ASSESSING STRATEGIES FOR MANAGING DRUG RESISTANCE
IN TREATMENT OF INFECTIOUS DISEASE: INSIGHTS FROM QUEUEING THEORY

by

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Abstract

Antimicrobials have been instrumental in the treatment of infectious disease: responsible for worldwide infection control and reductions in disease-induced morbidity, and mortality. However, in every case where new chemotherapeutic agents have been introduced, resistance to them has eventually evolved. Principally, the current strategy for dealing with this problem is to invest heavily in drug development, with the hope that new drugs become available before all existing drugs lose their efficacy. Instead of focusing on the ‘development side’ of the problem, another possible strategy is to invest in methods of slowing evolution of resistance.

We use a novel application of queueing theory to demonstrate that, when comparing equivalent changes in drug development versus evolution management, the latter has a much greater effect on ensuring a continued supply of effective antimicrobial agents. Our results therefore call for a reappraisal of the current emphasis on enhancing drug development as a means of managing resistance.
Co-Authorship

This thesis conforms to the manuscript format as outlined by the School of Graduate Studies and Research. Chapter 2 is a manuscript that is directly a result of this thesis and its co-authors:

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**Author Contributions** N.S.M. and T.D. conceived the model and critically revised the manuscript; N.S.M analysed the model, collected data and wrote the paper.
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Chapter 1

General Introduction

The advent of antimicrobials has made possible the treatment of many infectious diseases. Today, however, the proliferation of drug resistance threatens to negate many of these medical triumphs. Infectious disease is a challenging global health problem and remains one of the leading causes of morbidity, mortality and health care costs worldwide. The problem of drug resistance is ubiquitous in the treatment of infectious disease. For example, some strains of Klebsiella spp. and Mycobacterium tuberculosis are completely untreatable, while resistance to all antimalarials and all antiretrovirals has been identified.

Although drug development will be important in providing novel treatment of infectious disease, the success of any long-term strategy necessitates better management of available drugs. Specifically, strategies to preserve drug efficacy aim to prevent the emergence of resistance over the course of treatment and slow the spread of resistant infection in the population. The purpose of this introduction is to provide context in antimicrobial treatment and the evolution of drug resistance.

Antimicrobial resistance

Antimicrobials are biochemical agents used in medical treatment to aid in the clearance or control of infection by targeting disease-causing microbes. In general, a
drug may actively destroy a microbe or inhibit its growth and replication\textsuperscript{10}. The antimicrobial activity of a drug depends on drug dose and duration; however, overall drug efficacy is limited by the evolution of drug resistance\textsuperscript{11}.

Drug resistance is a trait that renders a microbe less susceptible to a drug. Microbes gain drug resistance via novel genes obtained through horizontal (e.g. plasmids or transposons) or vertical (e.g. mutation) transfer\textsuperscript{6,9}. Drug resistance manifests in a variety of ways including the modification of drug targets and enzymatic function as well as drug degradation, reduced uptake and drug efflux\textsuperscript{12,13}. Regardless of the mechanism, a resistant microbe experiences reduced antimicrobial activity (partially resistant) or the complete absence of drug activity (fully resistant). In the presence of a drug this imparts an advantage to the resistant (mutant) microbe over susceptible (wild-type) microbes\textsuperscript{12}. The selection of drug resistant microbes causes proliferation of drug resistance within an individual leading to drug or treatment failure, while the spread of resistant infection in a population decreases drug efficacy\textsuperscript{1}.

**Antimicrobial activity**

Typically, the antimicrobial activity of a drug is described by the degree of resistance at varying drug doses\textsuperscript{12}. A drug may not be effective at low concentrations such that microbes are insensitive to low drug doses. The initial decline of susceptible microbes occurs at the minimum inhibitory concentration of a drug\textsuperscript{12}. The microbial population decreases further as mutants with varying degrees of resistance are cleared at
increasing doses\textsuperscript{12}. The mutant prevention concentration of a drug defines the lowest concentration at which all microbes are cleared and resistance is undetectable\textsuperscript{12}.

Drug resistance, while advantageous to a microbe in the presence of a drug, is in many cases otherwise costly to fitness\textsuperscript{1}. For example, the evolution of resistance may result in reduced infectivity or ability to invade new hosts and reduced rates of growth or reproduction\textsuperscript{1}. Thus, even though resistant mutants can occur by chance at drug concentrations below the minimum inhibitory concentration, resistant microbes are outcompeted or suppressed by wild-type microbes. These dynamics are reversed at drug doses between the minimum inhibitory concentration and the mutant prevention concentration, the concentration range referred to as the mutation selection window\textsuperscript{12,14}. As resistance evolves in a microbial population it affects antimicrobial activity: increasing the mutation selection window or necessitating higher effective drug doses\textsuperscript{12,14}.

In vivo aspects of drug treatment pose additional challenges to antimicrobial activity. At higher doses, a drug can have toxic effects on the normal healthy function of host cells, which may prevent its use at concentrations above the mutant prevention concentration\textsuperscript{11}. Also, even if administered at a high dose, drug concentration declines as a drug is metabolized or expelled from the body. The drug half-life defines the time it takes for drug concentration to decrease by half its initial value when delivery is stopped. Therefore, the half-life of a drug can affect the evolution of resistance in microbes that
have not been cleared following a course of treatment or if reinfection occurs and exposes microbes to low drug doses\textsuperscript{13,15}. A drug’s half-life will depend on its chemical composition as well as the biochemical properties of different tissues, which make the site of infection and delivery mode of treatment important factors. Generally, a shorter half-life yields less opportunity for selection of drug resistant microbes\textsuperscript{15}.

**Treatment regimens**

Treatment regimens are developed according to a drug dose and treatment duration that aims to minimize toxicity (i.e., side effects) and maximize treatment efficacy (i.e., microbial clearance or alleviation of symptoms)\textsuperscript{11}. The conventional wisdom of antimicrobial treatment is to ‘hit hard and hit early’ to ‘ensure very high cure rates’; the premise being that fewer and more susceptible microbes are present earlier in infection and a high dose and long duration of treatment ensures radical elimination and thus minimal risk of developing drug resistance over the course of therapy\textsuperscript{16}. In general, there is a correlation between infection duration and the length of treatment. The goal of treatment for chronic or recurrent infections is the alleviation of symptoms, reduction in microbial burden and management of disease progression, which often requires long course or repeated treatment at high drug doses\textsuperscript{11}. On the other hand, in acute infection, the purpose of treatment is to clear infection, for which a single short-course therapy may be sufficient\textsuperscript{11}. The immune system is also central to infection dynamics and the course of treatment. In this regard, the immune system may be able to clear infection in the
absence of drugs or once the microbial load is reduced to a low enough level by treatment\textsuperscript{11}.

While aggressive chemotherapy has a basis in our understanding of drug resistance evolution, it should not be regarded as a general solution to the problem\textsuperscript{15,16}. For instance, as soon as resistance is acquired, the selection pressure imposed by radical treatment strongly favors drug resistance, increasing spread within an infected individual. Furthermore, differences among microbes in mutation rate, infection dynamics and immunological response pose dissimilar treatment demands. For example, in HIV therapy, there is a high risk of drug resistance evolving over the course of treatment (from de-novo mutation) as a result of chronic infection and viral mutability\textsuperscript{1}. This differs from treatment of malaria, in which drug resistance is more likely to originate from infection by resistant parasites (transmitted resistance) than from de-novo mutation\textsuperscript{1}. The long-term success of treatment depends on balancing clinical outcome with the risk of evolving resistance\textsuperscript{5,11,16}.

**Evolution of drug resistance**

The proliferation of drug resistance involves two processes. First, an individual who receives treatment acquires drug resistant infection, and second, drug resistant microbes are transmitted to other individuals, causing new infections that spread drug resistance in the population\textsuperscript{17}. At the level of the population, the use of a drug exposes microbes to an environmental stress that selects for drug resistance. This selection
pressure can vary in time and space as a result of infection dynamics in the population as well as the number of different drugs used to treat the infected population. In general, the spread of drug resistant infection is determined by the probability that a drug resistant microbe is transmitted to a new host who is then treated with the same drug\textsuperscript{18}. 

For a single individual, drug resistance is not problematic provided that another drug is available and is effective against the drug resistant microbe. Of course, drug resistance can develop to this drug too. At the level of the population, drug resistance could be avoided or slowed altogether if the use of drugs was stopped or rationed, but at the level of the individual, it is nonsensical to deny necessary treatment. This approach is nonetheless important in regards to the inappropriate use of antimicrobials, which does not jeopardize treatment success and must be averted to decrease overall selection pressure for drug resistance\textsuperscript{2}. The sensible use of antimicrobials is crucial to preserving efficacy at the level of the population and also the success of treatment for an individual.

**Thesis objectives**

This thesis explores strategies for managing drug resistance in treatment of infectious disease. In Chapter 2, we assess two general methods in dealing with the problem of antimicrobial resistance: drug development and evolution management. Using a combination of data and mathematical modelling, we conclude that slowing evolution is the most effective strategy. In Chapter 3, we discuss ideas in rational drug use to address the problem of drug resistance. Lastly, Chapter 4 is a summary of results from the thesis.
References


Chapter 2

Slowing evolution is more effective than enhancing drug development for managing resistance

Abstract

Drug resistance is one of the most serious public health problems and threatens to thwart our ability to treat many infectious diseases\textsuperscript{1-4}. In our efforts to manage infectious disease there have been repeated instances of the development of new drugs followed by the subsequent evolution of resistance. This pattern has been repeated so often that the evolution of resistance is now considered inevitable\textsuperscript{5-12}. In principle there are two ways in which this problem might be addressed – (i) enhancing the rate at which new drugs are brought to market, and (ii) slowing the rate at which resistance to currently used drugs evolves. We present a modelling approach based on queueing theory that explores how interventions aimed at these two facets of the problem affect the ability of the entire drug supply system to provide service. Analytical and simulation-based results show that, all else equal, slowing the evolution of drug resistance is more effective at ensuring an adequate supply of effective drugs than is enhancing the rate at which new drugs are developed. This lends support to the idea that evolution management is not only a significant component of the solution to the problem of drug resistance, but may in fact be the most important component.
In principle, the evolution of resistance to any particular drug is not problematic provided that an alternative drug is available. What matters is therefore the rate at which drug resistance evolves relative to the rate at which new drugs are brought to market. Consequently there are two ways that we might try to ensure the availability of effective drugs: (i) by increasing the rate of drug discovery, or (ii) by increasing the time it takes for resistance to evolve through better resistance management.

Approaches for increasing the rate of drug discovery are probably familiar, and include research devoted to developing screening technology for new compounds as well as developing new classes of antimicrobial agents. Approaches for slowing the evolution of resistance are perhaps less familiar, but include research into new strategies for reducing the inappropriate use of antimicrobials, determining when and where existing drugs should be used in combination versus as sequential monotherapies, as well as determining the optimal dose and timing of deployment for these existing drugs1,13-16. Although precise estimates are difficult to come by, it would appear that the research effort devoted to drug discovery currently far exceeds that devoted to resistance management1.

Is this current disparity in the effort devoted to drug discovery versus resistance management an effective use of resources for dealing with drug resistance? To answer this question we need to determine the benefits, in terms of ensuring effective drug availability, of increasing the rate of drug discovery versus slowing the rate of evolution
through better resistance management. At one level the answer to this question is obvious. If there is an upper limit to the number of drugs that can be developed for a particular disease, then at some point drug development will become effectively impossible. This would leave slowing evolution as the only option. But what if we are not yet facing this limitation on drug development? Here we show that even when there is no limit on the development of new drugs, slowing evolution is still inherently more effective. This thereby calls into question the current emphasis on the drug discovery side of the issue, and suggests that more emphasis ought to be given to evolution management.

**Modelling Drug Supply**

Historical data for the development of new antimalarial and antibiotic drugs, as well as the evolution of resistance to these, is presented in Figure 2.1. The processes underlying these data are complex, with both geographic and temporal variation in the drugs that are used to treat specific infectious diseases. We construct and analyse a simplified model of these processes that abstracts only the essential features. The results we present are generic (i.e., not specific to any particular drugs or diseases) but we illustrate them with specific examples whose parameter values are taken from data on malaria^{6-12}.

We define a “drug” as any whole treatment strategy, which might consist of one or multiple active ingredients. The “drug portfolio” is the collection of existing drugs that
are effective against a specific type of infection. For simplicity we assume that a single drug strategy is used at any given time, and its use is continued until resistance to this drug has appeared and reached some threshold frequency (e.g., 10% see [13]). The time it takes for this to occur is referred to as the ‘time to evolve resistance’, or equivalently the ‘drug lifespan’, and is denoted by the random variable $L$. At this point the use of the drug is effectively discontinued and another drug from the drug portfolio, if available, is then brought into use. During this process, new drugs are also in various stages of development and are occasionally brought into the drug portfolio. Although this is clearly a simplified description of reality, we show in the Supplementary Information how relaxing some of these assumptions (including allowing for multiple drugs to be used simultaneously, section 4) does not alter the important qualitative insights provided by our analysis.

The overall dynamics of the modelled drug supply system are shown schematically in Figure 2.2. Drug arrival into the drug portfolio, and the evolution of resistance both occur stochastically, resulting in periods of time for which effective treatment is available (i.e., when there is at least one effective drug available), separated by periods when there is no effective treatment. We refer to the length of time during which effective treatment is available as the “time to failure” (denoted by $T$). These periods are separated by time intervals during which no effective treatment is available (Figure 2.2). For example, the appearance of pan-resistant *Klebsiella pneumoniae* and
multidrug resistant Tuberculosis suggest that we might well have reached the time to failure for these diseases, and be heading into a period in which no effective treatment is immediately available.

We can view the expected time to failure as being the product of the expected number of drugs used before failure occurs, and the expected lifespan of each of these drugs. We will also be interested in the long-run fraction of time that effective treatment is available, and refer to this as the “drug availability” (Figure 2.2). The model is completely specified by the process of drug arrivals and the process of resistance evolution.

Recent analysis of a large data set for pharmaceutical production from companies between 1950-2008 has shown that the annual output of new drugs is Poisson distributed with a constant rate parameter\(^{17}\). This implies that the time between new drug arrivals is exponentially distributed. Consequently we define the random variable \(D\) to be the time between drug arrivals in the portfolio, and assume that \(D\) is exponentially distributed with rate parameter, \(\alpha\). The expected time between drug arrivals into the drug portfolio is therefore \(E[D] = 1/\alpha\).

The time to evolve resistance (i.e., the drug lifespan, \(L\)) represents the time between when a drug is first used and when resistance to the drug reaches a threshold frequency. We assume that this lifespan is determined by the evolution of resistance, and therefore different evolution management strategies will result in different drug lifespans.
Little is currently known about the distribution of $L$ but we can make some progress by examining the data from Figure 2.1. The analyses in Supplementary Information (section 1) suggest that, for some diseases at least (e.g., Malaria), $L$ is also approximately exponentially distributed (Supplementary Figure S2). There are many caveats associated with this conclusion, however, and therefore we consider two scenarios. First, we suppose that $L$ is exponentially distributed with rate parameter $\beta$. The expected drug lifespan is therefore $E[L] = 1/\beta$. Second, we consider a case where the distribution of $L$ is left arbitrary.

We begin the analysis by assuming that the average time between drug arrivals is larger than the average drug lifespan (i.e., $E[D]>E[L]$). This assumption is relaxed below when we consider a variable rate of drug development. This implies that, with probability 1, there will be periods of time when drugs are available as well as periods of time when they are not (Figure 2.2).

Two interventions are explored: (i) increasing the expected drug lifespan, $E[L]$, through better evolution management, or (ii) decreasing the expected time between drug arrivals, $E[D]$, through enhanced drug discovery. For completeness we explore both additive and multiplicative changes in each. In the additive case we consider increasing $E[L]$ by an additive amount or decreasing $E[D]$ by the same amount. In the multiplicative case we consider increasing $E[L]$ by a factor or decreasing $E[D]$ by the
same factor. We focus on two main system performance measures: the time to failure, $T$, which is a random variable, and the drug availability, $\rho$ (Figure 2.2).

**Results**

When the distribution of the time to evolution, $L$, is exponential an explicit equation can be derived for the probability density of the time to failure, $T$. We obtain

$$f_T(t) = \sqrt{\frac{\beta}{\alpha}} e^{-\alpha t - \beta t} I_1(2\sqrt{\alpha \beta t})$$

where $I_1(x)$ is a modified Bessel function of the first kind (Supplementary Information, section 2). Likewise, drug availability is given by

$$\rho = \frac{\alpha}{\beta}.$$  

Increasing the mean time to evolve resistance (i.e., increasing $E[L] = 1/\beta$) or decreasing the mean time between drug arrivals (i.e., decreasing $E[D] = 1/\alpha$) both shift probability mass in equation (1) from low to high values of $T$. However, changes in the mean time to evolve resistance do so to a greater extent (Figure 2.3a). This is true regardless of whether the changes are additive or multiplicative (Supplementary Information, section 2). Likewise, drug availability, $\rho$, is also increased more through an additive change in the mean time to evolve resistance, whereas both interventions have identical effects on $\rho$ when the changes are multiplicative (Supplementary Information, section 2).
When the distribution of time to evolve resistance is arbitrary we can no longer derive an explicit expression for the distribution of time to failure. Nevertheless it is possible to obtain an equation for an integral transform of this distribution, from which we can calculate any moment of the distribution of time to failure (Supplementary Information, section 2). We focus here on the first moment (i.e., expected time to failure), which is

\[ E[T] = \frac{E[L]}{1 - E[L]/E[D]} \]  

(3)

The expression for drug availability in this case is identical to equation (2) (Supplementary Information, section 2). Again we can see that the expected time to failure, \( E[T] \), increases more with a change in \( E[L] \) than it does with a change in \( E[D] \) (Figure 2.3b). And again this is true regardless of whether the changes are additive or multiplicative. The conclusions about drug availability are identical to the case where the distribution of time to evolution is exponential.

Finally, we also explored the case where the rate of drug development \( \alpha \) varies as an inverse function of the drug portfolio size (Supplementary Information, section 3). We studied this situation to better understand the consequences of having drug development speed up and slow down in response to drug demand. It also allows us to examine a case where the mean time between drug arrivals is shorter than the mean drug lifespan (i.e., \( E[D] < E[L] \)). Again, the results show that slowing evolution increases the expected time
to failure and drug availability more than speeding up the rate of drug arrivals (Supplementary Table S2).

Discussion

Our results illustrate that slowing the evolution of drug resistance has a greater effect on the performance of the drug supply system than does speeding up drug development. What is the underlying mechanism behind this result?

Both types of interventions increase the chance of developing new drugs before the system as a whole fails. Decreasing the time between drug arrivals does so because, on average, more drugs will arrive in a given period of time. Increasing the time to evolve resistance does so because it extends the window of opportunity for a new drug to be brought to market before failure occurs. In fact, when the changes for each intervention are multiplicative it can be shown that, on average, the same number of drugs will arrive and be used before failure occurs in both cases. The difference lies in how the interventions affect the lifespan of each drug. Recall that we can express the mean time to failure, $E[T]$, as the product of the expected number of drugs that are used before failure and the expected lifespan of each drug. Mathematically,

$$E[T] = E[N] \times E[L]$$

(4)
where $N$ is the number of drug used before system failure. As already described, multiplicative changes in both interventions have identical effects on $E[N]$. But changes in the time to evolve resistance also affect $E[L]$ whereas changes in drug development do not. As a result, increasing the expected time to evolve resistance has a compounding effect that is absent when changing the drug development time. Moreover, this effect is even greater when we consider additive changes in each intervention because changing the time to evolve resistance then increases $E[N]$ more than does changing the time for drug development.

Drug availability is the proportion of time for which there is effective treatment, which means drug availability will improve as a result of increasing time to failure or limiting periods for which no effective treatment is available. Hence, even though there is a greater increase in time to failure when evolution is slowed, it is important to consider how enhancing the rate of drug arrivals reduces the fraction of time for which there is no effective treatment. In fact, as a result of a multiplicative change, the increase in time to failure from slowing evolution of resistance is equivalent to the increase in drug availability from speeding up drug development. However, if the change is additive, the added benefit to time to failure from slowing evolution exceeds the effect that decreasing time between drug arrivals has on drug availability, causing drug availability to increase more when evolution of resistance is slowed.
Our simplified model of the drug supply system assumes that, when available, drugs are used one at a time. However, the data in Figure 2.1 suggests that multiple drugs are often used simultaneously (although perhaps in different geographic regions\textsuperscript{18,19}). Modelling the simultaneous use of multiple drugs is difficult because one would need to specify how the rate of resistance evolution to each drug is affected by the number of drugs in use (something for which virtually no data are available). Under some assumptions, however, allowing for simultaneous multiple drug use results in a model that is formally identical to the model presented here (Supplementary Information, section 4). This shows that, under some conditions, all of the insights obtained in our simplified model carry over to this more complex situation. It also strongly suggests that, even for other simultaneous drug use scenarios, where an exact correspondence with the simple model no longer holds, the important processes elucidated here will continue to operate. Other, additional, processes might then occur as well however and therefore this is an important area for future research.

Our analysis does not consider how investments can be delivered to the system. Additive and multiplicative changes were used to determine the importance of speeding up drug arrivals relative to slowing evolution of drug resistance, which implies that changing drug development and changing drug lifespan in the same manner requires the same amount of resources or effort. However, it might be less costly or easier to change drug lifespan than to change drug development or vice versa. Further research in this area
might consider assessing strategies using empirically supported cost functions involved in slowing resistance or speeding up drug development\textsuperscript{4,20-22}.  

Even though we provide evidence that slowing evolution of drug resistance is more beneficial to the effective management of resistance than speeding up drug development, we stress that this in no way negates the importance of pharmaceutical innovation and drug discovery. Indeed, the two approaches to resistance management need not always be traded off against one another. For example, slowing the evolution of drug resistance is, in many ways, fundamentally linked to drug development. Investment and advancement in drug development might lead to smarter drugs with enhanced efficacy and greater longevity (including drug cocktails, combination therapies, etc.). Thus our intention is not to suggest that there is, by necessity, an antagonism between the two approaches. The results do demonstrate, however, that a greater emphasis on evolution management might yield promising results for this pressing problem.

References


Figure 2.1. Drug supply timeline for antimalarials and antibiotics. The timeline gives the time of drug introduction and the subsequent evolution of resistance. Using these data we show the observed periods of time that effective treatment is available (green bars) separated by periods during which there is a risk of ineffective treatment (dashed red-lines) as a result of resistance. The colour fading is meant to show that first observation of resistance does not absolutely equate with complete loss of treatment efficacy.
Figure 2.2. Illustration of drug supply. A schematic timeline defining the time to failure, $T$, and drug availability, $\rho$. ‘Effective treatment available’ means that there is at least one effective drug available.
Figure 2.3. Effects on time to failure from enhancing drug development and slowing evolution. a, The effect on the time to failure density $f_T(t)$ when the average time between drug arrivals is reduced by 2 years (orange line) and the average time to evolve resistance is extended by 2 years (blue line) compared to baseline conditions (black line; $E[L] = 5$ years, $E[D] = 8.3$ years). b, The change in expected time to failure ($E[T]$) resulting from additive perturbations in $E[L]$ (blue line) and $E[D]$ (orange line) plotted for varying current drug availability ($\rho$).
Chapter 3

Rational drug use

The result from Chapter 2 suggests that slowing evolution is the best approach to managing drug resistance. The prudent use of antimicrobials is fundamental to ensuring the availability of effective treatment. Antimicrobial stewardship is a common notion that embodies principles of responsible and sustainable resource management\(^1,2\). In this respect, we discuss strategies to slow resistance evolution and show how a focus on evolution management constitutes rational drug use.

Antimicrobial consumption

In addressing the problem of antimicrobial resistance, rational drug use is generally perceived as reducing overall consumption of antimicrobials\(^3-5\). This is based on the principle that antimicrobial consumption determines the degree of drug exposure in the microbial environment and therefore the overall selection for resistance\(^6\). This is supported by studies comparing antimicrobial use among countries, communities and hospitals, which have shown that greater antimicrobial consumption is associated with greater prevalence of drug resistance\(^7-9\). In addition, drug resistance is found to be more common in individuals who have received previous drug treatment\(^10,11\).

The increased antimicrobial consumption over time has yielded a greater prevalence of drug resistance, resulting in higher health-care costs and disease
morbidity\textsuperscript{3,5,12,13}. This has spurred efforts to decrease overall consumption of antimicrobials by targeting the overuse and misuse of antimicrobials in patient treatment, agriculture and veterinary medicine\textsuperscript{3,5,14,15}. The unnecessary use of antimicrobials includes inappropriate drug treatment, redundant use of broad-spectrum drugs, and the use of antimicrobials as growth promoters\textsuperscript{4,5,16–18}. Poor adherence to treatment regimens and the availability of poor quality antimicrobials is also considered a contributing factor in the selection for antimicrobial resistance\textsuperscript{4–6,19,20}. Guidelines to curb antimicrobial consumption include policy development, improved surveillance and management of antimicrobial resistance, improved training of medical professionals, raised public awareness and education of the issues of antimicrobial resistance, regulation of antimicrobial availability, proper disease diagnosis and treatment, adherence to treatment regimens, and promotion of alternatives to antimicrobial treatment\textsuperscript{2,4,5,11,21}.

**Aggressive chemotherapy**

At the level of the individual, rational drug use ought to constitute treatment of infectious disease that balances evolution of drug resistance with clinical therapeutic outcome\textsuperscript{2}. In this regard, the conventional practice of aggressive chemotherapy in ‘hitting hard and early’ to ‘ensure very high cure rates’ has been challenged as the one-size-fits-all approach to treatment of infectious disease\textsuperscript{6,8,22–25}. Research suggests that unless aggressive chemotherapy results in complete microbial clearance, this form of treatment imposes a radical selection pressure that promotes evolution of drug resistance\textsuperscript{22,24,25}. 

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Given that there are differences in pharmacology among drugs, and that microbes encompass a variety of life histories as well as infectious and immunological dynamics, it is reasonable to think that treatment should be specific to a disease-drug combination, and not governed by a one-size-fits-all approach. To yield comprehensive rational drug use we must re-evaluate the use of antimicrobials at high dose and long duration.

**Multiple drug use**

The pharmaceutical industry has provided many drug options to treat infectious diseases such as HIV, Tuberculosis and Malaria, with more drugs in the pipeline\textsuperscript{23,26,27}. Thus, a complete definition of rational drug use ought to also include how to optimally use an arsenal of drug options\textsuperscript{6,23,25}. Perhaps, this could involve using more than one drug at a time. Strategies such as combination therapy, drug cycling and drug mixing are proposed methods of slowing the emergence and spread of drug resistance that use multiple drugs\textsuperscript{6,28–30}. Whereas combination therapy involves treating an individual with more than one drug, drug mixing and drug cycling use multiple drugs to treat a population by varying which drug is used for each new infection\textsuperscript{6}. In any case, using multiple drugs is rational only when it slows drug resistance evolution compared to using component drugs one at a time.
Combination therapy

Combination therapy is often regarded as effective when it increases drug potency and decreases the likelihood that an individual acquires resistant infection over the course of treatment (from de-novo mutation)\textsuperscript{31,32}. However, studies have suggested that the use of combination therapies can in fact promote drug resistance evolution\textsuperscript{25,33}. For instance, a partially resistant microbe may only experience the antimicrobial activity of some component drugs. Therefore, if combination therapy is based on dose synergy, a partially resistant microbe may be exposed to lower doses of component drugs, outcompeting wild-type microbes and expediting evolution of resistance to the whole combination therapy\textsuperscript{31}. Further evaluation of combination therapy ought to consider the usefulness of antagonistic dose interactions in slowing the evolution of drug resistance\textsuperscript{31}. Similarly, a more complete understanding of mutational pathways and gene interactions is needed to help inform when combination therapy constitutes rational drug use compared to using drugs as monotherapies\textsuperscript{6,25,31}.

Population drug heterogeneity

Whereas using one drug at a time can exert constant selection for drug resistance, population drug heterogeneity yields selection pressure that is varying in time or space\textsuperscript{29}. Drug cycling rotates drugs according to a schedule that brings temporal variation in selection pressure, and drug mixing creates spatial variation by alternating which drug is
used among infected individuals\textsuperscript{29}. Compared to using one drug at a time, strategies of drug cycling and drug mixing mean that it less likely that two infected individuals are treated with the same drug. For instance, if resistance occurs in one individual it is less likely that a transmitted infection will be treated with the same drug, thus preventing the spread of resistance\textsuperscript{29}. However, multidrug resistance is a major problem in that it can render infection completely untreatable. It is therefore important to weigh the risk of evolving multidrug resistance with the benefit of slowing resistance to individual drugs, as this will determine when strategies of drug cycling or drug mixing constitute rational drug use\textsuperscript{6,34}.

**Malaria treatment guidelines**

We consider the treatment of malaria as a prototype for rational drug use. Treatment guidelines for malaria instruct diagnosis before treatment with antimalarials, adherence to treatment regimens, the use of artemisinin-combination therapy as frontline treatment and the removal of component monotherapies\textsuperscript{21,35}. In particular, we examine problems that arise in the formulation of these guidelines.

**Diagnostic testing and treatment**

The advent of rapid diagnostic testing has changed treatment of malaria from treating all febrile cases to treating only those with confirmed malaria parasitemia from diagnostic testing\textsuperscript{35}. Among other goals, this initiative aims to reduce the number of non-
malarial febrile cases unnecessarily treated with antimalarials. However, diagnostic testing is imperfect and infection with low parasite densities is undetectable. Thus, it is possible that some cases of malaria are undiagnosed and untreated. Factors such as the frequency of low-density infection, malaria-specific immunity, age of infection, and number of infectious bites may affect false-negative rates in malaria diagnosis. In addition, treatment of non-malarial cases with antimalarial also has a prophylactic effect that may help reduce disease burden in a population and, in particular, decrease the risk of malaria infection in immuno-compromised individuals. Further research is needed to assess the impact of diagnostic testing in treatment of malaria.

**Adherence to treatment regimens**

It is also thought that increased adherence to treatment regimens along with increased availability of highly effective antimalarials, particularly artemisinin combination therapy, will better ensure efficacy of treatment and decrease the occurrence of resistant microbes. However, the aggressive chemotherapeutic approach to treatment of malaria may in fact promote the spread of antimalarial resistance. The history of drug resistance in malaria suggests that antimalarial resistance spreads quickly from its origin. For example, resistance to chloroquine or sulfadoxine-pyrimethamine appears to have resulted from a small number of mutational events that spread globally. The high drug potency and long duration of treatment acts to clear parasites completely and quickly, preventing transmission of infection and the emergence of resistance over
the course of treatment. However, when resistant infection occurs, aggressive chemotherapeutic treatment radically selects for drug resistant microbes. Thus, adherence to treatment regimes may actually cause individuals to be exclusively susceptible to resistant infection and in doing so promote the spread of drug resistance in the population. Alternatives to aggressive chemotherapy may include reducing drug dose and duration to exploit the fitness cost associated with drug resistance as well as the dynamics of inter-strain competition in mixed infection.

**Artemisinin combination therapy**

Moreover, guidelines for the treatment of malaria strongly recommend the use of artemisinin combination therapies as frontline treatment and suggest against treatment with component monotherapies. The use of combination therapies is based on the convention that combination therapies enhance microbial clearance and that resistance to combination therapy occurs infrequently as it involves simultaneous mutations to more than one drug. Research has shown that the use of combination therapies in dose synergy to increase drug potency may in fact select for drug resistance as a result of cross-resistance to component drugs and the effect of different gene interactions. Furthermore, several studies have suggested that the use of multiple front-line malarial treatments may be the most effective strategy at slowing the spread of resistance in a population, optimizing the useful lifespan of each drug.
**Mass treatment strategies**

As a result of efforts in malaria control programs, there has been encouraging progress towards elimination of malaria in some countries\(^\text{46}\). This has prompted interest in strategies such as mass drug administration and mass screen and treatment, and some studies have suggested that mass drug administration is the most effective method of reducing malaria\(^\text{47-49}\). Unlike mass screen and treat, mass drug administration involves treating all members of a population including infected and non-infected individuals\(^\text{21}\). While mass drug administration provides a prophylactic benefit to a population and ensures that individuals with undetectable parasitemia are aptly treated, such an aggressive strategy may impose a radical selection pressure on resistant microbes\(^\text{47}\). The risk of evolving drug resistance ought to be considered when assessing the effectiveness of such strategies as undoubtedly this can have implications on global malaria control.

**Conclusion**

Antimicrobial resistance impacts the effectiveness of treatment to cure and control infectious disease. The formulation of malaria treatment guidelines presents challenges in addressing the problem of drug resistance. Managing drug resistance is a common good; however, further research is needed to develop a comprehensive basis for rational drug use.
References

35. WHO. *Universal access to malaria diagnostic testing an operational manual* (World Health Organization, 2011).


Chapter 4

Summary

In treatment of infectious disease, an individual uses a drug to cure infection, and, in doing so, inhibits transmission of infection to others in the population. The problem of drug resistance is thus two-fold. At the level of the individual, drug resistance prevents cure, and, at the level of the population, drug resistance leads to the unrestricted spread of infection. The management of drug resistance should therefore seek to ensure success of treatment for an individual and the overall control of disease in the population.

As demonstrated in Chapter 1, the dynamics of antimicrobial treatment and the evolution of drug resistance are complex and are not the same for all drug-disease combinations. Drug resistance is not a new phenomenon, yet methods of managing the evolution of drug resistance are lacking in clinical practice. While the problem of resistance for many microbial infections may have previously been circumvented by an abundant supply of effective antimicrobials, we are now beginning to realize that such a strategy is unsustainable as witnessed by the advent of multi-drug and totally-drug resistant strains. Thus, a functional understanding of drug resistance evolution is vital to developing strategies that promote the availability of effective antimicrobials.

Firstly, it is important to realize that developing more drugs will not solve the problem of drug resistance. As demonstrated in Chapter 2, slowing the evolution of drug resistance through better management strategies is more effective than enhancing drug development in ensuring that effective treatment remains available. Most importantly, this calls for a re-evaluation of the current emphasis on drug discovery and development
in efforts to reduce the burden of antimicrobial resistance. The judicious use of drugs is essential to managing drug resistance evolution. Chapter 3 discussed how rational drug use involves addressing the problem of drug resistance, which is further illustrated by challenges in the formulation of malaria treatment guidelines.

The evolution of resistance occurs as a result of the prolonged use of antimicrobials. There is no single one-size-fits-all solution to the problem of drug resistance. Mathematical modelling is extremely useful in the development of strategies to slow drug resistance evolution; however, the implementation and evaluation of best practices in drug resistance management will require a comprehensive approach to connect theory with application. In addition to medicine, problems of resistance are prevalent in the use of antimicrobials in animals for food production and pesticides in agriculture. Thus, an understanding of resistance evolution has the potential to impact all antimicrobial resources.
Supplementary Information

The following is Supplementary Information for Chapter 2 that provides details on data collection and analysis, model analysis, simulations of a variable rate of drug development and ideas in generalizing to multiple drugs. This document contains Supplementary Text comprising 4 sections, Supplementary Equations 1-6, Supplementary Tables 1-2 and Supplementary Figures 1-5. For in-text citations refer to the Chapter 2 reference list.

1 – Data

Data were collected from various sources to create a timeline of drug supply for antimalarials and antibiotics (Supplementary Table S1). The data consist of the date of introduction, and the date of first recorded resistance. When there existed multiple estimates for the same drug from a single source, we report the earliest date that the drug was introduced and the earliest date that resistance was first observed (this occurred when there was region-specific data on drug introduction or resistance). While it is reported that resistance has developed to every antimalarial, we excluded data on Lapdap, Amodiaquine, and Primaquine because the determination of drug resistance for these antimalarials was inconclusive (e.g., due to a lack of evidence or because of confounding factors in treatment failure such as cross resistance, side-effects, compliance and drug withdrawal\textsuperscript{23-25}).

We also used the available antimalarial data to give an example parameterization of the model. We stress, however, that this is intended merely as an illustrative case. All
of the results reported in the main text are general, and independent of the disease in question as well as the specific parameter values used. We nevertheless chose to include an example parameterization based on data because it helps to clarify the relevance of the general results and to make them more concrete.

Coming up with a suitable parameterization from the data is difficult because our simplified model lacks some of the features of the real data. Specifically, in the data many drugs have overlapping lifespans (elapsed time from date of drug introduction to date of observation of resistance). This suggests that more than one drug is used at a time during these periods. Our simple model assumes that one drug is used at a time (although Section 4 generalizes these results) and therefore we need to extract suitable estimates from the data under this assumption. For example, we cannot use the observed drug lifespans since the sum of individual drug lifespans would be greater than the observed time to failure, misrepresenting the current state of drug supply. As a result we employed two different approaches (see below) to estimate the time to evolve resistance from the data. The distribution of time to evolve resistance is almost identical under both approaches, and resembles an exponential distribution with rate parameter $\beta = 0.2$ (see Supplementary Figure S1). The distribution of time between drug arrivals also resembles an exponential distribution with rate parameter $\alpha = 0.12$, supporting an assumption based on results from [17] (see Supplementary Figure S1).

**Dividing overlapping periods by the number of drugs**

We can estimate the time to resistance of individual drugs by dividing overlapping periods by the number of drugs and summing the times that a particular drug
was used. Section 4 describes how this approach can be used to generalize the one-drug-at-a-time model to a multiple drug scenario. In effect, this gives an estimate of the time to evolve resistance for each drug in the absence of any other drug.

**Time to evolve resistance from earliest drug arrival to first drug failure**

Alternatively, we can consider time to evolve resistance as the time from the earliest drug arrival to the time that resistance is first observed to any drug in an overlapping period. Using this approach, estimates of time to resistance are not necessarily for a specific drug, but instead reflect the time to resistance for a group of drugs (and the factors experienced by these drugs) that are in use during an overlapping period.

**Simulating the current and future state of antimalarial supply**

Antimalarial drug supply was simulated using the parameter estimates from the antimalarial data as described above. Supplementary Figure S2 shows how periods of time to failure and drug availability observed from 1930-2012 in the antimalarial data agree with a characteristic simulation of the current state of drug supply. We can also envision what might happen to antimalarial supply in the future if we slowed resistance or enhanced drug development. In this case, we chose to compare an increase of 2 years in the mean time to evolve resistance with a decrease of 2 years in the mean time between drug arrivals. Supplementary Figure S3 shows that increasing the mean time to evolve resistance results in significantly longer periods of time to failure, which also means that drugs will be available for a longer fraction of time over the next 200 years.
Again we stress, however, that these simulation results are merely meant to be an illustrative example. The findings from the model are independent of the details of this simulation, and apply for any distribution of time to resistance, regardless of its shape or parameter values. The model also allows for the use of any (consistent) measure of resistance or drug failure since time to resistance is treated as a random process. In this example, the data report the first observation of resistance but we might wish to measure drug lifespan as the time until resistance is observed at some threshold frequency instead.

2 – Analysis

All models presented in the text are analogous to models from queueing theory. There are abundant results available for analysing their behaviour\(^\text{26}\). In what follows we make use of results found in [26].

*Exponentially Distributed Time to Evolve Resistance*

When the time to evolve resistance is exponentially distributed, the drug supply model is analogous to an M/M/1 queue\(^\text{26}\). Using \( f_r(t) \) to denote the probability density of the time to failure, and \( \tilde{f}_r(z) \) for its Laplace-Stieltjes transform (LST), standard results\(^\text{26}\) demonstrate that

\[
\tilde{f}_r(z) = \frac{\alpha + \beta + z - \sqrt{(\alpha + \beta + z)^2 - 4\beta \alpha}}{2\alpha}
\]

(Supplementary Equation 1)

where \( E[D] = 1/\alpha \) and \( E[L] = 1/\beta \) (Supplementary Equation 1 is also derived below in the case of an arbitrary distribution for the time to evolve resistance). Inverting the transform gives the density\(^\text{26}\)
where \( I_1(x) \) is a modified Bessel function of the first kind with order 1. Specifically, \( I_1(x) \) can be defined by the integral formula

\[
I_1(x) = \frac{1}{\pi} \int_0^\pi e^{x \cos \theta} \cos \theta \, d\theta.
\]

(Supplementary Equation 3)

Drug availability, \( \rho \), is the long run proportion of time an effective drug is available. In the context of queueing theory this is referred to as the “load” or “traffic intensity”. Standard results\(^{26} \) show that

\[
\rho = \frac{E[L]}{E[D]}.
\]

(Supplementary Equation 4)

Supplementary Equation 4 can be understood by recognizing that drug availability is the long-term time spent with at least one drug (which is, on average, \( E[T] \)) divided by the length of the cycle (which is, on average, \( E[T] + E[D] \)). In other words, the ratio

\[
\frac{E[T]}{E[T] + E[D]}.
\]

Using Supplementary Equation 2 we can calculate \( E[T] = E[L]/(1 - E[L]/E[D]) \).

Substituting this into the above ratio then gives Supplementary Equation 4.

We can now determine the effect of each intervention on Supplementary Equation 2 and Supplementary Equation 4. The density (Supplementary Equation 2) is a decreasing function of \( t \) and changes in \( E[D] = 1/\alpha \) or \( E[L] = 1/\beta \) affect the density differently. For example,

\[
\lim_{t \to 0} f_T(t) = \frac{1}{E[L]}.
\]
shows that increasing the expected time to evolve resistance (either additively or multiplicatively) decrease the probability density at $t = 0$ whereas decreasing the expected time between drug arrivals has no effect at this point. Consequently, given that the density function is continuous, interventions that target evolution will shift more probability density from near zero to larger values of $T$ than will interventions that target drug development.

For the drug availability, Supplementary Equation 4, we consider additive and multiplicative changes in turn. An additive change of size $x$ will either add $x$ to the mean time to evolve resistance or subtract $x$ from the mean time between drug arrivals. A multiplicative change of size $y > 1$ will either multiply the mean time to evolve resistance by $y$ or divide the mean time between drug arrivals by $y$.

For additive changes of size $x$ the inequality

$$\frac{E[L] + x}{E[D]} \geq \frac{E[L]}{E[D] - x}$$

holds for all $x$ that satisfy the assumption that $\rho$ is less than 1. Alternatively, multiplicative changes result in equal benefits to drug availability as

$$\frac{E[L] \times y}{E[D]} = \frac{E[L]}{E[D]/y}.$$ 

Therefore, when evolution of drug resistance is slowed, effective treatment will be available for a fraction of time greater than or equal to the effect from enhancing drug development.
**Arbitrary Distribution for the Time to Evolve Resistance**

When time to evolve resistance has an arbitrary distribution, the drug supply model is analogous to an M/G/1 queue\(^{26}\). We can derive an equation for the Laplace-Stieltjes transform (LST) of the time to failure distribution as follows.

Any time to failure period begins with the arrival of a new drug into the portfolio. While this drug is in use, additional new drugs might be added to the portfolio. Suppose, for example, there are \(K\) additional drugs added during the time that the first drug is being used (\(K\) is a random variable). Each of these additional drugs will eventually be used, and each will, themselves, spawn a time to failure period that has the same distribution as that of the first drug. In this way we can write

\[
T = L + T_1 + \cdots + T_K
\]

where \(L\) is the time to evolve resistance for the first drug, and the \(T_i\) are the time to failure periods for the additional \(K\) drugs that arrive before resistance evolves to the first drug.

Using \(f_L(t)\) and \(f_T(t)\) to denote the probability densities for the time to evolve resistance and time to failure respectively, the LST of \(f_T(t)\) is \(\tilde{f}_T(z) = E[e^{-zT}]\).

Conditioning on the lifespan of the first drug we obtain

\[
\tilde{f}_T(z) = \int_0^\infty f_L(t)E[e^{-zT} \mid L = t]dt,
\]

and further conditioning on the number of new drug arrivals, \(K\), during this time gives
\[
\tilde{f}_T(z) = \int_0^\infty f_L(t) \left( \sum_{k=0}^{\infty} E[e^{-(z+T_1+\cdots+T_k)} \mid L = t, K = k] P(K = k \mid L = t) \right) dt \\
= \int_0^\infty f_L(t) e^{-zT} \left( \sum_{k=0}^{\infty} E[e^{-zT_1} \cdots e^{-zT_k}] P(K = k \mid L = t) \right) dt \\
= \int_0^\infty f_L(t) e^{-zT} \left( \sum_{k=0}^{\infty} E[e^{-zT_1}] \frac{(\alpha t)^k e^{-\alpha t}}{k!} \right) dt
\]

where the final equality makes use of the fact that \( K \) is Poisson distributed. Now, using the fact that the \( T_i \) are independent and identically distributed, we obtain

\[
\tilde{f}_T(z) = \int_0^\infty f_L(t) e^{-zT} \left( \sum_{k=0}^{\infty} E[e^{-zT_1}] \frac{(\alpha t)^k e^{-\alpha t}}{k!} \right) dt \\
= \int_0^\infty f_L(t) e^{-zT} \left( \sum_{k=0}^{\infty} E[e^{-zT_1}] \frac{(\alpha t)^k e^{-\alpha t}}{k!} \right) dt.
\]

Finally, noting that \( \sum_{k=0}^{\infty} \frac{(\alpha t)^k e^{-\alpha t}}{k!} = e^{(z-1)\alpha t} \), this last expression simplifies to

\[
\tilde{f}_T(z) = \int_0^\infty f_L(t) e^{-zT} e^{(\tilde{f}_T(z)-1)\alpha t} dt \\
= \int_0^\infty f_L(t) e^{-zT_1} e^{(\tilde{f}_T(z)-1)\alpha t} dt
\]

or

\[
\tilde{f}_T(z) = \tilde{f}_L(z + \alpha - c\tilde{f}_T(z)) \quad \text{ (Supplementary Equation 5)}
\]

Supplementary Equation 5 is Takács functional equation relating the LST of the distribution of time to failure, \( T \), to the LST of the distribution of time to evolve resistance, \( L \).

We can now calculate any moment of interest for the distribution of the time to failure, in terms of the moments of the distribution of time to evolve resistance. In particular, \( E[T] = -\tilde{f}_T'(0) \), and therefore

\[
E[T] = \frac{E[L]}{1 - E[L] / E[D]} \quad \text{ (Supplementary Equation 6)}
\]
Notice that this is identical to the expression for $E[T]$ obtained in the case of exponentially distributed time to evolve resistance, and therefore Supplementary Equation 4 for drug availability remains valid even when the time to evolve resistance has an arbitrary distribution.

Incidentally, we can also derive Supplementary Equation 1 from Supplementary Equation 5 by using the fact that, when $L$ is exponentially distributed with parameter $\beta$, the LST of $L$ is $\tilde{f}_L(z) = \beta / (\beta + z)$. Substituting this into Supplementary Equation 5 gives

$$
\tilde{f}_T(z) = \frac{\beta}{\beta + z + \alpha - \alpha \tilde{f}_T(z)}.
$$

Solving this quadratic equation for $\tilde{f}_T(z)$ gives Supplementary Equation 1.

When the distribution of $L$ is arbitrary, we can consider the effect that additive and multiplicative changes have on any moment of the time to failure distribution. For the purposes of this analysis, we have chosen to focus on the first moment, the expected time to failure, $E[T]$ (Supplementary Equation 6). The expected time to failure can be broken up into two parts: the average number of drugs used before failure,

$$
E[N] = (1 - E[L]/E[D])^{-1}
$$

and the average lifespan of each drug, $E[L]$, such that

$$
E[T] = E[N] \times E[L].
$$

The likelihood that another drug arrives before failure will increase as a result of slowing the time to evolve resistance or decreasing the time between drug arrivals. An additive change of size $x$ increases the average number of drugs used before failure and, in particular, the inequality

$$
\left(1 - \frac{E[L]+x}{E[D]}\right)^{-1} \geq \left(1 - \frac{E[L]}{E[D]-x}\right)^{-1}
$$
holds for all $x$ that satisfy the assumption that $\rho$ is less than 1. Alternatively, there is an equivalent increase in the average number of drugs used before failure when evolution is slowed and drug development is enhanced multiplicatively since

$$
\left(1 - \frac{E[L] \times y}{E[D]}\right)^{-1} = \left(1 - \frac{E[L]}{E[D]/y}\right)^{-1}.
$$

This shows that increasing the mean time to evolve resistance will result in at least as many drugs used before failure as decreasing the mean time between drug arrivals. In addition, since increasing the mean time to evolve resistance also increases average drug lifespan, the total effect on average time to failure is that much greater when resistance is slowed than when drug development is enhanced.

We also show how increasing the mean time to evolve resistance or decreasing the mean time between drug arrivals affects the whole time to failure distribution. The drug supply system was simulated for a constant rate of drug arrivals by randomly selecting the time between drug arrivals from an exponential distribution with rate $\alpha$. The time it takes to evolve resistance to a drug was randomly selected from a normal distribution with expected time to evolve drug resistance, $E[L] = \mu$, and standard deviation $\sigma$. Supplementary Figure S4 shows that this entire distribution shifts more toward longer durations of time to failure when the evolution of drug resistance is slowed than when the rate of drug arrivals is sped up, thereby producing the larger change in expected value of $T$ described above.
3 – Variable rate of drug development

Model

We will also consider a variable rate of drug arrivals so that drugs arrive at a normal rate, $\alpha_p$, when there are lots of drugs in the drug portfolio and a fast rate, $\alpha_f$, when there are few effective drugs available. The normal rate of drug arrivals was varied to determine the effect of speeding up drug development. As before, these results were compared against the effect of slowing evolution of resistance. In these simulations, the proportion of time that drugs arrived at their respective rates was also considered.

The available empirical evidence suggests that annual drug production has been constant for over 55 years, remaining unchanged in spite of increased investment\(^{17}\). Even so, by including a fast rate, the time between drug arrivals is not necessarily longer than the time it takes resistance to evolve, relaxing the $E[D]>E[L]$ assumption of the previous model. Results from this simulations also show that slowing the evolution of resistance has a greater impact on time to failure and drug availability than does speeding up the normal rate of drug arrivals.

Results

Numerical results show that slowing the evolution of resistance benefits time to failure and drug availability more than speeding up the normal rate of drug arrivals (Supplementary Table S2). Slowing evolution of drug resistance also decreased the proportion of time that drugs arrived according to a fast rate of development (Supplementary Figure S5). This suggests that drug arrivals were occurring close to a
maximum rate, so that any further increase in the normal rate of drug arrivals would have little effect on system performance. In contrast, when evolution was slowed, a normal rate of drug arrival was used for a greater proportion of time implying that the average rate of drug arrivals slowed down when $E[L]$ increased.

4 – Generalizing to multiple drugs

Thus far, we have presented a model of drug supply that assumes one drug or drug therapy is used at a time. While this assumption is supported by current treatment guidelines and practice for malaria (wherein a single first line therapy is recommended for treatment and replaced when resistance emerges$^{13,27}$) in general, it is likely that more than one drug will be used to treat a disease when available. Note, by this we mean that individuals are still given a single drug, but different individuals might be given different drugs simultaneously.

To begin it is helpful to first consider how simultaneous drug use affects the total time required to evolve drug resistance for a set of drugs, relative to that required if the drugs in this set were used one at a time (i.e., sequentially). There are three possibilities: (i) conservation of evolution, (ii) compression of evolution, and (iii) expansion of evolution. These are defined as follows.

Suppose there are $n$ drugs currently available. We say that there is conservation of evolution if the total time it takes for resistance to evolve to all $n$ drugs when used simultaneously is the same as the time required for resistance to evolve to all $n$ drugs when used sequentially. Alternatively, we say that there is compression of evolution if
the time taken under simultaneous drug use is shorter, and expansion of evolution if it is longer. We will show that this provides a heuristic framework with which to examine multiple drug use.

It can be shown, using results from work-conserving queueing theory, that a model with simultaneous drug use is formally equivalent to a one-drug-at-a-time model when there is conservation of evolution. We propose a mechanistic basis by which this occurs. Suppose that the rate of evolution for individual drugs depends on the number of drugs in use, \( n \), such that the rate of evolution for each drug is slowed by a factor \( 1/n \) relative to the rate of resistance evolution if it were the only drug in use. Then it can be shown that the distribution of time to failure is unchanged from a one drug at a time model, as this is analogous to a work-conserving queue. In a similar way, we can account for drugs used at different frequencies by assuming that the rate of evolution of resistance to each is slowed by a factor equal to its frequency of use.

These ideas reveal that, under certain conditions (namely, conservation of evolution) the results of the simple model of the text are identical to those for a model that allows simultaneous multiple drug use. Therefore, increasing the mean time to evolve resistance is more effective than decreasing the mean time between drug arrivals in an evolution-conserving scenario of multiple drug use. This also provides a natural point of departure for exploring cases in which evolution is not conservative.

When multiple drug use results in compression of evolution, this means that there are interactions among drugs that result in a reduction of the time required to evolve resistance. This effect might arise from cross-resistance, wherein the mechanism of resistance to one drug also confers resistance to another drug, effectively reducing its
lifespan. This means that it is more important to slow resistance than to enhance drug development, as simply using more drugs will reduce the lifespan of each drug.

Alternatively, when multiple drug use results in the expansion of evolution, this means that there are interactions among drugs that bring about an increase in the time required for resistance evolution. At the population level, drug mixing has been suggested as a way of spatially varying the drug environment so that it is more difficult for microbes to evolve resistance to any one drug²⁹.
5 – Supplementary Tables

Supplementary Table S1. Data for antimalarials and antibiotics. The values indicate the time of drug introduction and first observation of drug resistance. The reference for each drug is provided; all data is from published sources.

<table>
<thead>
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<th>Drug</th>
<th>Drug Type</th>
<th>Introduced</th>
<th>Resistance</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>Antimalarial</td>
<td>1933.5</td>
<td>1957</td>
<td>(a)</td>
</tr>
<tr>
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<td>Antimalarial</td>
<td>1940</td>
<td>1953</td>
<td>(a)</td>
</tr>
<tr>
<td>Proguanil</td>
<td>Antimalarial</td>
<td>1948</td>
<td>1949</td>
<td>(b)</td>
</tr>
<tr>
<td>Pyrimethamine</td>
<td>Antimalarial</td>
<td>1951.5</td>
<td>1952.5</td>
<td>(c)</td>
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<tr>
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<td>Antimalarial</td>
<td>1977</td>
<td>1982</td>
<td>(d)</td>
</tr>
<tr>
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<td>Antimalarial</td>
<td>1988</td>
<td>1992</td>
<td>(b)</td>
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<td>1996</td>
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<td>2001.5</td>
<td>(c)</td>
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<td>Antimalarial</td>
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<td>(a)</td>
</tr>
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<td>Antibiotic</td>
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<td>1940.5</td>
<td>(e)</td>
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<td>(f)</td>
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<td>Antibiotic</td>
<td>1952</td>
<td>1988</td>
<td>(f)</td>
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<td>Antibiotic</td>
<td>1956</td>
<td>1988</td>
<td>(f)</td>
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<td>(e)</td>
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<td>1973</td>
<td>(f)</td>
</tr>
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<td>Gentamicin</td>
<td>Antibiotic</td>
<td>1967</td>
<td>1970</td>
<td>(g)</td>
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<tr>
<td>Oxyimino-beta-lactams</td>
<td>Antibiotic</td>
<td>1981</td>
<td>1983</td>
<td>(g)</td>
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<td>Linezolid</td>
<td>Antibiotic</td>
<td>1999.5</td>
<td>2003.5</td>
<td>(e)</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Antibiotic</td>
<td>2003.5</td>
<td>2005</td>
<td>(e)</td>
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Supplementary Table S2. Performance measures for a variable rate of drug development. Results from simulations (n = 100) with a variable rate of drug arrivals over a time interval of 300 years. The mean time between drug arrivals was 5 years (\(E[F] = 5\)) when there were less than 3 drugs in the system at the time of the last drug arrival. An additive change affects the mean time to evolve resistance or mean normal time between drug arrivals by 2 years, while a multiplicative change doubles the mean time to resistance or halves the mean normal time between drug arrivals. Average drug availability is the drug availability realized for each simulation averaged over all simulations. Average time to failure and down time is the average time to failure and down time for each simulation averaged over all simulations. Average proportion of time that drugs arrived from a particular rate is equal to the proportion of time the rate is used for each simulation averaged over all simulations.

<table>
<thead>
<tr>
<th>(Mean time between drug arrivals, Mean time to evolve resistance)</th>
<th>Initial conditions</th>
<th>Additive change</th>
<th>Multiplicative change</th>
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<tr>
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<td>10, 5</td>
<td>8, 3</td>
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<td>Average drug availability</td>
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<td>0.737</td>
<td>0.541</td>
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<td>0.592</td>
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<tr>
<td>Average time to failure (years)</td>
<td>6.227</td>
<td>18.629</td>
<td>6.444</td>
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<td>29.652</td>
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<tr>
<td>Average down time (years)</td>
<td>5.721</td>
<td>6.814</td>
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<td>Average proportion of time fast rate used</td>
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<td>0.471</td>
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<td>0.358</td>
<td>0.731</td>
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Supplementary Figure S1. Histograms of drug supply parameters from antimalarial data. **a**, The distribution of time between drug arrivals (\( \alpha = 0.12, \bar{D} = 8.3 \) years, \( \sigma_D = 7.7 \) years). The distribution of time to evolve resistance was estimated via two approaches: **b**, by dividing overlapping regions by the number of drugs (\( \beta = 0.2, L = 5 \) years, \( \sigma_L = 5.2 \) years) or **c**, using the time from earliest drug arrival to first drug failure (\( \beta = 0.2, L = 5 \) years, \( \sigma_L = 4.6 \) years). Using the estimate of the rate parameter in each panel, the solid line is the exponential density plot and the open circles give the probability (%) within the interval defined by the width of each bar. The dashed line is the average value of the variable of interest.
Supplementary Figure S2. The current state of antimalarial supply. This shows the time to failure (\( T \); green bars) and drug availability (\( \rho \)) observed from data and from simulation using parameter estimates (\( E[L] = 5, E[D] = 8.3 \)).
Supplementary Figure S3. Characteristic realizations of future antimalarial supply. A simulation over the next 200 years when the mean time between drug arrivals is reduced by 2 years or the mean time to evolve resistance is increased by 2 years (compared to initial conditions: $E[L] = 5$, $E[D] = 8.3$).
Supplementary Figure S4. Histograms of time to failure from simulation. a, For initial conditions ($E[D] = 10$, $E[L] = 3$, $\sigma_L = 0.1$), and after a multiplicative change is applied: b, halving the mean time between drug arrivals ($E[D] = 5$, $E[L] = 3$, $\sigma_L = 0.1$) or c, doubling the mean time to evolve drug resistance ($E[D] = 10$, $E[L] = 6$, $\sigma_L = 0.1$). The last bar in each histogram shows lengths of time to failure greater than or equal to 29 years and the dashed line indicates the average length of time to failure in each panel.
Supplementary Figure S5. Characteristic simulations of a variable rate of drug development. The pattern of time to failure (green bars) and down time (red lines) along with the periods that a fast rate (orange bars) and normal rate (blue lines) of drug arrivals were used over a time interval for a, initial conditions ($E[D] = 10, E[F] = 5, E[L] = 3, \sigma_L = 0.1$), and after an additive change is applied: b, subtracting 2 from the mean normal time between drug arrivals ($E[D] = 8, E[F] = 5, E[L] = 3, \sigma_L = 0.1$) or c, adding 2 to the mean time to evolve drug resistance ($E[D] = 10, E[F] = 5, E[L] = 5, \sigma_L = 0.1$). The mean time between drug arrivals when there are less than 3 drugs in the drug portfolio is held constant at 5 ($E[F] = 5$). Drug availability is shown at the bottom of each plot as the sum of time to failure (green area) relative to the sum of down time (red area) over the time interval. The proportion of time that drugs arrived from a fast rate (orange area) rate relative to a normal rate (blue area) is also shown.