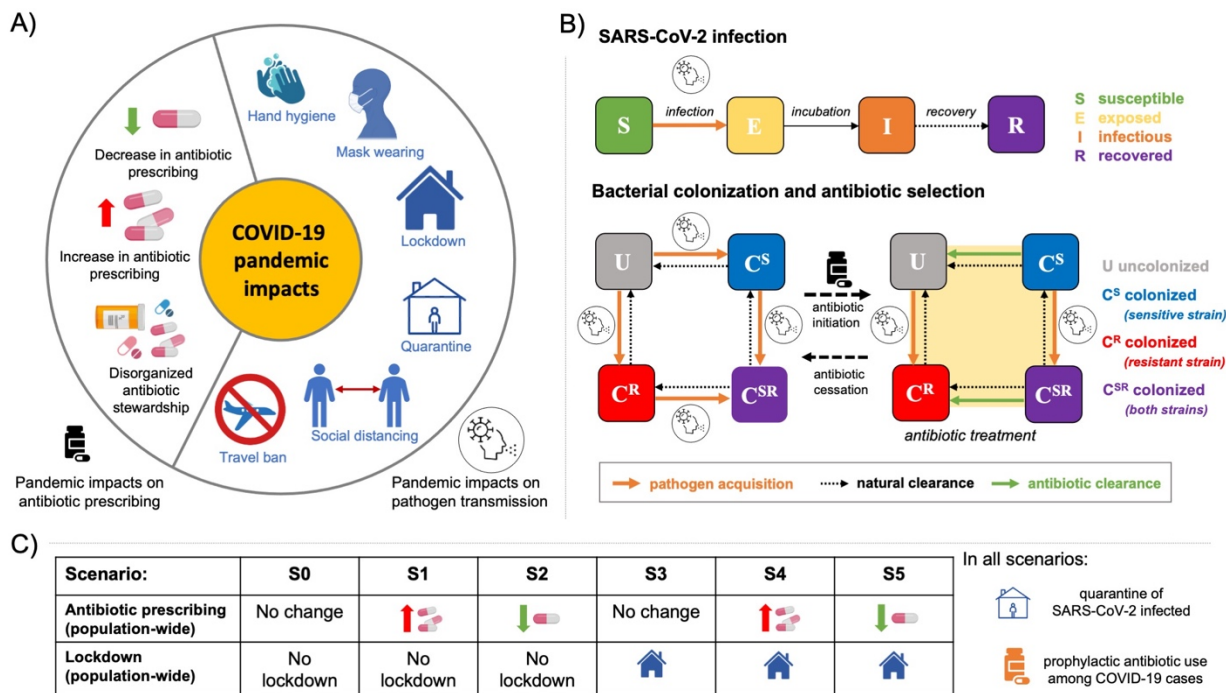
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557 **Figure 1. 2019-2020 antibiotic resistance trends in *Streptococcus pneumoniae* reported to EARS-Net**  
 558 **(European Antimicrobial Resistance Surveillance Network) [16].**

559 (A) Proportion of *S. pneumoniae* isolates resistant to penicillin across 24 European countries. (B) Proportion  
 560 of *S. pneumoniae* isolates resistant to macrolides (azithromycin/ clarithromycin/ erythromycin) across 24  
 561 European countries. Error bars show 95% confidence intervals. Dataset available at  
 562 [https://github.com/alekskovacevic/antibiotic\\_resistance](https://github.com/alekskovacevic/antibiotic_resistance).

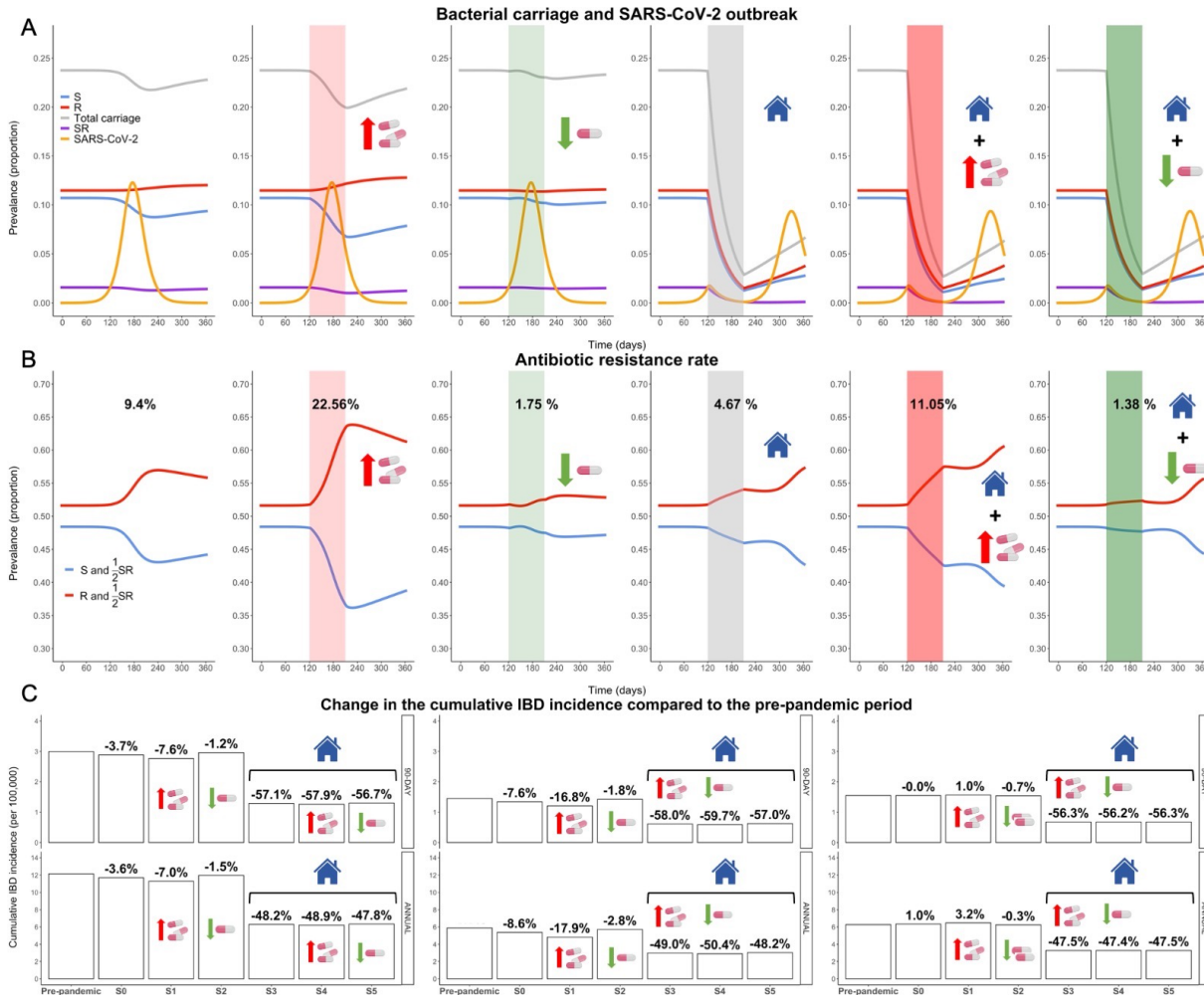
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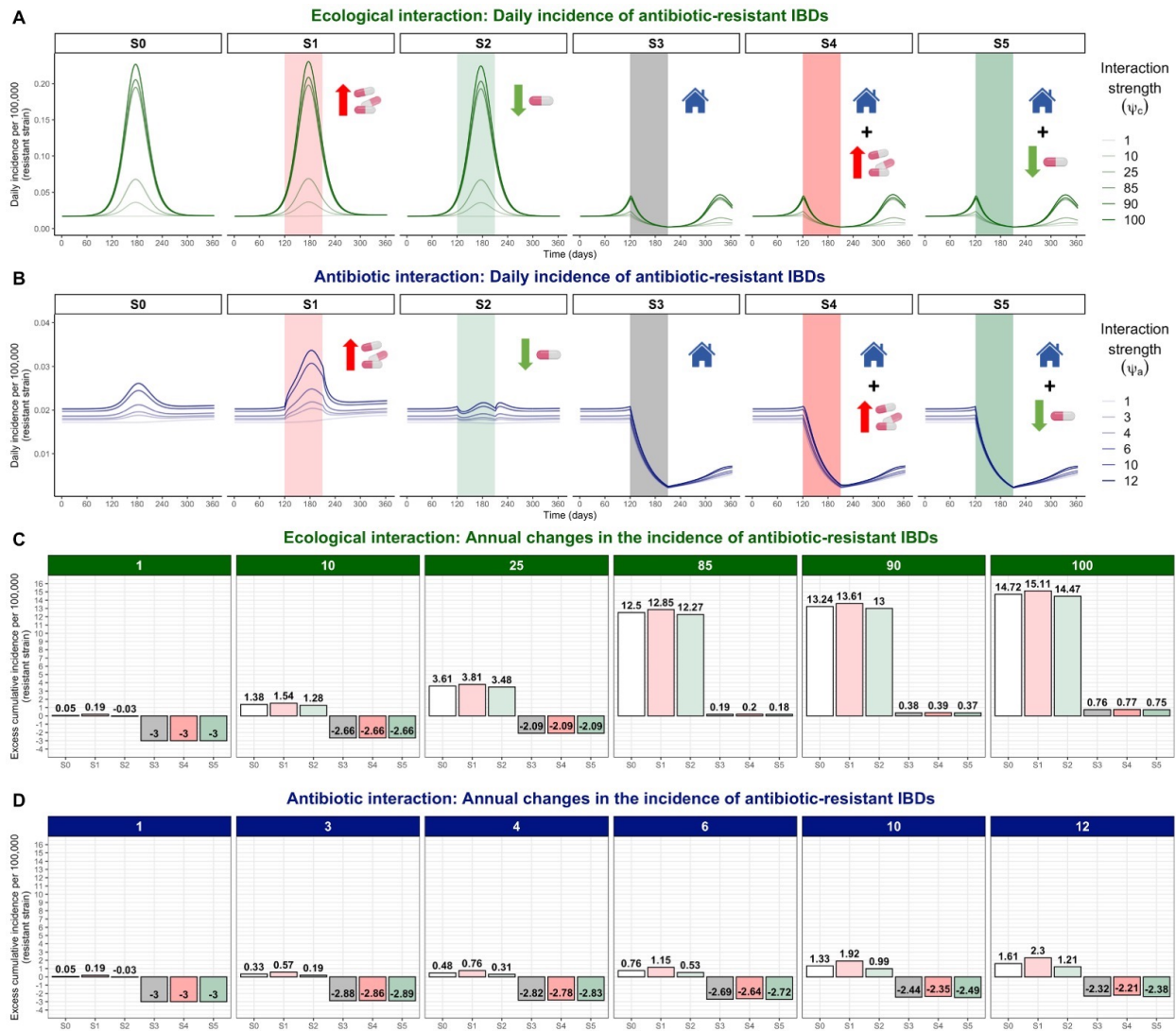
**Figure 2. A modeling framework for the selection and transmission of antibiotic-resistant bacteria in the community incorporating responses to the first wave of the COVID-19 pandemic. (A)** The COVID-19 pandemic impacts modify community antibiotic prescribing and pathogen transmission. **(B)** Diagram 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.



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



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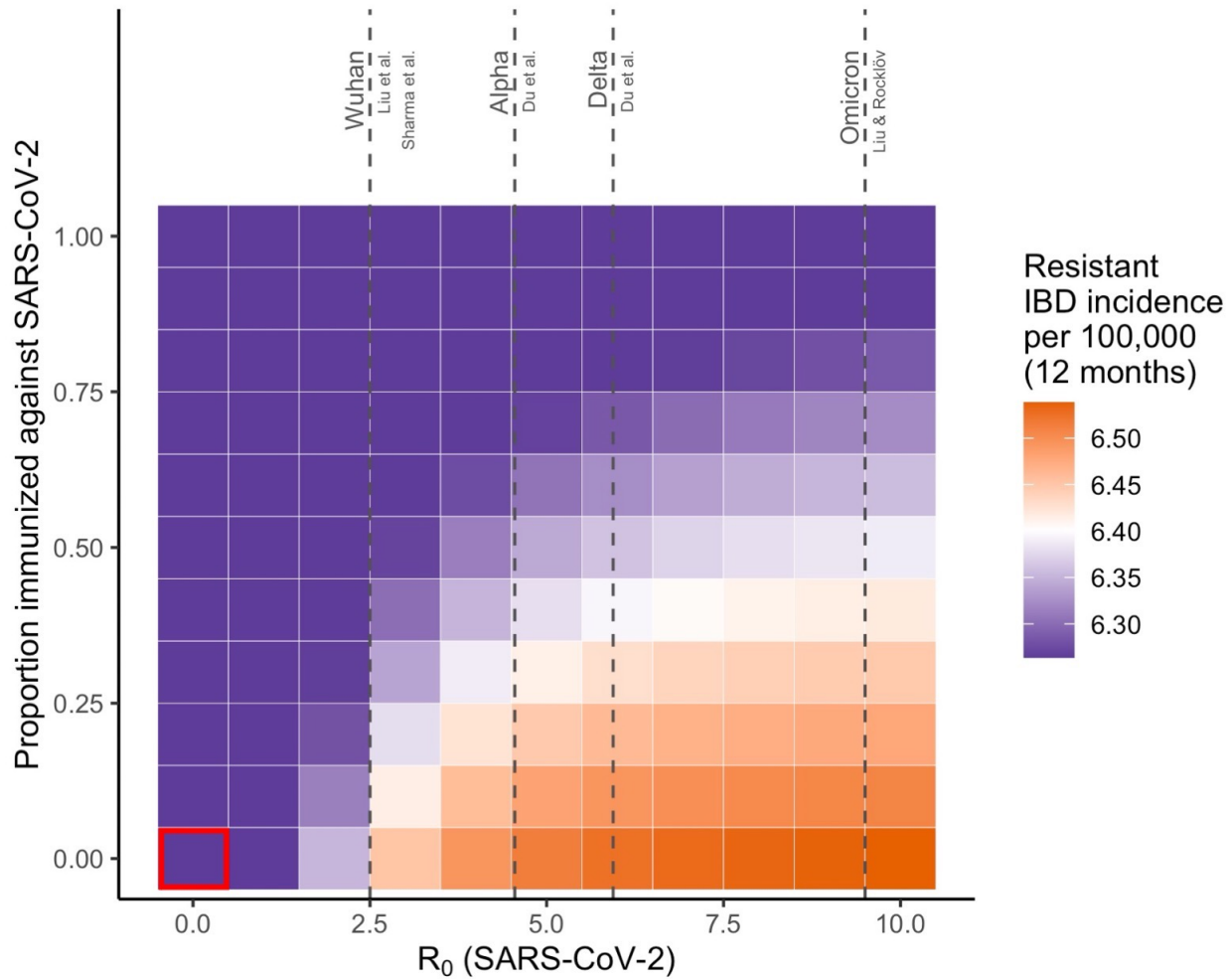
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**Figure 4. Within-host interactions favor the incidence of antibiotic-resistant invasive bacterial disease (IBD) across pandemic scenarios. (A) Impacts of ecological interactions.** When SARS-CoV-2 infection leads to faster progression from bacterial colonization to disease ( $\psi_c > 1$ ), 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 ( $\psi_a > 1$ ), 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.

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**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].

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