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 thought to be 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 POC-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 triggering targeted interventions that reduce their opportunities for transmission. We assess this diagnostic-imposed fitness cost in the context of a spectrum of bacterial population biologies and POC-RD conditional strategies, 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 both POC and 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).
Less often considered is a second potential benefit of POC-RD: to enable “Search & Destroy” (S&D) tactics to combat the most dangerous resistant pathogen strains, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant *Enterobacteriaceae* (CRE) (19–24). S&D strategies aim to identify and then isolate patients who are carrying problematic resistant strains until pathogen clearance can be confirmed. If resistant strains can be rapidly, accurately identified and their transmission curtailed by targeted infection-control measures, then S&D can create a *non-biological diagnostic-imposed fitness cost* borne only by targeted resistant strains. However, the magnitude of this fitness cost is hotly debated, especially in the context of MRSA control (25, 26), and, in any event, intensive medical interventions such as patient isolation are not a practical or economical option in many circumstances.

In this paper, we ask when it is possible to create *net selection against resistance*, even when there are no biological fitness costs associated with resistance and all non-antibiotic intervention options are only moderately effective. We define “net selection against resistance” as maintaining the fitness of one or more resistant strains below that of the drug-sensitive strain, so that the frequency of these resistant strains will decline toward zero. This can be accomplished, generally speaking, when diagnostics permit medical personnel to artificially shape the pathogen fitness landscape so that resistant strains are disproportionately disadvantaged. We show that the potential to reduce or even reverse selection on resistance depends on two key factors. (i) **Pathogen lifestyle**: is symptomatic disease tightly coupled to transmission (obligate pathogen), or can the 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 only two 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            | Selection against drug-1 resistance is **possible** while prescribing the best-available antibiotic treatment to all patients. |
| Simple Obligate  | Yes           | Selection against pan resistance is **possible only if either** some patients with sensitive infection are left untreated or a highly-effective infection intervention (“isolation”) is available. |
| Opportunistic    | No/Yes        | Selection against drug-1 resistance **may be impossible**, even if all those with sensitive infection were 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 susceptibility and a resistance diagnostic that can be used at the point of care to determine an infecting pathogen’s susceptibility pattern (“resistance profile”) prior to treatment. The model encompasses a spectrum of pathogen lifestyles, from “simple obligate pathogens” (immediately causing disease upon transmission, Fig 1A,B) to “opportunistic pathogens” (transmission from an asymptomatic carriage phase as well as during symptomatic disease, Fig 1C).
**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). For notational simplicity and to focus on the most challenging case, we assume that there are no biological fitness costs associated with resistance.

**Figure 1.** Schematic of the obligate/SIS (A,B) and opportunistic/SCIS (C) epidemiological models. Boxes denote proportions of hosts in mutually exclusive states: for uninfected (susceptible) hosts, 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.

**Point-of-care resistance diagnosis (POC-RD) and targeted treatment and control:**

Suppose that a resistance diagnostic is available that can, at the point of care, determine which strain is causing each patient’s infection (Fig. 1B). Health care providers and public health officials (hereafter “providers”) could then prescribe drug 1 and standard transmission control (STC) measures for all patients found to have pan-sensitive infection; drug 2 and heightened transmission control (HTC) measures for those found to have drug-1-resistant infection; drug 1 and HTC for those found to have drug-2-resistant infection; and HTC without antibiotic treatment for those found to have pan-resistant infection. We will use notation HTC$_X$ to refer to the HTC measures that can be feasibly targeted to prevent transmission of the strain with resistance profile $X=1,2,12$.

**Epidemiological dynamics:** Transmission and disease dynamics are described in general by a Susceptible-Carriage-Infected (SCIS) epidemiological model (the SIS model is a limiting case), with carriage compartments $C_X$ and infection compartments $I_X$ describing the prevalence, respectively, of asymptomatic and symptomatic infections with resistance profile $X=0,1,2,12$. Consider the relatively simple case in which drug-2 resistance has not yet emerged. Under drug-1-resistance-targeted treatment and
control, epidemiological dynamics are schematized in Fig 1C and described by a system of four differential equations:

\[
\dot{C}_0(t) = (\beta^C C_0(t) + \beta^I I_0(t))S(t) - (\gamma^C + \phi_1^C + \phi_2^C + d)C_0(t)
\]

\[
\dot{I}_0(t) = dC_0(t) - \gamma^I I_0(t)
\]

\[
\dot{C}_1(t) = (\beta^C C_1(t) + \beta^I I_1(t))S(t) - (\gamma^C + \phi_2^C + d)C_1(t)
\]

\[
\dot{I}_1(t) = dC_1(t) - \gamma^I I_1(t)
\]

plus the constraint that prevalences add to one: \(S(t) + C_0(t) + I_0(t) + C_1(t) + I_1(t) = 1\).

For notation, see table 2.

| Notation | Details |
|----------|---------|
| \(x, X\) | Two antibiotics \(x \in \{1, 2\}\) are available and strains with up to four resistance profiles \(X \in \{0, 1, 2, 12\}\) are in circulation. “Strain \(X\)” refers to a strain that is resistant to all drugs \(x \in X\) and sensitive to all drugs \(x \notin X\), with “strain 0” being the pan-sensitive strain. |
| \(d \geq 0\) | Rate at which infection develops from carriage (in the limit \(d \to \infty\), we recover the SIS case) |
| \(\beta^C, \beta^I > 0\) | Transmission rates from carriage and during infection, if uncontrolled |
| \(\gamma^C > 0\) | Baseline carriage clearance rate |
| \(\phi_x^C \geq 0,\) | Carriage clearance rate of drug-\(x\)-sensitive strain due to bystander exposure to drug \(x\) |
| \(\gamma_0^I > 0\) | Baseline infection clearance rate |
| \(\gamma_x^I > \gamma_0^I\) | Infection clearance rate of drug-\(x\)-sensitive strain when treated with drug \(x\) |
| \(\tau_x = \frac{1}{\gamma_x^I}\) | Mean duration of drug-\(x\)-sensitive infection when treated with drug \(x = 1, 2\) or when left untreated \(x = 0\) |
| \(Z_x^I, Z_x^C \leq 1\) | Proportional reduction in transmission during infection \(Z_x^I\) or during
asymptomatic carriage \( Z^C_X \) due to heightened transmission control (HTC_X) measures targeted against strain \( X \)

| \( C_X(t), I_X(t) \) | Population-wide mass of hosts colonized by \( (C_X(t)) \) or infected with \( (I_X(t)) \) strain \( X \) at time \( t \geq 0 \)
| \( \alpha^*_1, \alpha^*_12 \) | Maximal proportion of pan-sensitive infections that can be treated with drug 1 when POC-RD is available, without selecting for drug-1-resistance \( (\alpha^*_1) \) or pan-resistance \( (\alpha^*_12) \); referred to as “maximal sustainable antibiotic use”
| \( L^I_X \) | Mean duration of infection caused by strain \( X \)
| \( L^C_X \) | Mean duration of asymptomatic colonization ("carriage") by strain \( X \) before clearance or progression to infection
| \( P^C_X \) | Likelihood that colonizing strain \( X \) will progress to cause infection before being cleared from the host
| \( r_X \geq 0 \) | Rate at which resistant strain \( X \) is discovered while in the carriage state

**Table 2: Notation.**

**Selection for/against resistance:** Let \( R_{0,X} \) denote the reproductive number of strain \( X \). For each \( X = 1,2,12 \), we use the difference \( R_{0,X} - R_{0,0} \) to quantify the extent of selection for or against the resistant strain \( X \). We say there is selection against drug-1, drug-2, and/or pan resistance if \( R_{0,1} - R_{0,0} < 0 \), \( R_{0,2} - R_{0,0} < 0 \) and/or \( R_{0,12} - R_{0,0} < 0 \), respectively.

See the SI for extensions of our analysis to settings with biological fitness costs associated with resistance; public health interventions aimed at discovering drug-resistant infections more quickly; intermediate resistance (see also the Discussion); diagnostic delay; resistance-conferring mutation; host migration; and diagnostic escape.
Results

Case #1: 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 from an expository point of view to begin by considering the implications of POC-RD in a simple SIS model (Fig 1A,B).

Leveraging POC-RD to select against drug 1 resistance: In the absence of POC-RD, any drug-1 use would necessarily put the drug-1-resistant strain at a selective advantage. The availability of POC-RD changes this logic by allowing providers to target drug-1-resistant infections with alternative treatments (drug 2) and heightened control (HTC1). Suppose for the moment that drug-2 treatment is equally effective against drug-1-resistant infection as drug-1 treatment is against pan-sensitive infection, i.e., \(\gamma^I_2 = \gamma^I_1\) and hence \(\tau_2 = \tau_1\). Armed with POC-RD, providers can prescribe the best-available antibiotic treatment to all patients while also selecting against drug-1 resistance. To see why, note that the pan-sensitive strain’s reproductive number \(R_{0,0} = \tau_1 \beta^I\) when treated with drug 1 and subjected to standard control (STC), while the drug-1-resistant strain’s reproductive number \(R_{0,1} = \tau_2 \beta^I Z_1^I\) when treated with drug 2 and subjected to HTC1. Since by assumption \(\tau_2 = \tau_1\), \(R_{0,1} - R_{0,0} = -\tau_1 \beta^I (1 - Z_1^I) < 0\), allowing for selection against drug-1 resistance so long as HTC1 measures are even modestly effective (any \(Z_1^I < 1\)). More broadly, when drug 2 is not equally effective as drug 1, \(R_{0,1} - R_{0,0} = \ldots\)
\[ -\tau_1 \beta^I \left(1 - \frac{Z^I_1}{\tau_1}\right) \] So long as \( Z^I_1 < \frac{\tau_1}{\tau_2} \), it remains possible to select against drug-1 resistance even as all patients with pan-sensitive infection are treated with drug 1.

**Leveraging POC-RD to select against drug-2 resistance:** Armed with POC-RD, providers can prescribe the best-available antibiotic treatment to all patients while also selecting against drug-2 resistance. To see why, note that the drug-2-resistant strain's reproductive number \( R_{0,2} = \tau_1 \beta^I Z^I_2 \) when treated with drug 1 and subjected to HTC2 while the pan-sensitive strain's reproductive number \( R_{0,0} = \tau_1 \beta^I \); so, \( R_{0,2} - R_{0,0} = -\tau_1 \beta^I (1 - Z^I_2) < 0 \) as long as HTC2 measures are even modestly effective (any \( Z^I_2 < 1 \)).

**Sustainable antibiotic use in the face of drug-1 resistance:** Suppose for the moment that drug-2 resistance has not yet emerged in the target-pathogen population. By the previous analysis, the drug-1-resistant strain can be held at a reproductive disadvantage, even as all patients receive the best-available treatment, so long as \( Z^I_1 < \frac{\tau_1}{\tau_2} \). But what if drug 2 is less effective than drug 1 (so that \( \tau_1 < \tau_2 \)) and HTC1 effectiveness is sufficiently modest that \( Z^I_1 > \frac{\tau_1}{\tau_2} \)? In this case, at most fraction \( \alpha^*_1 \) of those with pan-sensitive infection can be treated without selecting for drug-1 resistance, where

\[ \alpha^*_1 = \frac{\tau_0 - \tau_2 Z^I_1}{\tau_0 - \tau_1} \in (0,1) \]

*Equation 1*

\( \alpha^*_1 \) is the “maximal sustainable antibiotic use in the face of drug-1 resistance”; see SI.B for the derivation of \( \alpha^*_1 \).
Sustainable antibiotic use in the face of pan resistance: The pan-resistant strain's reproductive number when subjected to HTC\(_{12}\) is \(R_{0,12} = \tau_0 \beta^I Z_{12}^I\). If HTC\(_{12}\) measures are sufficiently effective that \(Z_{12}^I < \frac{\tau_1}{\tau_0}\), then POC-RD enables providers to prescribe the best-available treatment for all infections while also selecting against pan resistance. On the other hand, if \(Z_{12}^I > \frac{\tau_1}{\tau_0}\), then at most fraction \(\alpha_{12}^*\) of those with pan-sensitive infections can be treated without selecting for pan resistance, where \(\alpha_{12}^* = \frac{\tau_0 (1 - Z_{12}^I)}{\tau_0 - \tau_1} \in (0,1)\). (The derivation of \(\alpha_{12}^*\) is similar to that of \(\alpha_1^*\).) Overall, the maximal fraction of pan-sensitive infections that can be treated with drug 1 without selecting for any resistant strain ("maximal sustainable antibiotic use") is \(\alpha^* = \min\{\alpha_1^*, \alpha_{12}^*\}\).

Impact of resistance emergence on maximal sustainable antibiotic use: An interesting implication of our analysis is that the emergence of drug-2 resistance in the pathogen population (through host migration, mutation, horizontal gene transfer from another bacterial population, etc) does not have any impact on maximal sustainable antibiotic use, so long as POC-RD is available that can detect all drug-1-resistant and drug-2-resistant strains in circulation ("multidrug POC-RD"). The reason is simple: multidrug POC-RD allows drug-2-resistant infections to be controlled even more effectively than pan-sensitive infections, since drug-2-resistant infections can be treated with drug 1 (same as pan-sensitive infections) but also subjected to HTC (more than pan-sensitive infections). However, the subsequent emergence of pan resistance can potentially reduce maximal sustainable antibiotic use. In particular, so long as \(Z_1^I \leq Z_{12}^I\) (meaning that no stronger infection HTC measures can be deployed against the pan-resistant strain than against the drug-1-resistant strain), \(\alpha_{12}^* < \alpha_1^*\) and the emergence of pan...
resistance reduces maximal sustainable antibiotic use $\alpha^*$ from $\alpha^*_1$ to $\alpha^*_2$. On the other hand, if stronger infection HTC measures (such as isolation of infected persons or slaughter of infected livestock) are held in reserve for use against pan-resistant infections and these measures are sufficiently effective that $Z_{12}^I \leq Z_{12}^{I_2}$, then $\alpha^*_{12} \geq \alpha^*_1$ and the emergence of pan resistance also has no effect on maximal sustainable antibiotic use.

**Impact of POC-RD on maximal sustainable antibiotic use:** POC-RD allows all patients with drug-1-resistant infection to be treated with drug 2 and, since $\alpha^*_1 > 0$ and $\alpha^*_2 > 0$, allows at least some patients with pan-sensitive infection to be treated with drug 1 without selecting for drug-1 resistance, drug-2 resistance, or pan-resistance. By contrast, if POC-RD were not available, any amount of drug-1 and drug-2 use would necessarily select for drug-1 resistance, drug-2 resistance, and pan resistance. Thus, one can interpret $\alpha^*_1$ (and $\alpha^* = \min(\alpha^*_1, \alpha^*_2)$) as the extent to which POC-RD allows drug 1 to be sustainably prescribed once drug-1 resistance (and pan resistance) has emerged in the pathogen population. In Fig 2, we illustrate $\alpha^*_1$ and $\alpha^*$ for a generic acute pathogen (10 day infection, $R_0 = 2$ in absence of treatment), together with maximal sustainable antibiotic use given no biological fitness cost of resistance and no POC-RD. In the SI, we introduce a more complex model with diagnostic delay, where patients are initially treated with the first-line drug 1 until diagnostic information is received after delay $D$. Fig 2 illustrates that our results are relatively robust to diagnostic delay, with delays of up to 1 day still allowing the effective management of patient and public health in the absence of pan resistance.
Figure 2. Rapid resistance diagnostics enable conditional treatment and infection control strategies that can select against resistance for obligate pathogens even with widespread antibiotic use. The maximal proportion of sensitive infections that can be treated without causing an increase in resistance (\(x\)) is plotted 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), for which; RD available with delay and pan-resistance not yet emerged (RD, no \(l_2\)); RD available with delay and pan-resistance widespread (RD, \(l_2\)). Details in SI.B. Parameters (rates per day): , , .

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

The analysis thus far applies to obligate pathogens where transmission only occurs during symptomatic disease. However, many disease-causing bacteria are opportunistic pathogens capable of transmission from an asymptomatic carriage state (at rate \(r\)) where they can live harmlessly in a host microbial compartment such as the gut or the nasopharynx. While in carriage, such pathogens face “bystander exposure” to antibiotics used to treat infections caused by other pathogens or to treat noninfectious conditions (30). Take for example the pneumococcus (\(S. pneumoniae\)), one of the top bacterial causes of death globally (31) and a leading cause of antibiotic prescription.
Despite the severe burden of disease, the pneumococcus is subjected in the US to approximately 9.1 times more courses of any antibiotic during asymptomatic carriage than during disease. Fig 3 compares the volume of bystander selection to target antibiotic exposure for several major bacterial pathogens. An alternate representation of the proportions of bystander exposure is presented in Tedijanto et al (30).

An implication of our analysis (below) is that, for pathogens like *S. pneumoniae*, *E. coli*, *H. influenzae*, and *C. difficile* that overwhelmingly face bystander exposure to antibiotics, even the strongest possible medical interventions informed by point-of-infection resistance diagnostics can be insufficient to halt the rise of resistance to any drug in routine use. On the other hand, for pathogens like *N. gonorrhoeae* that face far less bystander exposure, POC-RD-targeted interventions can potentially select against resistant strains and hence reverse the rise of resistance in these pathogen populations.
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 (30) for source references and details 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 (32) and carriage prevalence (33); see SI.F for details.

Reproductive-number analysis when POC-RD is available: For each antibiotic-resistance genotype $X = 0,1,2,12$, let $L_X^C$ be the expected length of time that strain $X$ spends in carriage prior to being cleared from the host or moving on to cause infection, let $P_X^C$ be the probability that strain $X$ progresses to cause infection before clearance, and let $L_X^I$ be the expected duration of strain-$X$ infection. When POC-RD is available so that strain-$X$ infections can be subjected to HTC$_X$, each strain’s reproductive number is $R_{0,X} = L_X^C \beta^C + P_X^C Z_X^I \beta^I L_X^I$ (with $Z_0 = 1$ since pan-sensitive infections are subjected to standard transmission control). To derive $L_X^C$ and $P_X^C$, note that each strain progresses to infection at rate $d$, clears due to immune response at rate $\gamma^C$, and clears due to bystander exposure at rate $\sum_{x \in X} \phi_x^C$. Since one of these carriage-ending events occurs at rate $d + \gamma^C + \sum_{x \in X} \phi_x^C$, the expected duration of the carriage phase is $L_X^C = \frac{1}{d + \gamma^C + \sum_{x \in X} \phi_x^C}$ and the likelihood that it ends with infection is $P_X^C = \frac{d}{d + \gamma^C + \sum_{x \in X} \phi_x^C}$. Each strain’s reproductive number therefore takes the form
Equation 2

\[ R_{0_X} = \frac{\beta_c + dZ_X^I \beta^I V^I_X}{d + y_c + \sum_{x \in X} \phi^c_x} \]

where the expected duration of infection \(I^I_X\) depends on how infections are treated.

**Potentially inevitable selection for pan resistance and drug-1 resistance:** The pan-sensitive strain’s reproductive number is at most \(R_{0,0} = \frac{\beta_c + d\beta^I \tau_0}{d + y_c + \phi^c_1 + \phi^c_2}\) (achieved if pan-sensitive infections are always left untreated so that they have expected duration \(\tau_0\)), while the pan-resistant strain’s reproductive number is at least \(R_{0,12} = \frac{\beta_c}{d + y_c}\) (achieved if all pan-resistant infections are perfectly isolated so that \(Z^1_{12} = 0\)). \(R_{0,12} > R_{0,0}\) whenever the rate \(\phi^c_1\) of bystander selection due to drug-1 exposure is sufficiently high (\(\phi^c_1 > \frac{d\beta^I \tau_0 (d + y_c)}{\beta_c} - \phi^c_2\)). In such cases, selection for pan resistance in the target-pathogen population is inevitable despite the availability of POC-RD, even if all pan-sensitive infections could be left untreated and all pan-resistant infections could be perfectly isolated. Similarly, the drug-1-resistant strain’s reproductive number is at least \(R_{0,1} = \frac{\beta_c}{d + y_c + \phi^c_2}\), with \(R_{0,1} > R_{0,0}\) whenever \(\phi^c_1 > \frac{d\beta^I \tau_0 (d + y_c + \phi^c_2)}{\beta_c}\). In such cases, selection for drug-1 resistance in the target-pathogen population is also inevitable despite the availability of POC-RD.

**Sustainable antibiotic use in the face of drug-1 resistance:** Suppose for the moment that drug-2 resistance has not yet emerged in the target-pathogen population and that \(\phi^c_1\) is low enough so that selection for drug-1 resistance is not inevitable. For concreteness, suppose that fraction \(\alpha \in [0,1]\) of pan-sensitive infections are treated with drug 1 (so
that such infections’ expected duration $L'_0 = \alpha \tau_1 + (1 - \alpha)\tau_0$) while drug-1-resistant infections are all treated with drug 2 (so that $L'_1 = \tau_2$) and subjected to HTC1. The pan-sensitive strain’s reproductive number is then $R_{0,0}(\alpha) = \frac{\beta C + dZ_1^1 \beta \tau_1}{d + y C + \Phi_C^1 + \Phi_C^2}$ while the drug-1-resistant strain’s reproductive number $R_{0,1} = \frac{\beta C + dZ_1^1 \beta \tau_2}{d + y C + \Phi_C^1 + \Phi_C^2}$. The maximal fraction of pan-sensitive infections that can be treated without selecting for drug-1 resistance is $\alpha^*_1$, defined implicitly by the condition $R_{0,0}(\alpha^*_1) = R_{0,1}$.

**Sustainable antibiotic use in the face of pan resistance:** Suppose now that drug-1, drug-2, and pan resistance have all emerged in the target-pathogen population and that $\Phi_C^1$ is low enough so that selection for pan resistance is not inevitable. Building on the previous analysis, suppose that drug-2-resistant infections are treated with drug 1 (so that $L'_2 = \tau_1$) and subjected to HTC2 while pan-resistant infections are untreated (so that $L'_2 = \tau_0$) and subjected to HTC12. The drug-2-resistant strain’s reproductive number is then $R_{0,2} = \frac{\beta C + dZ_2^1 \beta \tau_1}{d + y C + \Phi_C^1}$, while the pan-resistant strain’s reproductive number $R_{0,12} = \frac{\beta C + dZ_2^1 \beta \tau_0}{d + y C}$. The maximal fraction of pan-sensitive infections that can be treated with drug 1 without selecting for drug-2 resistance is $\alpha^*_2$, defined implicitly by the condition $R_{0,0}(\alpha^*_2) = R_{0,2}$, and the maximal fraction that can be treated with drug 1 without selecting for pan resistance is $\alpha^*_{12}$, defined implicitly by the condition $R_{0,0}(\alpha^*_{12}) = R_{0,12}$. Overall, the maximal fraction of patients with pan-sensitive infection who can be sustainably treated without selecting for any resistant strain is $\alpha^* = \min\{\alpha^*_1, \alpha^*_2, \alpha^*_{12}\}$.

In Fig 4, we parameterize our SCIS model with parameters illustrative for the pneumococcus, to show the maximal sustainable antibiotic use given POC-RD for a
bacterium with substantial bystander exposure (Fig 3). Even in the absence of pan-resistant strains, the long-carriage duration of most pneumococcal serotypes (median serotype-specific carriage duration is approximately 10 weeks) ensures that bystander selection dominates the relatively weak impact of POC-RD during rare and brief infection events (median infection duration in absence of treatment is 8 days).

**Figure 4. POC-RD alone cannot reverse selection on pneumococcal resistance, due to long carriage times.** The maximal proportion of sensitive infections that can be treated without causing an increase in drug 1 resistance ( ) is plotted against the expected duration of carriage. Two POC-RD scenarios are shown: with ( ) and without ( ) transmission control. Serotype 6A (bold font) represents the median carriage duration serotype; serotypes with shorter carriage durations are also illustrated via vertical arrows. The remaining parameters (rates per day) are $d = 0.001$, $\beta = 5 \times 10^{-4}$, $\gamma = 0$, $\delta = 1$, $\zeta = 0.125$. We make the simplifying assumption that baseline carriage and infection transmission rates are identical ( ) given which does not depend on . 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 socially isolated even when they do not have active infection? Consider the South Swedish Pneumococcal Intervention Project (SSIP) (34, 35), a public health intervention launched in January 1995 in Malmohus County, Sweden that aimed to reduce penicillin-resistant pneumococcus (PRP) transmission, especially at preschool daycares. Anytime a preschool-age child was identified with active 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.

In SI.C, we extend our analysis of the SCIS model to examine the potential of carriage RD-based interventions to generate selection against resistance. A key result is that, in order to select against drug-1-resistance, the drug-1-resistant strain must be discovered while in carriage at a rate $r_1$ that strictly exceeds the rate $\phi_1^C$ at which the sensitive strain is cleared from carriage due to bystander exposure to drug 1. In Fig 5, we again parameterize our SCIS model for the pneumococcus as in Fig 4, under two extreme scenarios of carriage duration (36): 20 weeks (Fig 5A, serotype 6B) and 2 weeks (Fig 5B, serotypes 1,4,5). The blue parameter space in Fig 5 highlights the combinations of carriage discovery rate ($r_1$, x-axis) and HTC effectiveness against drug-1-resistant bacteria discovered in carriage ($Z_1^C = 1$, y-axis) that lead to a net selection against drug-1 resistance. Fig 5A illustrates the most problematic serotype from a POC-RD
perspective, due to the dominance of bystander selection. Given the introduction of annual carriage surveillance (ensuring ), our parameterized model predicts that HTC interventions (such as removal of an infant from nursery) would need to reduce strain-1 transmission from carriage by at least 20% in order to select against the drug-1-resistant genotype. This threshold effectiveness for carriage HTC depends only weakly on the intervention chosen during infection episodes (e.g., level of drug withholding ), due to the overwhelming importance of selection during carriage for this serotype. In contrast, for the shortest duration serotypes (Fig 5B) we see that the control contour depends more heavily on and, under the reasonable scenario that there is minimal withholding ( approaches one), the control contour again requires a greater than 20% reduction in strain-1 transmission during carriage. Epidemiological studies of the impact of child-care attendance on pneumococcal carriage suggest that a 2-fold reduction in transmission due to removal from daycare is not unreasonable (37).
Figure 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 ($Z^C_1$). (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 ($\alpha = 0$) and without ($\alpha = 1$) treatment withholding for susceptible genotype infections. 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 $d = 0.001$, $\phi_1^C = 5 \times 10^{-4}$, $\phi_2^C = 0$, $\gamma_1^I = \gamma_2^I = 1$, $\gamma_0^I = 0.125$, $\gamma^C = 0.006$ (A), $\gamma^C = 0.07$ (B). We make the simplifying assumption that baseline carriage and infection transmission rates are identical given which $\alpha^*$ does not depend on $\beta$. 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 grossly 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 classmates of children who developed PRP infections were tested. Thus, even if PRP were rare in the general population, each child tested through SSPIP would have a substantial likelihood of PRP carriage. By introducing simple contact-tracing principles, the effective rate of carriage discovery can be much higher for a given level of investment in patient sampling.

Discussion

The antibiotic-resistance crisis is placing increasing pressure on healthcare globally and is widely viewed as a one-way street toward a dangerous “post-antibiotic world” (1, 4).
In this paper, we ask whether resistance diagnostics (RD), when combined with public health interventions such as heightened transmission control (HTC) for drug-resistant bacterial strains, can substantially change the trajectory of resistance evolution. In the early decades of the antibiotic era, doctors had no choice but to treat and control infection *unconditionally*, inevitably making antibiotics “exhaustible resources” whose value to society is diminished by use (2, 3). By enabling resistant strains to be targeted with alternative treatments and additional control *conditional* on their resistance profile, RD changes the traditional logic of rising resistance and even the basic economic character of antibiotics: once RD becomes available, antibiotics are no longer necessarily exhaustible resources (38).

In this paper, we show that antibiotics can in principle be transformed into “renewable resources” whose value to society increases over time even as they are put to widespread use, so long as (i) RD is available to detect the target pathogen and determine its antibiotic-sensitivity profile, (ii) prescribers use RD to adopt conditional treatment strategies, (iii) identified resistant cases are subject to more stringent transmission control, and (iv) bystander selection on the target pathogen is either minimal (Fig 3) or counter-acted (Fig 5). For obligate pathogens that face minimal bystander selection, point-of-care resistance diagnostics (POC-RD) can potentially be sufficient to create a net selection against resistant pathogen strains, reducing these strains’ prevalence over time in the pathogen population. However, for opportunistic pathogens that face extensive bystander selection, POC-RD alone is insufficient—identifying resistant strains when they are not yet causing infection (so-called “carriage RD”) is essential to reverse the rise of resistance strains. This distinction and note of
caution is important as society seeks to allocate resources most effectively in the struggle against antibiotic resistance.

Our analysis identifies strategies to renew sensitivity to an antibiotic in a pathogen population, the most effective of which depend on the availability of other antibiotics that can be used to treat resistant infections. The potential to restore antibiotic sensitivity is therefore limited once pan-resistant strains are in circulation. Consider now the impact of the discovery of a new antibiotic (drug 3) to which these bacteria are still sensitive. Drug 3’s discovery transforms previously pan-resistant bacteria into treatable “multidrug-resistant bacteria.” Providers can now deploy targeted treatment and HTC to hold the multidrug-resistant strain at a reproductive disadvantage. In this way, introducing a new antibiotic to which disease-causing strains are not yet resistant may make it possible to reverse the rise of previously pan-resistant bacteria, restoring the effectiveness of pre-existing antibiotics. Moreover, as multidrug resistance to pre-existing antibiotics grows less prevalent over time, the number of patients who need the new antibiotic will itself decline over time, allowing the new antibiotic to be held in reserve for increasingly rare cases for which it is the only effective treatment. In particular, it may not be necessary to discover even more new antibiotics beyond drug 3, so long as resistance to drug 3 does not emerge in the target pathogen population before sensitivity to drug 1 and drug 2 can be restored.

Our analysis shows that maximal sustainable antibiotic use depends on the effectiveness of the HTC measures that can be feasibly targeted against drug-1-resistant and pan-resistant infections. By design, HTC measures impose additional barriers to resistant-bacterial transmission by (i) identifying resistant bacteria (during
infection and/or asymptomatic colonization) and (ii) deploying additional resources specifically to prevent their transmission. Many sorts of HTC measures could be relevant in different contexts. Some examples: for hospital-associated infections, imposing heightened contact precautions when a hospitalized patient is found to have resistant infection (19, 21); for pneumococcal infection, requiring young children found to be infected or colonized with penicillin-resistant pneumococci to stay home from daycare (34); for sexually transmitted diseases, providing expedited partner therapy (EPT) when a patient is found to have resistant infection (39); or, for livestock-associated infections, eradicating an entire herd when resistant infection is identified. Note that HTC effectiveness may vary depending on the resistant strain being targeted, e.g., EPT measures may be less effective against pan-resistant strains since partners’ transmissibility cannot be controlled through treatment, while other measures may only be economically feasible against some strains, e.g., eradicating an entire herd may only be economical when pan-resistant infection is found, since other strains can be controlled through resistance-targeted treatment. More research is needed to quantify the effectiveness of HTC measures in practice.

Additional strategic options can be used to reduce the prevalence of bacterial strains with intermediate resistance, if POC-RD is available that provides quantitative (e.g., genomically inferred MIC score (40)) information on the degree of intermediate resistance. Details are provided in SI.B but, to see the point, imagine that POC-RD had been available when penicillin was first introduced that could quantitatively determine the penicillin sensitivity of gonorrhea infections. Neisseria gonorrhoeae strains emerged in the 1940s and 1950s that were less sensitive to penicillin but, at the time, these
strains could still be effectively treated with a higher dose (41). Armed with quantitative POC-RD, doctors would have been able to target intermediate-resistant gonococci with a higher penicillin dose—taking away the treatment-survival advantage that intermediate-resistant gonococci would otherwise enjoy—and could also have deployed additional public health resources to find and treat others who might still be spreading intermediate-resistant gonococci. Such a policy of **targeted treatment and heightened discovery** could have potentially held intermediate-resistant gonorrhea strains at an overall reproductive disadvantage relative to highly-sensitive strains.

The example of the gonococcus raises the key challenge of bystander exposure to antibiotics, as gonorrhea infection is initially asymptomatic and therefore does not drive immediate medical attention and exposure to POC-RD. During the asymptomatic phase of infection, drug-sensitive gonococcal genotypes are at risk of being cleared due to antibiotics taken for other medical concerns. In Fig 3, we outline how the extent of the bystander challenge is even greater for commensal opportunistic pathogens (42, 43) which spend proportionately longer in asymptomatic carriage states. Parameterizing our SCIS model (incorporating a carriage / asymptomatic stage $C$, prone to bystander selection) for the key commensal opportunist *S. pneumoniae* illustrates that selecting against resistance via POC-RD-informed strategies alone is not a plausible outcome for this particular pathogen (Fig 4), given the lengthy duration of carriage and relatively rare and brief infection events caused by this species.

We explore a strategic response to this concern: conditional interventions in response to diagnostic information during asymptomatic carriage. Fig 5 illustrates that coupling differential transmission control to carriage RD can drive net selection against
resistance, even for the most carriage-prone serotypes of the pneumococcus. The South Sweden Pneumococcal Isolation Project (SSIP) offers a concrete example of using carriage RD to drive public health interventions. While SSPIP targeted pneumococcal strains that remained treatable by other antibiotics, similar programs could target pan-resistant strains and, if sufficiently intensive and comprehensive, potentially select against these pan-resistant strains even as those with sensitive infection continue to receive antibiotic treatment. We note that, in theory, our logic of conditional interventions during carriage could be extended to incorporate broader ‘microbiome’ resistance diagnostics (M-RD) and M-RD-conditioned interventions. While simple in outline, implementation presents technical challenges on several fronts, not least in establishing meaningful sampling protocols, designing appropriate narrow-spectrum interventions (10, 44–49), and designing appropriate strategic rules for intervention choice given potentially conflicting microbiome and infection-site resistance profiles. We also note that, independent of any M-RD innovations, the widespread uptake of POC-RD-informed antibiotic use will likely reduce bystander selection due to an overall reduction in antibiotic use (e.g., in the context of viral infections) and a potential shift toward narrower-spectrum antibiotics being prescribed against known pathogen targets.

In the supplementary material, we show that our SIS model findings are robust to (i) environmental infection reservoirs (SI.D), (ii) host migration from high-resistance regions (SI.D), (iii) resistance-conferring mutation (SI.D), (iv) competitive release (SI.D), (v) diagnostic errors (SI.E), and (vi) diagnostic escape (SI.E). Inflows of resistant cases (mutation, migration) together with diagnostic errors weigh on the scale in favor of
resistant strains but can all be counteracted by sufficiently high reproductive penalties to correctly-targeted resistant strains. Diagnostic escape (50) presents a qualitatively distinct challenge where diagnostic tests themselves become obsolete due to evolutionary responses in the pathogen (e.g., loss or modification of resistance marker). The risk of diagnostic escape highlights the importance of active resistance surveillance and rapid new-diagnostic development.

Point-of-care resistance diagnostics are already a top public-health priority, with a major emphasis on rapidity (<1 hour) (51). Rapid point-of-care diagnostics are critical for early effective treatment of life-threatening infections when treatment cannot be delayed. However, most antibiotic prescriptions are for less severe infections where patients can wait longer to benefit from more complete diagnostic information (13). Our analyses illustrate that, for the public health goal of selecting against resistance in obligate pathogens, we have more time to act—delays until treatment on the order of hours or even days following initial infection may still allow for selection against resistance (Fig 2), and the dynamics of effective interventions during carriage play out at even slower timescales (Fig 5). However, our conclusions depend critically on the ability of RD to distinguish multiple resistances in a multi-drug context, highlighting the importance of diagnostic breadth as well as rapidity. Diagnostic-informed approaches to reversing resistance face another time 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 (52, 53), we may then be unable to reverse the continued rise of untreatable bacterial disease.
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