Assessing the public health impact of tolerance-based therapies with mathematical models

Nathanaël Hozé[1], Sebastian Bonhoeffer[1], Roland Regoes[1]
[1] Institute of Integrative Biology, ETH Zurich,
Universitätstrasse 8092 Zurich, Switzerland

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Corresponding authors : Nathanaël Hozé (nathanael.hoze@env.ethz.ch) and Roland Regoes (roland.regoes@env.ethz.ch).

Abstract

Disease tolerance is a defense strategy against infections that aims at maintaining host health even at high pathogen replication or load. Tolerance mechanisms are currently intensively studied with the long-term goal of exploiting them therapeutically. Because tolerance-based treatment imposes less selective pressure on the pathogen it has been hypothesised to be "evolution-proof". However, the primary public health goal is to reduce the incidence and mortality associated with a disease. From this perspective, tolerance-based treatment bears the risk of increasing the prevalence of the disease, which may lead to increased mortality. We assessed the promise of tolerance-based treatment strategies using mathematical models. Conventional treatment was implemented as an increased recovery rate, while tolerance-based treatment was assumed to reduce the disease-related mortality of infected hosts without affecting recovery. We investigated the epidemic and endemic phases of two types of infections: acute and chronic. Additionally, we considered the effect of pathogen resistance against conventional treatment. We show that, for both acute and chronic infections, tolerance-based therapy enlarges the population of infected hosts, which in turn increases the prevalence and incidence of the disease. For low coverage of tolerance-based treatment, chronic infections can cause even more deaths than without treatment. Overall, we found that conventional treatment always outperforms tolerance-based treatment, even when we allow the emergence of pathogen resistance. Our results cast serious doubts on the potential benefit of tolerance-based over conventional treatment. Any clinical application of tolerance-based treatment of infectious diseases has to consider the associated detrimental epidemiological feedback.

Introduction

Hosts can respond to infections in various ways. The host can reduce the pathogen replication or load and thus improve its health. In evolutionary ecology, such a response is called "host resistance".

Another possible host response is "disease tolerance" , that induces a state, in which the host, at a given pathogen load, suffers less from the negative consequences of being infected.

In evolutionary ecology, disease tolerance has received attention as a host strategy that impacts the evolutionary dynamics of host-pathogen systems very differently from host resistance [1, 2]. For example, resistance genes are predicted to disappear in the long run. First, they drive the pathogen population to extinction, but eventually resistance genes are lost, since they do not confer any fitness advantage without pathogen pressure. Host resistance might select for resistant pathogens. Tolerance genes, on the other hand, do not drive the pathogen to extinction. They even increase the prevalence of the pathogen, thus increasing the selective pressure favoring themselves. This positive evolutionary feedback often leads to the fixation of tolerance genes [3, 4] — although scenarios explaining polymorphisms in tolerance have been considered [5].

The particular molecular and immunological mechanisms that confer host resistance are clinically relevant as they provide targets for therapeutic agents. The most common treatment agents, such as antibiotics or antivirals, aim at reducing pathogen replication or burden and are often based on host resistance mechanisms. A class of agents against HIV, for example, inhibits the coreceptor CCR5 — a treatment strategy inspired by a naturally occurring polymorphism in the gene encoding CCR5 that reduces the susceptibility of individuals to HIV infection [6].

But tolerance mechanisms can also be exploited therapeutically. For example, widely used anti-inflammatory drugs reduce the negative impact of an infection without targeting the pathogen directly. Other examples of tolerance mechanisms involve *Plasmodium* that leads to the release of heme from erythrocytes, which has proinflammatory properties. The inflammation triggers a reactive oxygen species response that can lead to liver failure in individuals with malaria. Some individuals, however, express an enzyme — heme oxygenase 1 (HO-1) — that prevents liver failure by limiting the reactive oxygen species response. Because this does not affect the level of the pathogen it represents a tolerance mechanism. Inhibiting the reactive

oxygen species response with a pharmacological agent that acts similarly to HO-1 has been shown to limit liver failure in mouse models [7]. HO-1 was also shown to provide host tolerance by preventing free heme from promoting severe sepsis [8]. Additional tolerance mechanisms against severe sepsis have recently been discovered [9], which involve the inhibition of cytokine production by anthracyclines. Similarly, based on the observation that sickle human hemoglobin confers tolerance to malaria, it was proposed that modulation of HO-1 via the transcription factor NF-E2-related factor 2 (Nrf2) might be a therapeutic target for treating cerebral malaria [10]. We refer to treatment strategies that are based on tolerance mechanisms as *tolerance-based treatment*.

Tolerance-based treatment is seen to have great promise [11] — in part, simply as a complement to more conventional treatment based on the exploitation of host resistance mechanisms. Some even hypothesize that tolerance-based treatment is resistance-proof as it does not exert any selection pressure on the pathogen [1, 12].

However, also negative consequences of tolerance-based treatment have been considered. Treated hosts could become healthy carriers of the pathogens, hence giving them more opportunity for transmission [3, 13, 14, 15]. Moreover, it was postulated that damage-limitation treatments — a form of tolerance-based treatment — might select for increased pathogen transmission [15, 16]. In an evolutionary context, it was also found that pathogen virulence may increase in a tolerant host population [17]. In the context of public health, this translates into a risk of evolution towards higher virulence in response to tolerance-based treatment. But in the study by Miller et al. this higher virulence did not affect host mortality because all hosts carried the tolerance gene.

Generally, the translation of insights from evolutionary ecology to the public health situation is hindered by the fact that tolerance genes usually fix in the host population, and hosts are therefore protected from dying. Tolerance-based treatment, even if it confers great benefits to individual hosts, cannot be expected to be applied to the entire population. As a consequence, disease-induced mortality could increase when tolerance-based treatment is rolled out.

Here, we assess the promise of tolerance-based treatment (TOL) on the population level and investigate the public health impact of treatment at various levels of coverage. While most previous studies focused on changes in the incidence and prevalence of the disease, we specifically focus on the disease-

induced mortality. To this end, we use mathematical models. Specifically, we extend the well-known epidemiological SIR model, featuring susceptible, infected, recovered individuals, by an additional compartment of treated individuals. We investigate the effect of TOL for two types of infections: acute and chronic.

While, at the individual level, TOL can be effective, and may even prevent the evolution of pathogen resistance in the long run, it is problematic epidemiologically. As TOL introduces asymptomatic carriers of the disease, it may increase mortality when its coverage is low. We indeed show that for chronic infections the disease-induced mortality increases for low treatment coverage. Comparing TOL to conventional treatment, based on a reduction of load (ROL), we find that for both, acute and chronic infections, ROL always outperforms TOL even when we consider that pathogen resistance can emerge against ROL.

Methods

Compartment model for a single treatment

We consider an extended SIR model in which infected patients can be treated. The model is depicted in Fig 1. Susceptible (uninfected) hosts S enter the population at a rate Λ, and die at a per capita rate δ. They can be infected by individuals that are either untreated (I) or treated (I_θ). Susceptible hosts become infected at a rate that depends on the number of susceptible S, the total number of infected $I + I_\theta$ and transmission rates β and $\beta(1-c_\theta)$, where c_θ is a cost of transmission associated to treatment. This reflects contact-dependent transmission from infected hosts to uninfected hosts. Infected hosts die at a rate $\delta + v$, with $v \geq 0$ indicating a higher mortality of infected than susceptible. Infected can recover at a per capita rate r and become part of the recovering population R. Similarly, treated infected die at a rate $\delta + v_\theta$ and can recover at a per capita rate r_θ. Untreated infected individuals are treated at a rate θ, and become immediately treated infected. The model is

summarized by the system of ordinary differential equations

$$\begin{aligned} \dot{S} &= \Lambda - \delta S - \beta S(I + (1 - c_\theta)I_\theta) \\ \dot{I} &= \beta S(I + (1 - c_\theta)I_\theta) - (\delta + v)I - \theta I - rI \\ \dot{I}_\theta &= \theta I - (\delta + v_\theta)I_\theta - r_\theta I_\theta \\ \dot{R} &= rI + r_\theta I_\theta - \delta R. \end{aligned} \tag{1}$$

We assume that treatment is instantaneous and that infected individuals become treated infected at a rate θ. Infected individuals leave the infected state at a rate $\delta + v + r + \theta$, and a fraction

$$\varphi = \frac{\theta}{\theta + r + v + \delta} \tag{2}$$

of them become treated infected. This rate ratio can be regarded as the probability for an infected individual to be treated instead of leaving to another state (death or recovery). Our current model can easily be modified to consider independently a non-instantaneous treatment rate τ and a fraction of treated population $0 \leq f \leq 1$. In that case, the term θ in the system of equations (1) has to be replaced by the rate $f\tau$, and the fraction of infected hosts that effectively become treated infected is equal to $\varphi = \frac{f\tau}{f\tau+r+v+\delta}$. The fraction of effectively treated increases from $\varphi = 0$ for $f = 0$ to $\varphi_{max} = \frac{\tau}{\tau+r+v+\delta}$ for $f = 1$. All the following measures of the efficacy of treatment (Figs. 2 and 3) are presented for a fraction of treated population ranging from 0 to 1. These results can be directly extended to the non-instantaneous treatment rate model, where the fraction of treated population has to be limited between 0 and φ_{max} to account for the additional parameter τ.

Implementation of the treatments

For the implementation of the TOL, we assume that the death rate is lower for treated than untreated individual ($v_{TOL} = v_\theta < v$), but that the hosts are still infectious ($r_{TOL} = r_\theta = r$). Moreover, we consider that the transmission rates of treated and untreated hosts are the same ($c_{TOL} = c_\theta = 0$).

For a ROL the hosts recover faster than without a treatment, but the mortality rate is the same ($r_{ROL} = r_\theta > r$ and $v_\theta = v$). In the numerical

applications we chose the transmission rate to be the same with and without treatment ($c_{ROL} = c_\theta = 0$).

In addition, we consider a treatment that combines the properties of TOL and ROL (TOL+ROL). We translate this effect by combining the benefits of the two treatments, the increased recovery rate of the ROL and the decreased mortality rate of the TOL ($r_{TOL+ROL} = r_{ROL}$ and $v_{TOL+ROL} = v$).

In this study, we will evaluate the benefits of a treatment by considering three measures. First, the *incidence*, defined as the number of new infections in a period of time, is

$$\beta S(I + (1 - c_\theta)I_\theta). \tag{3}$$

Second, the *prevalence* of the disease, which is the ratio of infected individuals over the total population, is

$$\frac{I + I_\theta}{S + R + I + I_\theta}. \tag{4}$$

Finally, we will measure the *disease-induced mortality*, which is the fraction of deaths that are due to the disease over the total number of deaths, given by

$$\frac{vI + v_\theta I_\theta}{\delta S + \delta R + (v + \delta)I + (v_\theta + \delta)I_\theta}. \tag{5}$$

Throughout this study, we evaluate how these three measures vary at equilibrium with the fraction of treated population. Model (1) has two equilibria: the disease free equilibrium (DFE) and the endemic equilibrium (EE). Whether one equilibrium or the other is attained depends on the relative value of the model parameters (See Supplementary Text S1 for details on the equilibrium values and the equilibrium stability analysis).

Moreover, the efficacy of the treatments are evaluated for two types of infection: an acute infection, which is highly transmissible, with fast death and recovery rates, and a chronic infection, with a slower dynamics than the acute infection, and for which no recovery is possible in the absence of treatment.

Model of pathogen resistance to the conventional treatment

In an extension of the model, we assumed that ROL can induce pathogen resistance to treatment, and added to the compartment model the number

I_R of hosts that are infected by pathogens resistant to treatment. Treated individuals can develop resistance to treatment at a rate s_{RES}, called acquired (or de novo) resistance. Susceptible individuals can be infected by treated, untreated, or resistant hosts. If a susceptible individual is infected by a non-resistant, it becomes infected non-treated, but becomes resistant if it is infected by a resistant individual. Individuals infected by the resistant pathogen die at a rate $\delta + v_{RES}$. The model is an extension of model (1) with an additional compartment for the infected resistant and the corresponding transition rates (Fig 1) and is described by the set of equations

$$\begin{aligned}
\dot{S} &= \Lambda - \delta S - \beta S(I + (1 - c_{ROL})I_{ROL} + (1 - c_{RES})I_{RES}) \\
\dot{I} &= \beta S(I + (1 - c_{ROL})I_{ROL}) - (\delta + v)I - rI - \theta_{ROL}I \\
\dot{I}_{ROL} &= \theta_{ROL}I - (\delta + v_{ROL})I_{ROL} - r_{ROL}I_{ROL} - s_{RES}I_{ROL} \qquad (6) \\
\dot{I}_{RES} &= \beta(1 - c_{RES})SI_{RES} + s_{RES}I_{ROL} - (\delta + v_{RES})I_{RES} - r_{RES}I_{RES} \\
\dot{R} &= rI + r_{ROL}I_{ROL} + r_{RES}I_{RES} - \delta R.
\end{aligned}$$

In our model, resistance can appear in two ways. First, individuals receiving ROL can acquire resistance at a rate s_{RES}, and second, susceptible individuals can be infected by resistant infected. Transmission of the resistant pathogen is described by a mass action law with an infection rate $\beta(1-c_{RES})$, where $c_{RES} > 0$ represents the fitness cost of transmission associated to pathogen resistance to treatment.

Similarly to the case without resistance to treatment, the system of equations has a disease-free and an endemic equilibrium. Additionally, there is a third equilibrium where all the infected individuals are resistant to the treatment. It can be shown analytically that there is always a threshold value of the treatment coverage such that only resistant pathogens exist at equilibrium, provided that the cost of transmission of the resistant pathogen c_{RES} is small enough. Details of the equilibrium values for the model of pathogen resistance are given in Supplementary Text S2.

Choice of parameters

Parameters in the absence of treatment: The death rate without a disease is set to $\delta = 1/70$ years^{-1} and Λ is determined so that the ratio Λ/δ is equal to a fixed population size in the case of no epidemic. We choose $\Lambda = 10^6\delta = 1.43\ 10^4$ years^{-1}. The transmission rate β is chosen so that the basic reproductive ratio $R_0 = \frac{\Lambda\beta}{\delta A} = 2$ when no treatment is applied. We assume that the TOL reduces the death rate of the disease, and that the ROL increases the recovery rate.

For an acute infection: The parameters r and v are chosen so that one out of fifty infected individuals dies without treatment. Hence, $\frac{v}{r+v+\delta} = \frac{1}{50}$. Moreover, we set the duration of the infection to be $\frac{1}{r+v+\delta} = 2$ weeks.

- Death rates $v = 0.01$ week^{-1} $v_{ROL} = v_{RES} = v, v_{TOL} = 0$.
- Recovery rates $r = 0.49$ week^{-1}, $r_{ROL} = 0.98$ week^{-1}, $r_{TOL} = r, r_{RES} = r$.
- Transmission rates $\beta = 1.0\ 10^{-6}$ week^{-1}, costs of transmission $c_{ROL} = c_{TOL} = 0$, and $c_{RES} = 0.2$ (fitness cost of pathogen resistance to treatment).
- Rate of acquired resistance $s_{RES} = 0.007$ week^{-1}.

For a chronic infection: Infected untreated individuals cannot recover, and die from the infection in 10 years.

- Death rates $v = 0.002$ week^{-1}, $v_{ROL} = v_{RES} = v, v_{TOL} = 0$.
- Recovery rates $r = 0, r_{ROL} = 0.02$ week^{-1} , $r_{TOL} = 0, r_{RES} = 0$.
- Transmission rates $\beta = 4.4\ 10^{-9}$ week^{-1}, costs of transmission $c_{ROL} = c_{TOL} = 0$, and $c_{RES} = 0.2$ (fitness cost of pathogen resistance to treatment).
- Rate of acquired resistance $s_{RES} = 0.007$ week^{-1}.

In the Supplementary Information, we provide results for various sets of parameters, and show that the main conclusions of this study remain unchanged (Fig S1).

Results

We investigated the impact of TOL on the population of hosts with a mathematical model. We based our model on the SIR model [18, 19, 20], which describes susceptible, infected, and recovered hosts. To describe treatment, we divided the compartment of infected individuals into a treated and an untreated compartment (see Figure 1). Treated individuals arise from infected untreated individuals at a given rate and remain infectious.

ROL treatment is implemented in this model as an increased recovery rate of treated individuals. Treated individuals are less infectious than untreated ones because they recover faster. Per unit time their infectiousness is not assumed to be affected by treatment. Tolerance-based treatment, on the other hand, does not affect the rate of recovery but lowers the disease-induced death rate of treated hosts. Because TOL, by definition, does not affect the pathogen load we assume that treated individuals are equally infectious as untreated ones per unit time. However, they cause more infections than untreated individuals because they live longer and thus have an extended infectious period.

We assess the effect of treatment on three epidemiological quantities: prevalence, incidence, and disease-induced mortality. We determine these quantities in the endemic equilibrium for different levels of treatment coverage. In the Method section, we show how we calculated these quantities from our model equations. Because TOL increases the infectious period, we expect the incidence and prevalence to rise. The effect of TOL on the population-wide disease-induced mortality depends on how the higher prevalence is balanced by the lower mortality of treated individuals.

We investigate the impact of TOL and ROL for acute and chronic infections. Acute infections are modeled with influenza in mind, and are characterized by a short period of infection and a high transmission rate. Specifically, an untreated infection is assumed to last two weeks and the case fatality proportion is set to 1/50. Chronic infections are assumed to last years and there is no recovery, as for HIV infection. For both types of infection, the basic reproduction number $R_0 = 2$ in the absence of treatment. We neglect seasonal fluctuations in any of the model parameters because this would preclude an equilibrium analysis.

Tolerance-based treatment is beneficial on the population level only when coverage is large

We assessed the efficacy of treatment by evaluating numerically the incidence, prevalence and disease-induced mortality for different levels of treatment coverage. We vary treatment coverage by changing the rate of treatment, θ. We define treatment coverage as the fraction of treated hosts, which is the product of the rate of treatment times the duration of an untreated infection: $\frac{\theta}{\theta+\delta+v+r}$.

ROL reduces the incidence, the prevalence and the disease induced mortality (Fig 2a-f). Thus, ROL is unambiguously effective on the population level, which is owed to the fact that it shortens the infectious period. For the parameters chosen here, chronic infections can even be eradicated by ROL if the coverage exceeds 55% (Fig 2d-f).

TOL, on the other hand, affects the epidemiology very differently. Unlike ROL, TOL increases incidence and prevalence (Fig 2a,b,d,e). This effect is due to TOL lengthening the infectious period. The rise is way less pronounced for acute than for chronic infections. For the acute infection, the incidence increases by only 2% with the treatment coverage (Fig 2a), while, for chronic infections, it rises from 140 to 260 new infections per week (Fig 2d). Similarly, the prevalence increases by 2% in acute infections (Fig 2b), as compared to the chronic infection where the prevalence rises from 0.11 to 0.93 (Fig 2e).

The effect of TOL on disease-induced mortality is similar to ROL. For large treatment coverage, disease-induced mortality is reduced for both, ROL and TOL. However, there are subtle differences: In chronic infections TOL can even increase the disease-induced mortality when the coverage is low (Fig 2f). This is due to the fact that there is no recovery from chronic infections in our model, and treated hosts keep infecting for life. This effect is maintained even when infected hosts can recover, provided that the time to recovery is long enough. Thus, for chronic infections, the population-level disadvantages of TOL outweigh the benefits to the individual.

Combining ROL and TOL decreases the mortality in acute infections

To assess if TOL could be a useful addition of our treatment repertoire when combined with ROL, we implemented a strategy we call TOL+ROL. Indi-

viduals receiving this combination treatment experience both, faster recovery (due to ROL) and decreased mortality (due to TOL) (see the system of equations(1) in the Methods section). Again, we calculate the endemic incidence, prevalence and disease induced mortality under TOL+ROL and compare it to these measures under TOL and ROL alone (Fig 2).

We find that TOL+ROL does not improve on ROL in terms of incidence and prevalence but it does not do worse either — a very conceivable outcome given that individuals receiving TOL+ROL live longer. Apparently, the gain in life expectancy of individuals receiving TOL+ROL does not translate into a substantial increase of incidence and prevalence (Fig 2a,b,d,e) because, due to fast recovery under TOL+ROL, this strategy does not produce many asymptomatically infected individuals that increase the force of infection. With respect to disease induced mortality, TOL+ROL outperforms ROL in acute infections (Fig 2c). This effect is a direct consequence of the lower mortality rate of individuals treated with TOL+ROL as compared to ROL.

Thus, TOL can be a useful additional treatment strategy, especially for acute infections, if combined with ROL. Unlike on its own, in combination with ROL it is certainly not predicted to have negative public health consequences. It can be shown that TOL+ROL has public health benefit across the entire range of possible treatment coverage if the faster recovery outweighs the increase in life expectancy. Formally, the duration of infection in treated individuals, $1/(\delta+v_\theta+r_\theta)$, needs to be smaller than that in untreated individuals, $1/(\delta+v+r)$.

Resistance to the ROL treatment

Up to this point in our analysis, TOL did not have any advantage over ROL. One supposed advantage of TOL, which we have not yet taken into account, is that it does not provoke pathogen resistance. The reason for this is that TOL does prolong rather than shorten the infectious period in treated individuals and thus increases pathogen fitness. Reduction of the pathogen load that follows ROL treatment, on the other hand, imposes a negative selection pressure on the pathogen by reducing the duration of infection. In response, the pathogen might evolve resistance.

To assess the promise of TOL more comprehensively, we included pathogen resistance to ROL into our model. To this end, we added a compartment for individuals infected with resistant pathogen strains (Fig 1). Individuals enter this compartment either after being infected and receiving treatment, which

may trigger de novo resistance emergence. Resistant pathogen strains are also assumed to be transmitted. We further assume that resistant pathogens render ROL ineffective, i.e. individuals infected with resistant pathogen strains have the same recovery and disease-induced death rates as untreated infected individuals. Lastly, we allow resistant pathogens to carry a fitness cost in terms of a lower transmission rate.

We do not implement the emergence of resistance as a stochastic process. While this would be admittedly more realistic, treating resistance deterministically is more favorable to TOL. We thus present the best case scenario for TOL.

We find that resistance outcompetes the wildtype pathogen strain if the treatment coverage exceeds a threshold, φ_{ROL}. For the parameters we chose, $\varphi_{ROL} = 0.2$ for acute and $\varphi_{ROL} = 0.4$ for chronic infections (Fig 3a and e). Below this threshold, wildtype and resistant pathogen strains coexist.

Below the threshold φ_{ROL}, the incidence, prevalence and disease-induced mortality are very similar to the model without pathogen resistance. Above the threshold, the three measures under ROL and TOL+ROL become independent of treatment coverage because treatment is assumed not to affect resistant pathogen strains. The incidence and prevalence under ROL and TOL+ROL still remain below the levels they attain under TOL even if we allow pathogen resistance to evolve. However, the disease-induced mortality under TOL can become smaller than under the other treatment strategies for high treatment coverage (Fig 3d and h). For chronic infections, the levels of treatment coverage for which TOL becomes advantageous is much larger than the threshold φ_{ROL}: TOL becomes beneficial if treatment coverage exceeds approximately 60% (Fig 3h). Some of these results depend critically on our equilibrium assumption (see Discussion).

Discussion

Tolerance mechanisms are currently considered to be exploited therapeutically [11]. Undoubtedly, once developed, tested and approved, TOL will benefit treated individuals. This clear benefit of TOL should not cloud our view for what is most important: the direct public health consequences of such treatment as measured by the number of lives saved population-wide. In this paper, we assessed the potential of TOL from the public health perspective.

We find that TOL is not more beneficial on the population level than ROL unless coverage is very high. This applies to acute and chronic infections alike, irrespective of whether we take pathogen resistance into consideration. The levels of coverage required to make TOL superior to ROL — above 50% in our simulations — could probably be attained only for chronic infections in countries with an excellent public health infra-structure. For acute infections, treatment coverage will be low. Thus, TOL on its own is not a promising treatment strategy from a public health perspective.

TOL is also of limited use as a supplement to other interventions. We considered the combination of TOL and ROL. Except for acute infections and low coverage, this combination is not better than ROL on its own.

Because specific agents for tolerance-based treatment are still in development, a mathematical modeling approach is currently the most appropriate way to assess the public health impact of TOL. Mathematical modeling also allows to gain insights into a wide range of different infections and to apply TOL and ROL at different levels of coverage, separately and in combination. Having said that, experimental study systems are being developed that will allow to directly assess the epidemiological effect of TOL. A recently developed transmission model, involving Salmonella infection of tolerant and non-tolerant mice, highlighted the role of tolerant mice in the spread of the infection [21]. While being certainly more biological, such transmission models cannot easily be scaled up to the population sizes a pathogen encounters during an epidemic. Furthermore, the treatment agents might have multiple effects that do not easily fall into the categories of TOL or ROL. Thus, even with transmission models, mathematical modeling will play a role in assessing the public health consequences of treatment.

Formally, our modeling of TOL bears most similarities with studies on the epidemiological and evolutionary aspects of imperfect vaccines [22, 23]. In particular, the anti-toxin vaccines discussed in these studies reduce the

virulence in the vaccinated hosts without affecting transmission, recovery, or infection probability, and are therefore identical to TOL in terms of their effect on the infection parameters of an individual. However, anti-toxin vaccines differ from TOL in that they are given also to uninfected hosts. Thus, these vaccines are equivalent to prophylactic TOL. As a consequence, the impact of anti-toxin vaccines on mortality differs from TOL: when evolution is not considered, the mortality continuously decreases with increasing vaccine coverage. In our study in contrast, we find that mortality first increases before decreasing for chronic infections.

Other notable mathematical model of TOL [15] studied the potential epidemiological and evolutionary effects of damage-limitation treatment, which targets pathogen virulence or increase host tolerance. The model of Vale et al. has similarity with a previous model by Miller et al. [17], that was formulated in the context of the evolutionary dynamics of tolerance genes. In these models, 100% of the hosts carried the tolerance gene. Translated into the context of TOL this represents a regime, in which all individuals receive damage-limitation treatment irrespective of whether they are infected or not. As a consequence, these models provided only limited insight into an assessment of a potential public health benefit of TOL: while the prevalence of the disease is predicted to be increased, disease-induced mortality is reduced. This model is similar to the vaccination model proposed by Gandon and colleagues [22] in that treatment is administered prophylactically. Moreover, Vale et al. [15] study the effects only in a scenario in which all hosts are tolerant, i. e. at 100% coverage.

In contrast, our analysis focuses on a treatment given only to infected individuals, and is thus not prophylactic. Moreover, the treatment is given to a fraction of the infected population. Thus, our model addresses the impact of treatment coverage on the epidemiological feedback of TOL. In particular, we focused on the disease-induced mortality — the most relevant entity for public health. This feedback is most pronounced at low treatment coverage where the increase in prevalence due to TOL meets a sufficient frequency of untreated, and hence vulnerable, hosts.

TOL could be useful when linked with transmission control, or if the tolerance induction goes hand-in-hand with a reduction of transmission. Sometimes such transmission reductions are a side effect of TOL [24]. Our model allows us to calculate the transmission reduction required for TOL not to increase disease prevalence: transmission has to be reduced by 2% in acute and by 88% in chronic infection (see Supplementary Text S3). However,

such transmission control might reduce pathogen fitness, and pathogen could evolve in response to TOL. In this study, we do not consider the potential evolutionary consequences of TOL. Recent papers [15, 16] suggest that TOL could increase pathogen virulence, especially when virulence and pathogen fitness are tightly linked [25]. Our model suggests that pathogen evolution could have a dramatic effect in chronic infections, where infected hosts are infectious for a long time. The mortality, that already increases because of the epidemiological feedback, will be amplified by the higher virulence of evolved pathogens. Further studies are needed to assess the public health implications of pathogen evolution in response to TOL. To go beyond the insights of Vale et al., such studies should focus on the non-prophylactic use of TOL and consider a broad range of treatment coverage.

Tolerance treatments might however be applied in hospitals, where transmission can be curbed. The benefits for the individual would not be outweighed by the damage for the population. Of particular interests are tolerance mechanisms involving free heme regulation, which suggest promising applications for treating severe sepsis [8], especially since available treatments are limited [26].

The main disadvantage of TOL that we identified does not rely on the evolution of the pathogen but arises simply through the epidemiological feedback that is amplified by TOL. Our results raise serious doubts about the promise of tolerance-based strategies applied without transmission control, especially when treating chronic infections.

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Figures

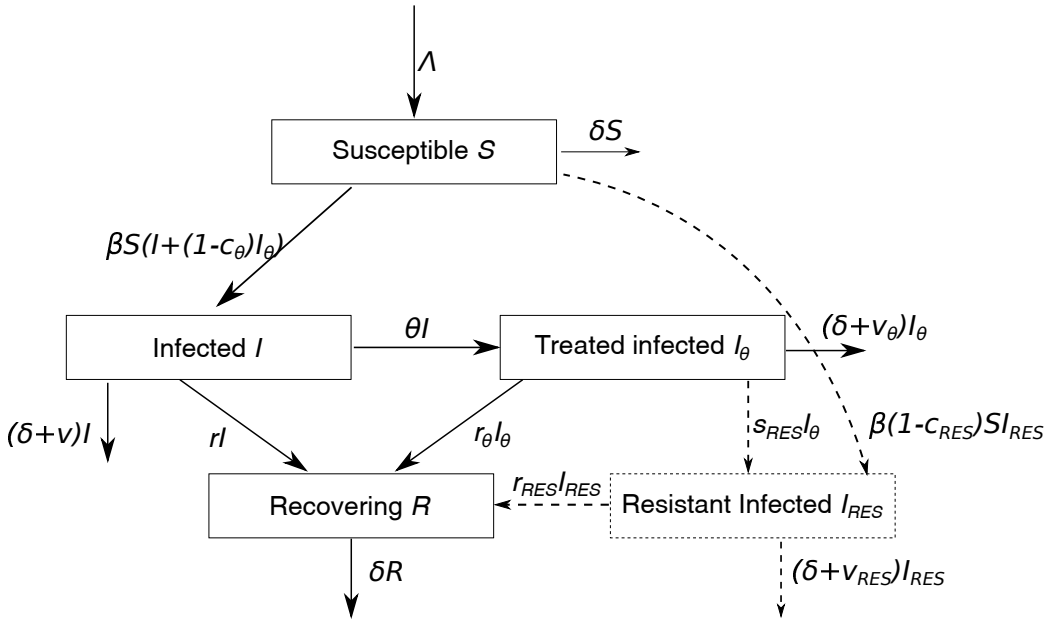

Figure 1: **Schematic of the compartment model.** The main model is presented in eq. (1). The extended model, that includes resistance to treatment, is represented in dashed lines in the schematic and is detailed in eq. (6).

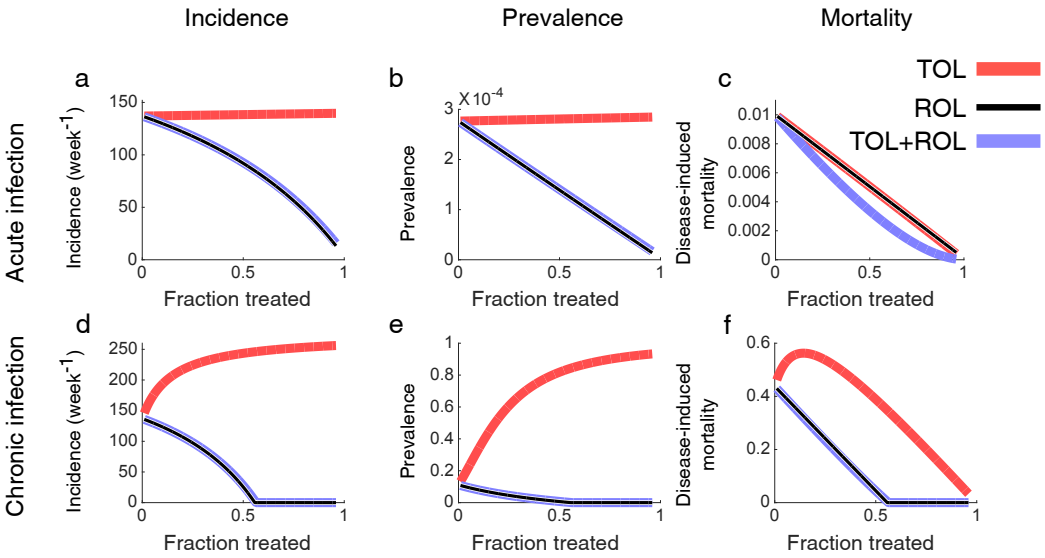

Figure 2: **Evaluation of the efficacy of TOL and ROL in acute and chronic infections.** Equilibrium values of the incidence (a,d), prevalence (b,e), and fraction of mortality due to infection (c,f), which normalizes the disease-induced mortality by the overall mortality. These epidemiological measures are plotted against the fraction of the population that receives treatment. The effect of TOL is displayed in light red, that of ROL in black, and that of TOL and ROL combined in blue. Parameters for both acute and chronic infections are given in the Methods section.

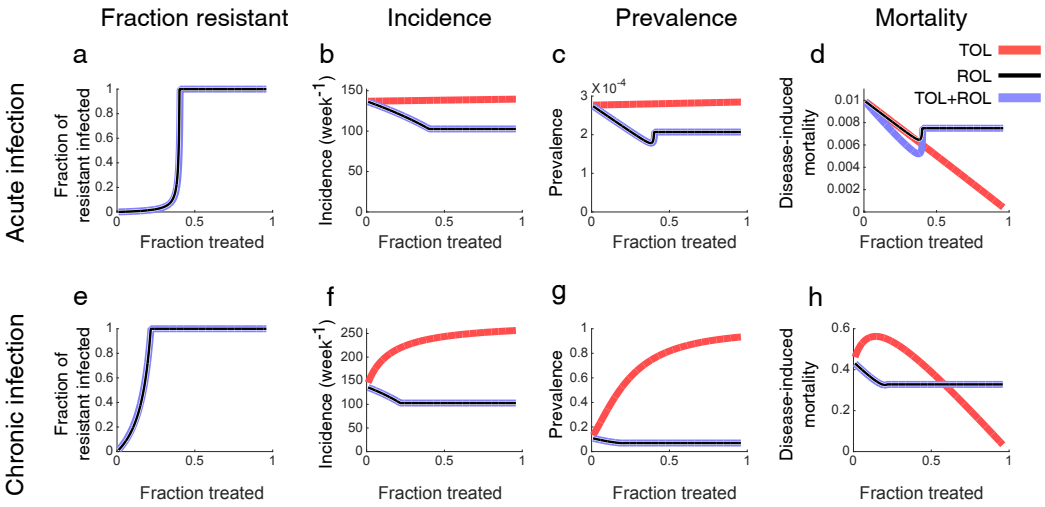

Figure 3: **All pathogens become resistant to treatment for large coverage of the ROL treatment.** Fraction of the population infected by the resistant pathogen over the total infected population (a, e), and equilibrium values of the incidence (b,f), prevalence (c,g), fraction of mortality due to infection (d,h). These epidemiological measures are plotted against the fraction of the population that receives treatment. The effect of ROL is displayed in black, that of TOL and ROL in blue. TOL, which does not lead to resistance, is represented in red and is reproduced for comparison from Fig 2. Parameters for both acute and chronic infections are given in the Methods section.

Supporting Information

- **S1 text.** Equilibrium analysis of the tolerance-based treatment model.
- **S2 text.** Equilibrium analysis with pathogen resistance to treatment.
- **S3 text.** Impact of the different treatments on the basic reproduction number.
- **Fig S1.** Robustness of the results to parameter changes.