Resistance diagnostics as a public health tool to combat antibiotic resistance: A model-based evaluation

Short title: **Resistance diagnostics as a tool to reverse selection on resistance**

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Abstract

Rapid point-of-care resistance diagnostics (POC-RD) are a key tool in the fight against antibiotic resistance. By tailoring drug choice to infection genotype, doctors can improve treatment efficacy while limiting costs of inappropriate antibiotic prescription. Here we combine epidemiological theory and data to assess the potential of RD innovations in a public health context, as a means to limit or even reverse selection for antibiotic resistance. POC-RD can be used to impose a non-biological fitness cost on resistant strains, by enabling diagnostic-informed treatment and targeted interventions that reduce resistant strains' opportunities for transmission. We assess this diagnostic-imposed fitness cost in the context of a spectrum of bacterial population biologies, and find that the expected impact varies from selection against resistance for obligate pathogens to marginal public health improvements for opportunistic pathogens with high 'bystander' antibiotic exposure during asymptomatic carriage (e.g. the pneumococcus). We close by generalizing the notion of RD-informed strategies to incorporate carriage surveillance information, and illustrate that coupling transmission-control interventions to the discovery of resistant strains in carriage can potentially select against resistance in a broad range of opportunistic pathogens.

Introduction

> "Because antibiotic resistance occurs as part of a natural evolution process, it can be significantly slowed but not stopped. Therefore, new antibiotics will always be needed to keep up with resistant bacteria." (CDC, "Antibiotic Resistance Threats in the United States, 2013") (1)

The antimicrobial resistance crisis threatens to undermine key features of modern medicine, at great costs in terms of patient morbidity, mortality and treatment expense (2–6). Current mainstream antibiotic-treatment strategies sow the seeds of their own downfall by strongly selecting for resistant strains, leading some to argue that continual new-antibiotic discovery is the only way to stay ahead of a "post-antibiotic future" (1, 7, 8). If this bleak vision is correct, there is an urgent need to buy time by extending the lifespan of existing antibiotics while research and development for new ones takes its course. More optimistically, it may be possible to improve how we use existing antibiotics and to implement other control measures so that an endless supply of new antibiotics is not required.

Among a number of innovative approaches to improve antibiotic use (9–15), one of the most promising leverages point-of-care resistance diagnostics (POC-RD) that provide prescribers with a rapid readout of the sensitivity/resistance profile of an infecting organism. POC-RD allows prescribers to choose older, cheaper, and/or narrower-spectrum antibiotics when such drugs are most appropriate for patients, thereby saving newer, more expensive, and/or broader-spectrum antibiotics for situations where they are really needed, and perhaps reducing the intensity of selection for resistance to these drugs (16–18).

57 Less often considered is a second potential benefit of resistance diagnosis: to enable
58 "Search & Destroy" (S&D) tactics to combat the most dangerous resistant pathogen
59 strains, such as methicillin-resistant *Staphyloccus aureus* (MRSA) and carbapenem-
60 resistant *Enterobacteriaceae* (CRE) (19–24). S&D strategies aim to identify and then
61 isolate patients who are carrying problematic resistant strains until pathogen clearance
62 can be confirmed. If resistant strains can be rapidly, accurately identified and their
63 transmission curtailed by targeted infection-control measures, then S&D can create a
64 *non-biological diagnostic-imposed fitness cost* borne only by targeted resistant strains.
65 However, the magnitude of this fitness cost is hotly debated, especially in the context of
66 MRSA control (25, 26), and, in any event, intensive medical interventions such as
67 patient isolation are not a practical or economical option in many circumstances.

68 In this paper, we ask: when it is possible to create *net selection against resistance*, even
69 when (i) there are no biological fitness costs associated with resistance, (ii) the best
70 available treatment cannot be withheld from any patient, and (iii) all non-antibiotic
71 intervention options are only moderately effective. We define "net selection against
72 resistance" as maintaining the fitness of one or more resistant strains below that of the
73 drug-sensitive strain, so that the frequency of these resistant strains will decline toward
74 zero. This can be accomplished, generally speaking, when diagnostics permit medical
75 personnel to artificially shape the pathogen fitness landscape so that resistant strains
76 are disproportionately disadvantaged. We show that the potential to reduce or even
77 reverse selection on resistance depends on two key factors. (i) <u>Pathogen lifestyle</u>: is
78 symptomatic disease tightly coupled to transmission (obligate pathogen), or can the
79 pathogen also transmit from an asymptomatic carriage phase (opportunistic pathogen)?

(ii) Pan resistance: are untreatable pan-resistant strains already in circulation? Table 1 offers a preview of our main findings in a simple setting with two equally-effective antibiotic-treatment options, "drug 1" (first-line treatment to which resistance has already emerged in the target-pathogen population) and "drug 2" (second-line treatment to which resistance may or may not have already emerged).

Lifestyle	Pan-resistant	Key findings
Simple Obligate	No	Net selection against drug-1 resistance is **possible**.
Simple Obligate	Yes	Net selection against pan resistance is **possible only if** *either* there are substantial biological fitness costs associated with pan resistance *or* a highly-effective infection intervention ("isolation") is available.
Opportunistic	No/Yes	Net selection against drug-1 resistance **may be impossible**, even if all those with sensitive infection are left untreated and all those with drug-1-resistant infection could be targeted for isolation—**unless interventions are also conditioned on asymptomatic carriage RD**

Table 1: Preview of main findings.

Methods

We describe a mathematical model for a single pathogen species ("target pathogen") with multiple strains having different antibiotic susceptibilities, in which health care providers and public health officials (hereafter "providers") can shape the pathogen fitness landscape by tailoring treatment and transmission-control measures informed by resistance diagnosis (RD).

Pathogen strains: Two antibiotics are available to treat infections caused by the target pathogen: drug 1 (first-line treatment that would be prescribed to all patients in the

absence of resistance diagnosis) and drug 2 (second-line treatment). Resistance to drug 1 and potentially also to drug 2 has already emerged in the target-pathogen population but not yet reached fixation. In particular, there are up to four resistance profiles in circulation: an untreatable "pan-resistant" strain (strain 12); a "drug-1-resistant" strain that remains sensitive to drug 2 (strain 1); a "drug-2-resistant" strain that remains sensitive to drug 1 (strain 2); and a "pan-sensitive" strain that can be effectively treated with either drug (strain 0) (Fig 1A). The model encompasses a spectrum of pathogen lifestyles, from "simple obligate pathogens" (causing disease immediately after colonization, Fig 1A,B) to "opportunistic pathogens" (transmitting from an asymptomatic carriage phase as well as during symptomatic disease, Fig 1C).

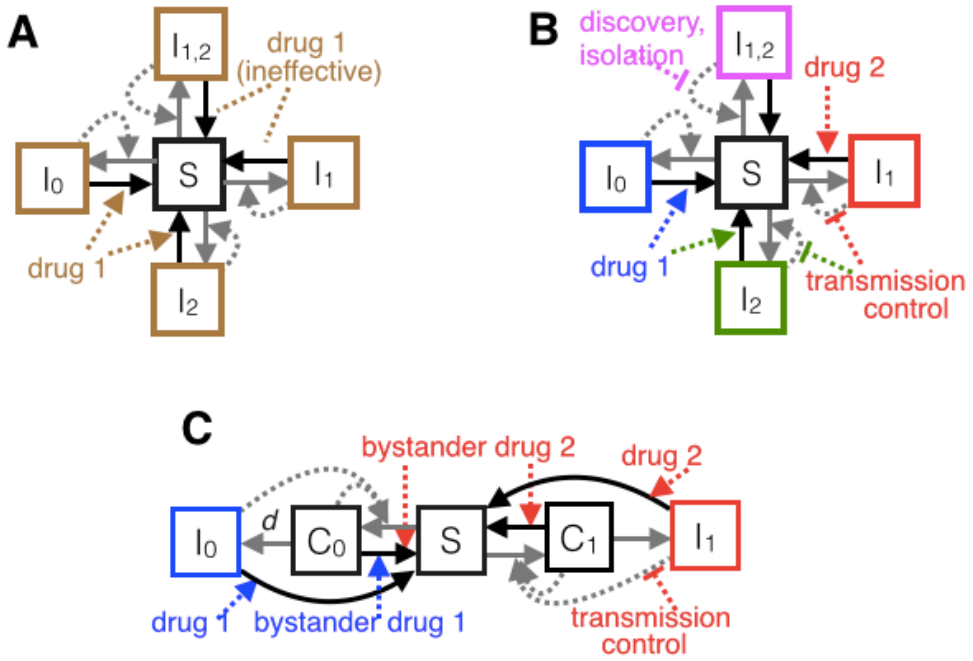

Figure 1. Schematic of the obligate/SIS (A,B) and opportunistic/SCIS (C) epidemiological models. Boxes denote proportions of hosts in mutually exclusive states: S for uninfected (susceptible) hosts, I_0 for hosts infected with a strain sensitive to both drugs, and I_1, I_2, I_{12} for hosts infected with strains resistant to drugs 1, 2, or both 1 and 2, respectively. In the SCIS model (**C**, showing only two pathogen genotypes for

clarity), C_0 and C_1 denote asymptomatic carriage of sensitive and drug-1-resistant bacteria, respectively, and d is the rate at which disease develops from carriage (when $d \to \infty$, we recover an SIS model). Box colors denote distinct clinical presentations in the absence (**A**) or presence (**B,C**) of multi-drug POC-RD. Solid arrows represent flows of individuals between states, and dashed arrows represent factors influencing those flows (e.g., antibiotic treatment). Grey and black arrows denote transmission and clearance, respectively. Equations describing the system are in SI.B.

<u>*Resistance diagnosis (RD)-informed treatment and control*</u>: We use standard reproduction-number analysis to investigate the pathogen-fitness impact of *RD-informed treatment and control*, depending on pathogen lifestyle (obligate vs opportunistic), what sort of resistance diagnostic is available, and what sort of transmission-control options can be feasibly targeted against each resistant strain, once identified. Cases considered include: point-of-care RD (POC-RD) with an obligate pathogen (Case #1, Fig 1B); POC-RD with an opportunistic pathogen (Case #2, Fig 1C); and carriage resistance surveillance ("carriage RD") with an opportunistic pathogen (Case #3). See the SI for omitted mathematical details as well as several extensions, including to settings with intermediate resistance, public health interventions aimed at discovering drug-resistant infections more quickly, resistance-conferring mutation, host migration, and diagnostic escape.

Notation	**Details**
Pathogen strains and pathogen-lifestyle parameters	
x	Drugs $x = 1,2$ are available to treat infections caused by the target pathogen.
X	Each strain is named for the drugs (if any) X = 0, 1, 2, 12 to which it is resistant: strain 0 is susceptible to both drugs ("pan-sensitive"); strain 1 is resistant only to drug 1; strain 2 is resistant only to drug 2; and strain 12 is

	resistant to both drugs ("pan-resistant").
$\beta^C, \beta^I > 0$	Transmission rates during carriage and during infection, if uncontrolled and if no biological fitness costs
$f_X \geq 0$	Biological fitness cost associated with strain *X* resistance, reducing transmission during carriage and infection by a factor of $1 - f_X$
$\gamma^C > 0$	Baseline carriage clearance rate
$\phi_x^C > 0$,	Carriage clearance rate of drug-x-sensitive strain due to bystander exposure to drug x
$d > 0$	Rate at which infection develops from carriage (in the limit $d \to \infty$, we recover the SIS case)
$\gamma_0^I > 0$	Baseline infection clearance rate when untreated or ineffectively treated
Diagnosis, treatment, and transmission-control parameters	
$D \geq 0$	Diagnostic delay, i.e., time from sample collection to result
$r_X \geq 0$	Rate at which resistant strain X is discovered while in the carriage state
$\gamma_x^I > \gamma_0^I$	Infection clearance rate of drug-x-sensitive strain when treated with drug x
$Z_X^I, Z_X^C \leq 1$	Proportional reduction in transmission during infection (Z_X^I) or during asymptomatic carriage (Z_X^C) due to heightened transmission control (HTC_X) measures targeted against strain X
Key derived variables	
$R_{0,X}$	Basic reproduction number of strain X
f_X^*	Threshold biological fitness cost for strain X not to enjoy a reproductive advantage, i.e., $R_{0,X} > R_{0,0}$ if $f_X < f_X^*$ and $R_{0,X} < R_{0,0}$ if $f_X > f_X^*$

Table 2: Notation.

Results

Case #1: POC-RD and a simple obligate pathogen (SIS model)

In the limiting case when the target pathogen immediately causes disease ($d = \infty$), what we call a "simple obligate pathogen," our SCIS model reduces to a standard Susceptible-Infected (SIS) epidemiological model (27–29). Few if any real-world bacterial pathogens fit this case, but it is useful conceptually as a limiting case (Fig 1A,B).

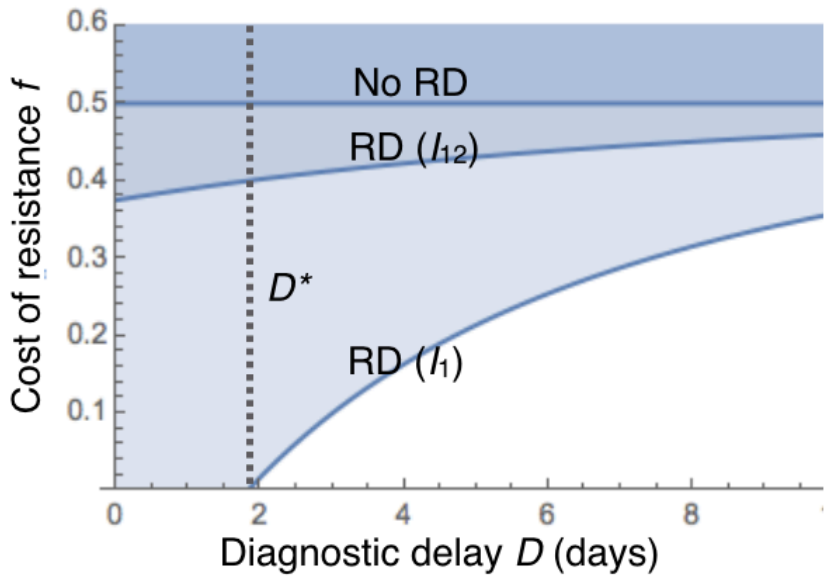

Figure 2. Rapid resistance diagnostics enable conditional treatment and infection control strategies that can select against resistance for obligate pathogens even with no biological costs of resistance. The minimal cost of resistance *f**(*D*) that allows universal treatment without causing an increase in resistance is plotted (contour lines) against diagnostic delay D. The dashed vertical line indicates the longest diagnostic delay (D^*) given which there is selection against drug-1 resistance while treating all cases. Three scenarios are shown: resistance diagnostics (RD) not available (No RD, contour plot of $f_1^*(\infty) = f_{12}^*(\infty)$); RD control of I_1 only (RD (I_1), contour plot of $f_1^*(D)$); RD control of I_{12} (and trivially, I_1) (RD (I_{12}), contour plot of $f_{12}^*(D)$). R_0 expressions are defined in Box 1, with further details in SI.B. Parameters (rates per day): $\gamma_0^I = 0.1, \gamma_1^I = \gamma_2^I = 0.2, \beta^I = 0.2, Z_1^I = 0.8, Z_{12}^I = 0.8$.

Fig 2 illustrates the impact of RD-informed treatment and transmission control on whether the drug-1-resistant and/or pan-resistant strains enjoy a reproductive advantage relative to the pan-sensitive strain, for a generic pathogen with average

duration of infection of 5 days (with effective treatment) or 10 days (without treatment). The blue parameter regions are where the drug-susceptible strain has a higher reproduction number (R_0) than the drug-1-resistant strain and/or the pan-resistant strain, as a function of diagnostic delay *D* and the biological fitness costs f_1, f_{12} of drug-1 and pan resistance, thereby creating net selection against these resistant strains.

*** START BOX 1 ***

Box 1. Reproductive numbers (R_0) for strains in the SIS model. See SI.B for more detailed derivations.

Pan-sensitive strain: Strain-0 infections are treated with drug 1 and subjected to standard transmission control, whether or not RD is available. Since strain-0 infections clear at rate γ_1^I under drug-1 treatment and strain 0 transmits at rate β^I under standard control, strain 0's reproduction number is

$$R_{0,0} = \beta^I / \gamma_1^I$$

Equation 1

Drug-1-resistant strain: Since strain-1 infections clear at rate γ_0^I during the diagnostic-delay period, a patient will remain infected long enough for RD results to become available (triggering drug 2 and transmission control) with probability $e^{-D\gamma_0^I}$. Depending on diagnostic delay D and fitness cost f_1, strain 1's reproduction number takes the form

$$R_{0,1} = \beta^I (1 - f_1) \left(\frac{1 - e^{-D\gamma_0^I}}{\gamma_0^I} + \frac{e^{-D\gamma_0^I} Z_1^I}{\gamma_2^I} \right)$$

Equation 2

177 *Drug-2-resistant strain*: Since strain-2 infections are susceptible to drug 1 and therefore
178 clear at rate γ_1^I during the diagnostic-delay period, such infections will be diagnosed
179 before clearance with probability $e^{-D\gamma_1^I}$. Strain 2's resulting reproduction number is

180 $$R_{0,2} = \frac{\beta^I(1-f_2)}{\gamma_1^I}\left(1 - e^{-D\gamma_1^I}(1-Z_2^I)\right)$$

181 *Equation 3*

182 *Pan-resistant strain*: Strain-12 infections clear at the untreated rate γ_0^I during and after
183 the diagnostic-delay period. However, diagnostic results (if available before infection
184 clearance, probability $e^{-D\gamma_0^I}$) can trigger heightened transmission control, reducing strain
185 12's reproduction number to

186 $$R_{0,12}(f_2, D) = \frac{\beta^I(1-f_{12})}{\gamma_0^I}\left(1 - e^{-D\gamma_0^I}(1-Z_{12}^I)\right)$$

187 *Equation 4*

188 *** END BOX 1 ***

189 The solid contours in Fig 2 illustrate the critical threshold resistance costs for the drug-1-
190 resistant strain ($f_1^*(D)$) and the pan-resistant strain ($f_{12}^*(D)$), the smallest fitness costs
191 that allow universal treatment while keeping the resistant strain at a reproductive
192 disadvantage relative to the sensitive strain. The introduction of RD has the greatest
193 impact on the drug 1 resistant strain (Fig 2, strain I_1). In the limit of no diagnostic delay
194 ($D = 0$), we find that $f_1^*(0) = \frac{Z_1^I\gamma_1^I - \gamma_2^I}{Z_1^I\gamma_1^I}$. This implies that resistance to drug 1 (given
195 available drug 2) can be selected against even in the absence of resistance costs

196 $(f_1^*(0) < 0)$ so long as *either* drug 2 is more effective than drug 1 *or* drug 2 is less

197 effective than drug 1 but transmission control is sufficiently effective that $Z_1^I < \frac{\gamma_2^I}{\gamma_1^I}$.

198 Control of a circulating pan-resistant strain I_{12} is more challenging, even with POC-RD.

199 Absent fitness costs ($f_{12} = 0$), net selection against pan resistance can be maintained

200 only if $Z_{12}^I < \frac{\gamma_0^I}{\gamma_1^I}$, meaning that transmission control of the pan-resistant strain is more

201 effective than drug-1 treatment at speeding clearance. In the case of more modest

202 transmission control (Fig 2, $Z_{12}^I = 0.8$), net selection against pan resistance requires

203 that there be sufficient fitness costs associated with pan resistance. (In the POC-RD

204 limit when $D = 0$, the threshold fitness cost $f_{12}^*(0) = 1 - \frac{\gamma_0^I}{Z_{12}^I \gamma_1^I}$.)

205 Both thresholds $f_1^*(D)$ and $f_{12}^*(D)$ are increasing in D, as longer delays reduce the

206 effectiveness of diagnostic-informed treatment and control, and converge in the $D \to \infty$

207 limit to the "no-RD fitness-cost threshold" absent any resistance diagnosis: $\lim_{D\to\infty} f_1^*(D) =$

208 $\lim_{D\to\infty} f_{12}^*(D) = \frac{\gamma_1^I - \gamma_0^I}{\gamma_1^I}$. In Fig 2 with baseline clearance $\gamma_0^I = 0.1$/day and drug 1 assisted

209 clearance $\gamma_0^I = 0.2$/day, the no-RD fitness-cost threshold equals 0.5, greatly exceeding

210 typical reported costs of resistance. To give some context on empirical estimates of

211 costs of resistance, f, a recent meta-analysis estimated f = 0.21 (+/- 0.024) for

212 chromosomally encoded resistance and f = 0.09 (+/- 0.024) for plasmid-encoded

213 resistance (30), albeit using growth rate rather than epidemiological transmission

214 measures of fitness effects.

215

216 **Case #2: an opportunistic pathogen** with a carrier state (SCIS model)

217 Many disease-causing bacteria are opportunistic pathogens capable of transmission
218 from an asymptomatic carriage state, while living harmlessly in a host microbial
219 compartment such as the gut or the nasopharynx. Such pathogens face "bystander
220 exposure" to antibiotics used to treat infections caused by other pathogens or to treat
221 noninfectious conditions (31). Take for example the pneumococcus (*S. pneumoniae*),
222 one of the top bacterial causes of death globally (32) and a leading cause of antibiotic
223 prescription. Despite the severe burden of disease, the pneumococcus is subjected in
224 the US to an estimated 9.1 times more courses of any antibiotic during asymptomatic
225 carriage than during disease. Fig 3 compares the volume of bystander selection to
226 target antibiotic exposure for several major bacterial pathogens. An alternate
227 visualization of the proportions of bystander exposure (absent *C. difficile*) is presented
228 in Tedijanto et al. (31).

229 An implication of our analysis is that, for pathogens like *S. pneumoniae*, *E. coli*, *H.*
230 *influenzae*, and *C. difficile* that overwhelmingly face bystander exposure to antibiotics,
231 even the strongest possible medical interventions informed by point-of-care resistance
232 diagnostics can be insufficient to halt the rise of resistance to any drug in routine use.
233 Mathematical details underpinning this analysis, including derivations of each strain's
234 reproduction number with and without POC-RD, are provided in SI.C.

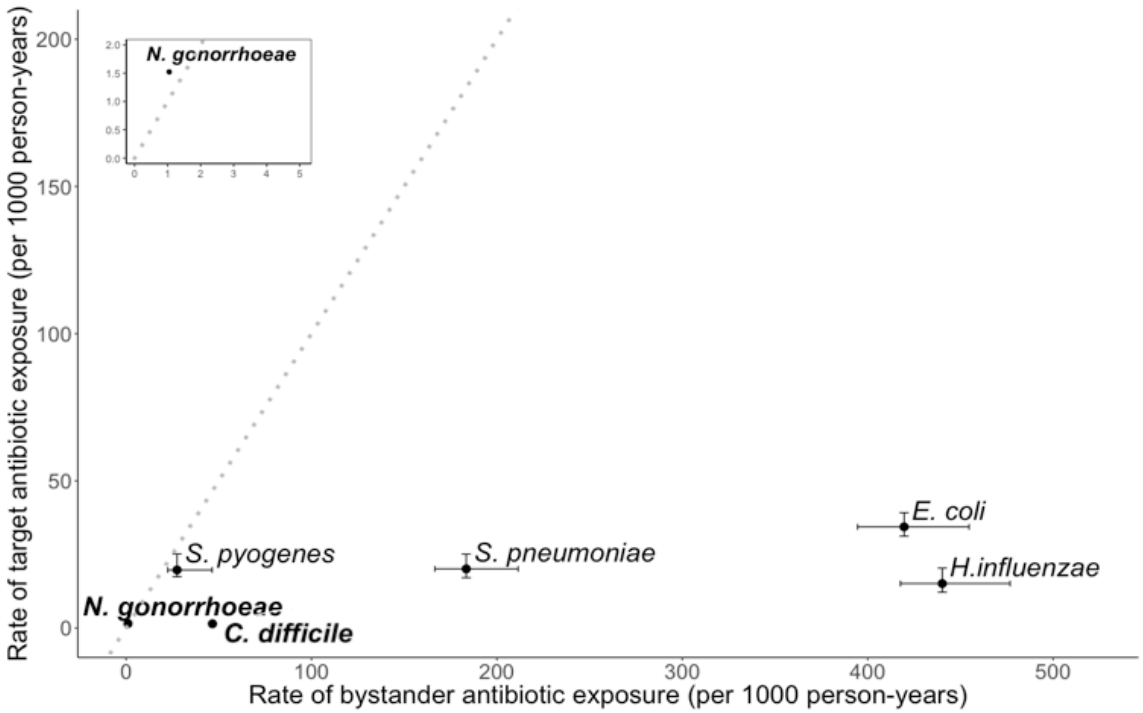

Figure 3. Incidental antibiotic exposure during asymptomatic carriage exceeds disease-related antibiotic exposure for key human pathogens. Bold font: Tier 1 urgent resistance concerns according to the Centers for Disease Control and Prevention (CDC) (1). Standard font: The most frequent etiologic agents of the top indications for antibiotic prescription in US ambulatory care. "Target antibiotic exposure" is defined as any antibiotic use associated with disease caused by that organism; "bystander antibiotic exposure" refers to the incidence of antibiotic exposure in asymptomatic carriage, roughly calculated as the product of the incidence of antibiotic prescription in ambulatory care and the proportion of the population in the relevant age group that carries the bacterium, less the number of target antibiotic exposures. The dotted line is where incidence of antibiotic exposure in carriage is equal to incidence of antibiotic exposure due to disease. See Tedijanto et al. (31) for method details, source references, and an alternate visualization of the same data on *N. gonorrhoeae*, *S. pyogenes*, *S. pneumoniae*, *E. coli*, and *H. influenzae*. Values for *C. difficile* were calculated using the same methodology and additional sources for disease incidence (33) and carriage prevalence (34); see SI.F for details.

In Fig 4, we parameterize our SCIS model for the pneumococcus, to show the threshold strain-1 fitness cost f_1^* (contour lines) for a population with substantial bystander

exposure (the I_1 resistant strain is counter-selected in the blue regions above the contour lines). Pneumococcal serotypes show considerable variation in carriage duration (Fig 4, arrows on *x*-axis) (35) and, unsurprisingly, our analysis illustrates that bystander selection becomes increasingly problematic for longer carriage serotypes – represented by a higher threshold resistance cost f_1^* to balance selection on resistance. Our parameterized model indicates that the threshold costs even in the absence of RD are of a similar magnitude to *average* costs of plasmid encoded resistance discussed earlier (30). However, more problematic is the common observation of cost-free resistances (including single SNPs) in the pneumococcus (36, 37), indicating that these average costs are liable to decrease in response to selection.

Even in the absence of pan-resistant strains, POC-RD has a weak impact due to the rarity and brevity of infection events (median infection duration in the absence of treatment is 8 days) relative to long periods of carriage and associated bystander selection. As a result, we anticipate ongoing selection for low-cost resistant strains, with or without POC-RD-informed strategies (Fig 4).

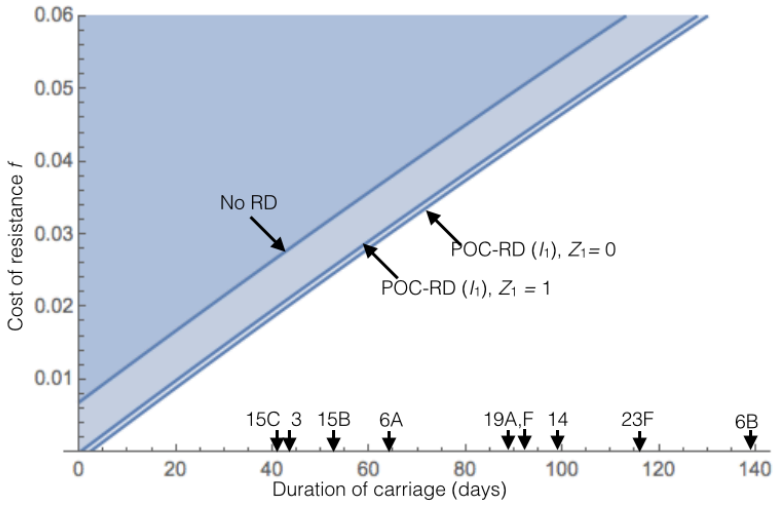

Fig 4. POC-RD alone cannot reverse selection on cost-free pneumococcal resistance. The minimal cost of resistance (f_1^*) that allows universal treatment without causing an increase in strain-1 resistance is plotted (contour lines) against the expected duration of carriage. Two POC-RD scenarios are shown: with ($Z_1^I = 0$) and without ($Z_1^I = 1$) transmission control. Arrows on the *x* axis are serotype specific mean carriage duration estimates from (35) (serotypes with ≥15 recorded carriage episodes only). The remaining parameters (rates per day) are d = 0.001, ϕ_1^C = 5x10^{-4}, ϕ_2^C = 0, $\gamma_1^I = \gamma_2^I$ = 1, γ_0^I = 0.125. We make the simplifying assumption that baseline carriage and infection transmission rates are identical ($\beta^C = \beta^I = \beta$) given which f_1^* does not depend on β. Details on parameterization are in SI.G.

Case #3: carriage resistance diagnostics

Our pessimistic conclusion concerning the public health merits of POC-RD for commensal opportunists such as *S. pneumoniae* (Fig 3,4) is based on the inevitability of bystander selection during prolonged carriage phases—but what if bystander selection could be opposed by public health interventions during carriage? For example, what if resistant-strain carriers could be identified and subjected to transmission control interventions even when they do not have active infection? Consider the South Swedish Pneumococcal Intervention Project (SSPIP) (38, 39), a public health intervention launched in January 1995 in Malmöhus County, Sweden that aimed to reduce penicillin-resistant pneumococcus (PRP) transmission, especially at preschool daycares. Any time a preschool-age child was identified with symptomatic PRP infection, providers would obtain nasopharyngeal cultures from all other children in the same daycare classroom. Children found to be carrying PRP were then required to remain home until subsequent testing proved them to be PRP-negative, penalizing PRP strains by reducing their opportunities for transmission from carriage.

297 In SI.C, we extend our analysis of the SCIS model to examine the potential of carriage
298 RD-based interventions to generate selection against resistance. A key result is that, in
299 order to select against drug-1-resistance, the drug-1-resistant strain must be discovered
300 while in carriage at a rate r_1 that exceeds the rate ϕ_1^C at which the sensitive strain is
301 cleared from carriage due to bystander exposure to drug 1. In Fig 5, we again
302 parameterize our SCIS model for the pneumococcus as in Fig 4, under two extreme
303 scenarios of carriage duration (35): 20 weeks (Fig 5A) and 2 weeks (Fig 5B). The blue
304 parameter space in Fig 5 highlights the combinations of carriage discovery rate (r_1, x-
305 axis) and HTC effectiveness against drug-1-resistant bacteria discovered in carriage (Z_1^C
306 y-axis) that lead to a net selection against drug-1 resistance.

307 Fig 5A illustrates the most problematic serotype from a POC-RD perspective, due to the
308 dominance of bystander selection. Given the introduction of annual carriage
309 surveillance (ensuring $r_1 > \phi_1^C$), our parameterized model predicts that HTC
310 interventions (such as removal of an infant from nursery) would need to reduce strain-1
311 transmission from carriage by at least 20% in order to select against the drug-1-
312 resistant genotype in the worst case scenario of zero resistance costs (f_1= 0).
313 Epidemiological studies of the impact of child-care attendance on pneumococcal
314 carriage suggest that a 2-fold reduction in transmission due to removal from daycare is
315 not unreasonable (40).

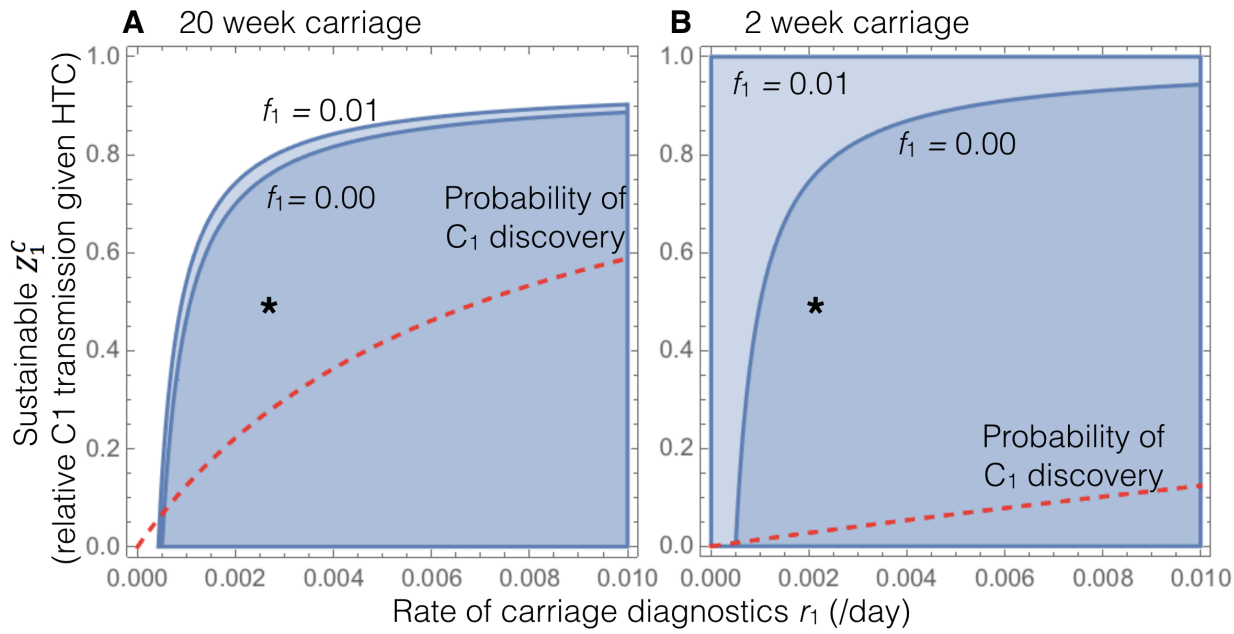

Fig 5. POC-RD plus Carriage RD can reverse selection on pneumococcal resistance, even for long carriage-duration serotypes. The parameter space generating net selection against resistance is plotted in blue as a function of the rate of carriage discovery (r_1) and the effectiveness of carriage HTC (Z_1^C). (A), longest carriage-duration serotype (6B, median 20 weeks). (B), shortest duration-carriage serotypes (1,4,5; ~2 weeks). In both (A) and (B), two POC-RD scenarios are shown: with ($f = 0.01$) and without ($f = 0$) biological cost of resistance. The red dashed line represents the probability of strain 1 discovery while in the carriage state ("C_1 discovery"), an increasing function of the rate of carriage diagnosis. The remaining parameters (rates per day) are d = 0.001, ϕ_1^C = 5x10^{-4}, ϕ_2^C = 0, $\gamma_1^I = \gamma_2^I$ = 1, γ_0^I = 0.125, γ^C = 0.006 (A), γ^C = 0.07 (B). We make the simplifying assumption that baseline carriage and infection transmission rates are identical ($\beta^I = \beta^C = \beta$), given which the space of parameter generating net selection against resistance does not depend on β. Details on parameterization are in SI.G. The asterisk positions the outcome of an annual intervention with 50% efficacy in reducing C_1 transmission.

The analysis underlying Fig 5 in SI.C implicitly assumes that all uninfected hosts are tested for drug-1-resistant carriage at a constant rate. While this assumption is useful here from an expositional point of view to highlight ideas, we note that such an approach would be inefficient in practice since many hosts would be tested even when their likelihood of drug-1-resistant carriage is low. By contrast, in SSPIP, only

338 classmates of children who developed PRP infections were tested. Thus, even if PRP
339 were rare in the general population, each child tested through SSPIP would have a
340 substantial likelihood of PRP carriage. By introducing simple contact-tracing principles,
341 the effective rate of carriage discovery can be higher for a given level of investment in
342 patient sampling.

343

344 **Discussion**

345 The antibiotic-resistance crisis is placing increasing pressure on healthcare globally and
346 is widely viewed as a one-way street toward a dangerous "post-antibiotic world" (1, 4).
347 In this paper, we ask whether resistance diagnostics (RD), when combined with public
348 health interventions such as heightened transmission control (HTC) for drug-resistant
349 bacterial strains, can substantially change the trajectory of resistance evolution.

350 In the early decades of the antibiotic era, doctors had no choice but to treat and control
351 infection *unconditionally*, creating a selective pressure favoring strains that were
352 resistant to whatever antibiotic was being widely prescribed. In that context, once
353 resistant strains emerge with zero biological fitness costs, all antibiotics become
354 "exhaustible resources" whose value to society is diminished by use (2, 3). In this paper,
355 we show that exhaustible resource antibiotics can in principle be transformed into
356 "renewable resources" whose value to society can be maintained over time even as
357 they are put to widespread use, so long as (i) RD is available to detect the target
358 pathogen and determine its antibiotic-sensitivity profile, (ii) prescribers adopt RD-
359 informed treatment strategies, (iii) identified resistant cases are subject to more

360 stringent transmission control, and (iv) bystander selection on the target pathogen is
361 either minimal (Fig 2) or counteracted (Fig 5). For obligate pathogens that face minimal
362 bystander selection, POC-RD-informed treatment reduces the advantage that resistant
363 strains would otherwise enjoy (41) but, as we show, RD-informed treatment plus
364 heightened control can potentially be sufficient to create a net selection against resistant
365 pathogen strains, reducing their prevalence over time in the pathogen population.
366 However, for opportunistic pathogens that face extensive bystander selection, POC-RD
367 alone is insufficient—identifying resistant strains when they are not yet causing infection
368 (so-called "carriage RD") is essential to reverse the rise of resistance. This note of
369 caution is important as society seeks to allocate resources most effectively in the
370 struggle against antibiotic resistance.

371 Our analysis identifies strategies to renew or maintain sensitivity to an antibiotic in a
372 pathogen population, the most effective of which depend on the availability of other
373 antibiotics that can be used to treat resistant infections. The potential to restore
374 antibiotic sensitivity is therefore limited once pan-resistant strains are in circulation.
375 Consider now the impact of the discovery of a new antibiotic (drug 3) to which these
376 bacteria are still sensitive. Drug 3's discovery transforms previously pan-resistant
377 bacteria into treatable "multidrug-resistant bacteria." Providers can now deploy targeted
378 treatment and HTC to hold the multidrug-resistant strain at a reproductive disadvantage.
379 In this way, introducing a new antibiotic to which disease-causing strains are not yet
380 resistant may make it possible to reverse the rise of previously pan-resistant bacteria,
381 restoring the effectiveness of pre-existing antibiotics. Moreover, as multidrug resistance
382 to pre-existing antibiotics grows less prevalent over time, the number of patients who

383 need the new antibiotic will itself decline over time, allowing the new antibiotic to be held
384 in reserve for increasingly rare cases for which it is the only effective treatment. This
385 potential decline in drug 3 use highlights the importance of having drug 3 resistance
386 diagnostics available when drug 3 is introduced, when we envisage the greatest use.
387 Indeed, if drug 3's introduction is coupled with drug 1-3 resistance diagnostics, it may
388 not be necessary to discover even more new antibiotics *beyond* drug 3, as diagnostics
389 will allow 'search and destroy' tactics against rare 1-3 pan resistant strains. We note
390 that rolling out drug 3 at the same time as a drug 3 diagnostic raises the challenge of
391 diagnosing resistance before widespread clinical use and clinical resistance discovery,
392 necessitating increased investment in resistance discovery in the laboratory and
393 phenotypic resistance surveillance in the clinic.

394 Whether net selection against resistant strains can be maintained depends on the
395 effectiveness of the HTC measures that can be feasibly targeted against each resistant
396 strain. By design, HTC measures impose additional barriers to resistant-bacterial
397 transmission by (i) identifying resistant bacteria (during infection and/or asymptomatic
398 colonization) and (ii) deploying additional resources specifically to prevent their
399 transmission. Many sorts of HTC measures could be relevant in different contexts.
400 Some examples: for hospital-associated infections, imposing heightened contact
401 precautions when a hospitalized patient is found to have resistant infection (19, 21); for
402 pneumococcal infection, requiring young children found to be infected or colonized with
403 penicillin-resistant pneumococci to stay home from daycare (38); for sexually
404 transmitted diseases, providing expedited partner therapy (EPT) when a patient is found
405 to have resistant infection (42); or, for livestock-associated infections, eradicating an

406 entire herd when resistant infection is identified. Note that HTC effectiveness may vary
407 depending on the resistant strain being targeted, e.g., EPT measures may be less
408 effective against pan-resistant strains since partners' transmissibility cannot be
409 controlled through treatment, while other measures may only be economically feasible
410 against some strains, e.g., eradicating an entire herd may only be economical when
411 pan-resistant infection is found, since other strains can be controlled through RD-
412 informed treatment. More research is needed to quantify the effectiveness of HTC
413 measures in practice.

414 Additional strategic options can be used to reduce the prevalence of bacterial strains
415 with intermediate resistance, if RD is available that provides quantitative (e.g.,
416 sequence-based inference of minimal inhibitory concentration (43)) information on the
417 degree of intermediate resistance. Details are provided in SI.B but, to see the point,
418 imagine that POC-RD had been available when penicillin was first introduced that could
419 quantitatively determine the penicillin sensitivity of gonorrhea infections. *Neisseria*
420 *gonorrhoeae* strains emerged in the 1940s and 1950s that were less sensitive to
421 penicillin but, at the time, these strains could still be effectively treated with a higher
422 dose (44). Armed with quantitative POC-RD, providers would have been able to target
423 intermediate-resistant gonococci with a higher penicillin dose—taking away the
424 treatment-survival advantage that intermediate-resistant gonococci would otherwise
425 enjoy—and could also have deployed additional public health resources to find and treat
426 others who might still be spreading intermediate-resistant gonococci. Such a policy of
427 *RD-informed treatment and heightened discovery* could have potentially held
428 intermediate-resistant gonorrhea strains at an overall reproductive disadvantage relative

429 to highly-sensitive strains, though only with HTC would it have been possible to avoid
430 rapid selection of the highly resistant strains (45). See SI.B for mathematical details.

431 The example of the gonococcus raises the key challenge of bystander exposure to
432 antibiotics, as gonorrhea infection is initially (and in some, entirely) asymptomatic and
433 therefore does not drive immediate medical attention and exposure to POC-RD. During
434 the asymptomatic phase of infection, drug-sensitive gonococcal genotypes are at risk of
435 being cleared due to antibiotics taken for other medical concerns (46). In Fig 3, we
436 outline how the extent of the bystander challenge is even greater for commensal
437 opportunistic pathogens (47, 48) which spend proportionately longer in asymptomatic
438 carriage states. Parameterizing our SCIS model (incorporating a carriage /
439 asymptomatic stage, prone to bystander selection) for the key commensal opportunist
440 *S. pneumoniae* illustrates that selecting against resistance via POC-RD-informed
441 strategies alone is not a plausible outcome for this particular pathogen (Fig 4), given the
442 lengthy duration of carriage and relatively rare and brief infection events caused by this
443 species.

444 We explore a strategic response to this concern: conditional interventions in response to
445 diagnostic information during asymptomatic carriage. Fig 5 illustrates that coupling
446 differential transmission control to carriage RD can drive net selection against
447 resistance, even for the most carriage-prone serotypes of the pneumococcus. The
448 South Swedish Pneumococcal Intervention Project (SSPIP) offers a concrete example
449 of using carriage RD to drive public health interventions. While SSPIP targeted
450 pneumococcal strains that remained treatable by other antibiotics, similar programs
451 could target pan-resistant strains and, if sufficiently intensive and comprehensive,

452 potentially select against these pan-resistant strains even as those with sensitive
453 infection continue to receive antibiotic treatment.

454 We note that, in theory, our logic of conditional interventions during carriage could be
455 extended to incorporate broader 'microbiome' resistance diagnostics (M-RD) and M-RD-
456 informed interventions. While simple in outline, implementation presents technical
457 challenges on several fronts, not least in establishing meaningful sampling protocols,
458 designing appropriate narrow-spectrum interventions (10, 49–54), and designing
459 appropriate strategic rules for intervention choice given potentially conflicting
460 microbiome and infection-site resistance profiles. We also note that, independent of any
461 M-RD innovations, the widespread uptake of POC-RD-informed antibiotic use will likely
462 reduce bystander selection due to an overall reduction in antibiotic use (e.g., in the
463 context of viral infections) and a potential shift toward narrower-spectrum antibiotics
464 being prescribed against known pathogen targets.

465 Our focus on homogenous, closed populations ensures that R_0 maximization is always
466 favored by selection, simplifying the evolutionary analysis (55). However, the basic idea
467 underlying our analysis of modulating strain-fitness landscapes applies more broadly to
468 models where R_0 is not a sufficient proxy for fitness, such as in cases of multiple
469 carriage (55), host population structure (56), or an open population (28).

470 In the supplementary material, we extend our SIS model analysis to consider the effect
471 of antibiotic rationing whereby some patients are left untreated (SI.B) and show that our
472 findings are robust to (i) environmental reservoirs of resistant bacteria (SI.D), (ii) host
473 migration from high-resistance regions (SI.D), (iii) resistance-conferring mutation (SI.D),
474 (iv) competitive release (SI.D), (v) diagnostic errors (SI.E), and (vi) diagnostic escape

475 (SI.E). Inflows of resistant cases (mutation, migration) together with diagnostic errors
476 weigh on the scale in favor of resistant strains but can all be counteracted by sufficiently
477 high reproductive penalties to correctly-targeted resistant strains. Diagnostic escape
478 (57) presents a qualitatively distinct challenge where diagnostic tests themselves
479 become obsolete due to evolutionary responses in the pathogen (e.g., loss or
480 modification of resistance marker). The risk of diagnostic escape highlights the
481 importance of active resistance surveillance and rapid new-diagnostic development.

482 Point-of-care resistance diagnostics are already a top public-health priority, with a major
483 emphasis on rapidity (<1 hour) (58). Rapid point-of-care diagnostics are critical for early
484 effective treatment of life-threatening infections when treatment cannot be delayed.
485 However, most antibiotic prescriptions are for less severe infections where patients can
486 wait longer to benefit from more complete diagnostic information (13). Our analyses
487 illustrate that, for the public health goal of selecting against resistance in pathogens with
488 minimal bystander selection, we have more time to act—delays until treatment on the
489 order of hours or even days following initial infection may still allow for selection against
490 resistance (Fig 2), However, our conclusions depend critically on the life-history of the
491 target pathogen, with the message that reversing resistance in opportunistic pathogens
492 subject to 'bystander' selection is not generally plausible with POC-RD information
493 alone (Fig. 4), and will require additional interventions conditioned on carriage RD (Fig
494 5). Our conclusions also depend on the ability of RD to distinguish multiple resistances
495 in a multi-drug context, highlighting the importance of diagnostic breadth as well as
496 rapidity. Diagnostic-informed approaches to reversing resistance face another time
497 constraint—our proposed strategies for resistance-targeted intervention are most

effective when pan-resistant strains are still rare (SI.B). If we fail to act decisively while bacteria that are resistant to all antibiotics remain rare (59, 60), we may then be unable to reverse the continued rise of untreatable bacterial disease.

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