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# Effective use of a Limited Antiviral Stockpile for Pandemic Influenza

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**Abstract** Just allocation of resources for control of infectious diseases can be profoundly influenced by the dynamics of those diseases. In this paper we discuss the use of antiviral drugs for treatment of pandemic influenza. While the primary effect of such drugs is to alleviate and shorten the duration of symptoms for treated individuals, they can have a secondary effect of reducing transmission in the community. However, existing stockpiles may be insufficient for all clinical cases. Here we use simple mathematical models to present scenarios where the optimum policies to minimise morbidity and mortality, with a limited drug stockpile, are not always the most intuitively obvious and may conflict with theories of justice. We discuss ethical implications of these findings.

**Keywords** Pandemic influenza · Antiviral drugs · Public health

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## Introduction

A pandemic influenza virus is one to which the great majority of the human population has no prior immunity. Past pandemics have ranged in disease severity, from the devastating "Spanish flu" of 1918 (Johnson and Müller 2002) to the comparatively mild "Hong Kong flu" of 1968 (Kilbourne 2006). Nonetheless, all pandemics have exerted a considerable and global impact on society, including a death rate exceeding those of seasonal influenza outbreaks. The SARS outbreaks of 2003 (Fan and the Asian Development Bank 2003) demonstrated the great potential for social and economic disruption caused by the spread of a lethal pathogen. There is every reason to expect that an influenza pandemic will have a very significant impact when it arises.

It is now widely accepted that we should be speaking of "when" and not "if" a pandemic happens (Taubenberger et al. 2007). There is, however, much uncertainty surrounding the subtype and strain that will be involved: H5N1 influenza is causing much concern (WHO 2008) because of its high case fatality rate in humans, but H7N7 and H9N2 are equally plausible pandemic candidates, having also caused many human cases (Centers for Disease Control and Prevention 2003; Wan et al. 2008). At the time of writing (May 2009) an H1N1 influenza A virus, closely related to viruses found in pigs (Swine Flu), is the latest variant to threaten a pandemic with official reports of over 1,000 cases in 21 countries. The

WHO's phase of pandemic alert stands at phase 5, awaiting a confirmed outbreak in a community outside the WHO-designated Americas region to rise to the top, "pandemic" level.

Because pandemic viruses cannot be predicted in advance it is not possible to protect humans with a vaccine of high efficacy before the pandemic spreads. In fact, it is unlikely that an effective vaccine will even be available during the first six months of a pandemic (Webby and Webster 2003). During this time antiviral drugs will be the first line of defence for pharmaceutical intervention, and several countries have been stockpiling such drugs, mainly oseltamivir (tradename Tamiflu) (Ward et al. 2005). These stockpiles are being widely used in the ongoing outbreaks of H1N1 both to treat known cases and to prevent the establishment of known outbreaks by treating the close contacts of cases. The currently circulating viral strain is mild making it hard to tell if the drugs are effective either in ameliorating symptoms or in reducing onward transmission. The widespread use of drugs for prophylaxis on a national scale would be prohibitively expensive, and so, in the UK and US pandemic plans, for example (US Dept of Health and Human Services 2005, UK Department of Health 2007), the primary role of oseltamivir is for therapeutic (post-symptomatic) treatment. Treatment by oseltamivir of *seasonal* influenza, taken within 48 h of symptoms, alleviates and shortens the duration of symptoms, as well as reducing the risk of mortality (McGeer et al. 2005), and it is hoped that the drug will have the same effect against a pandemic influenza virus.

Stated objectives for public health interventions are consistent across many countries: the Australian plan states that "antivirals will be used as part of a comprehensive public health intervention to reduce illness and death" (Australian Department of Health and Ageing 2006), while public health advisory committees in the US "considered the primary goal of a pandemic response to decrease health impacts including severe morbidity and death" (US Dept of Health and Human Services 2007). According to the UK plan, "The priority in an influenza pandemic is to reduce the impact on public health (i.e. reduce illness and save lives). Interventions will therefore be applied where they will achieve maximum health benefit" (UK Department of Health 2007).

The US and the UK currently have drug stockpiles sufficient to treat 25% of the population. However, what if this turns out to be insufficient? Specifically, if a stockpile is potentially insufficient for all clinical cases, should we treat only priority cases in an effort to preserve the drug supply, or should treatment continue to be dispensed to as many clinical cases as possible until the stockpile is exhausted? UK policy is in line with the former; at first all symptomatic cases will receive treatment and, if supplies run low, drugs will be prioritised for health care workers and those most at risk (UK Department of Health 2007). This policy makes sound intuitive sense, but is it the best way to minimise morbidity and mortality? Is it consistent with a principle of just allocation of limited resources?

In this paper we take these questions as starting points to argue that the problem of resource allocation goes deeper than merely the direct effects of treatment. Infectious disease dynamics are intrinsically "nonlinear", meaning, for example, that an epidemic started by two infectious individuals is not twice as large as one caused by a single individual. The fundamental issue here is that drug treatment protects those taking the medicine *and* gives some protection to people they might otherwise have gone on to infect. This preventive effect is clearly positive, but it can lead to complex balances between treatment strategies that are good for the individual versus strategies that are good for the community.

The first part of this paper is concerned with how best to minimise numbers of infections, with a limited stockpile. This objective has clear advantages for the general population, and for continuity of the economy. The second part of this paper addresses the situation where a subgroup in the population has a particularly high risk of mortality. For instance, young adults suffered a higher mortality rate than any other age group in the "Spanish flu" pandemic of 1918 (Jordan 1927). In such a scenario, we argue that prioritizing the treatment of those at most risk of death is not always in agreement with minimising infection and overall numbers of deaths. In both cases we first use mathematical models to explore rational strategies from a consequentialist approach, and then discuss ethical implications.

## Minimising Infection–the Basic Model

Here we present an outline of the basic mathematical model; further technical details are given in the appendix. We assume a well-mixed population, in which the overall rate of infection is a product of the

number of infected cases, the rate of contact between members of the population, and the probability of infection per contact. This is expressed in equations given in the appendix.

$R_0$ is the basic reproductive number, the average number of secondary cases arising from a single clinical case, in an otherwise susceptible population, and in the absence of any treatment (Anderson and May 1992). Assuming a fixed amount of contact between members of the host population, we can take $R_0$ as a measure of the virus transmissibility. A pandemic-capable virus requires a value of $R_0$ greater than 1.

Now, consider a policy of dispensing treatment to a certain proportion of infected cases: that is, implementing a certain antiviral *coverage*. We make several simplifying assumptions. We assume a well-mixed population and neglect use of antiviral drugs for prophylaxis, assuming their dominant role is for post-symptomatic treatment. We also neglect drug resistance. Further, in the basic model we assume that the only effect of treatment is to reduce the duration of clinical symptoms, that there is no latent period of infection, and that all cases are symptomatic. Although seemingly strong assumptions, however, these do not change the qualitative nature of our results.

An aggressive (high coverage) antiviral programme will dispense treatment to all cases presenting with clinical symptoms, and a conservative (low coverage) programme will dispense treatment to only a limited number of those cases. Assume first that there is an unlimited supply of antiviral drugs. How many drugs would be used by the end of the epidemic?

Figure 1 shows the calculated drug usage for a range of coverage policies, for different plausible values of $R_0$. A notable feature of this graph is that aggressive policies are not always more drug-consuming than conservative ones. For example, in the case $R_0$=1.5, fewer drugs are dispensed overall if 90% of infected cases receive treatment than if only 60% do. This is because the potential benefits of treatment are not limited to those individuals receiving it; by accelerating their recovery, treatment also shortens their infectious period, and thus reduces the *spread* of disease, leading to fewer cases overall. If dispensed to sufficiently many cases, therefore, this effect can in fact reduce the overall number of drugs needed. In the extreme case of $R_0$=1.2 and with over 60% of cases receiving treatment, the treatment programme is

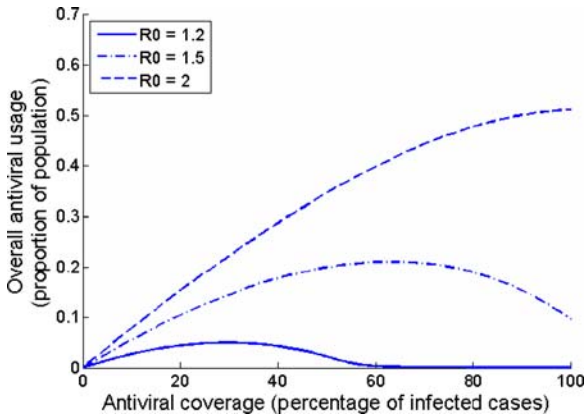


**Fig. 1** Predicted total antiviral usage for a range of disease transmissibility (R0). Assuming that infected cases recover in an average of 3.5 days and 5 days with and without treatment, respectively

effective in stamping out infection before it can spread widely and hence only a very small number of drugs are used. However, such an effect is, as one might expect, dependent on the viral transmissibility and on the drug efficacy. For a highly transmissible virus and/or a poorly effective drug, antiviral usage always increases with coverage, as in the example $R_0$=2 in the diagram.

The role of widespread treatment in reducing the spread of infection is an example of the fundamental role of infection dynamics in disease control. We can now consider how the picture might change if there were only a limited stockpile. This is implemented in the model by imposing zero antiviral coverage once the drug usage exceeds a given stockpile level. Say, for example, that there are enough drugs for a quarter of the population, as in the current US and UK stockpiles. Figure 2 shows how the epidemics would progress according to this model, for different coverage policies, assuming that $R_0$ is 1.7 (a moderate value). An aggressive 95% coverage exhausts the stockpile, but a conservative 30% coverage avoids doing so. On these grounds alone the latter might appear preferable. Nonetheless, the epidemic peak is significantly reduced and broadened by the aggressive policy. Analysis of this model, presented in detail elsewhere (Arinaminpathy and McLean 2008), also shows that although an aggressive policy exhausts the stockpile, it results in fewer cases overall than the conservative one.

These results are also valid in an extended model that includes more details, such as asymptomatic

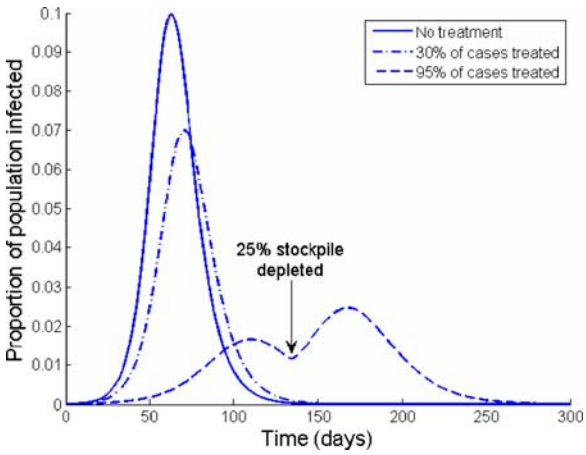


**Fig. 2** Predicted epidemic curves for different antiviral coverage policies, using same drug parameters as in Fig. 1, and assuming $R_0$=1.7. Note that the 'aggressive' policy of 95% coverage depletes the stockpile

cases, different stages in the course of illness and infectiousness, and a drug that reduces infectiousness as well as the infectious period: irrespective of whether or not an aggressive strategy depletes the stockpile prematurely, it leads ultimately to fewer cases, and a lower and broader epidemic peak than a conservative policy aiming to avoid runout. Here the public health planner, faced with the potential exhaustion of a stockpile, must choose between an assured supply of drugs, but a greater overall number of cases and pressure on health services, and on the other hand minimising the overall disease burden, but potentially denying treatment to those infected towards the end of the epidemic. This is particularly true if no vaccine, or alternative treatment, is available when the stockpile has been exhausted. This seems a likely scenario, given that it will take at least six months from the start of a pandemic for a effective vaccine to be available (Webby and Webster 2003). Any problem of resource allocation is burdened with a trade-off between the interests and welfare of individuals. In this case, however, the tension between the consequentialist approach (driving the aggressive coverage policy) and equitability (a key guiding principle in many pandemic plans) is amplified by the underlying disease dynamics.

Note that here we have deliberately limited ourselves to the simplest possible models, in order to highlight the dynamical effects of "aggressive" versus "conservative" antiviral deployment. More detailed models could include realistic inefficiencies in deployment, such as the delay between developing symptoms and receiving drugs, and the effect of non-pharmaceutical interventions such as social distancing. Nonetheless, this basic framework provides a useful method for focusing on the epidemiological effects of widespread antiviral treatment.

## Minimising Mortality

If the disease were to show specific targeting of mortality towards a sizeable subgroup of the population, such as young adults in 1918, then the overall priority may well be to minimise numbers of deaths. What is the best way to deploy a limited stockpile, to achieve this end?

In an extension of the basic model presented above, we now consider a twofold coverage policy: there is a certain antiviral coverage for the general population and another for the risk-group. The question now is how best to balance these two coverages, with respect to a limited stockpile. Here, there are two significant measures of the drug performance: its efficacy in reducing onward transmission, by speeding the recovery of treated cases, and its protection against mortality for individuals.

Figures 3 and 4 show plots of total mortality and total number infected, for two different scenarios for the drug effectiveness, and with a stockpile sufficient to treat 25% of the population. Further parameters are given in the figure legends. In the first scenario, depicted in Fig. 3, the drug is effective in both the general population and in the risk group, at reducing transmission and mortality. The ridges in the plotted surfaces correspond to policies under which the exhaustion of the stockpile coincides with the end of the epidemic. With any greater coverage in either group the stockpile would be prematurely exhausted. The first main point to note is that the policy for minimising mortality is not the same as that for minimising attack rate (numbers infected). For the former (see Fig. 3a), drugs should be prioritised for risk-group cases and any remaining stockpile used for the general population. For the latter (see Fig. 3b), the opposite is true and the general population instead takes priority. Despite this contradiction, most non-fatal infections of influenza do not result in lasting disability, and so many would argue that the policy to

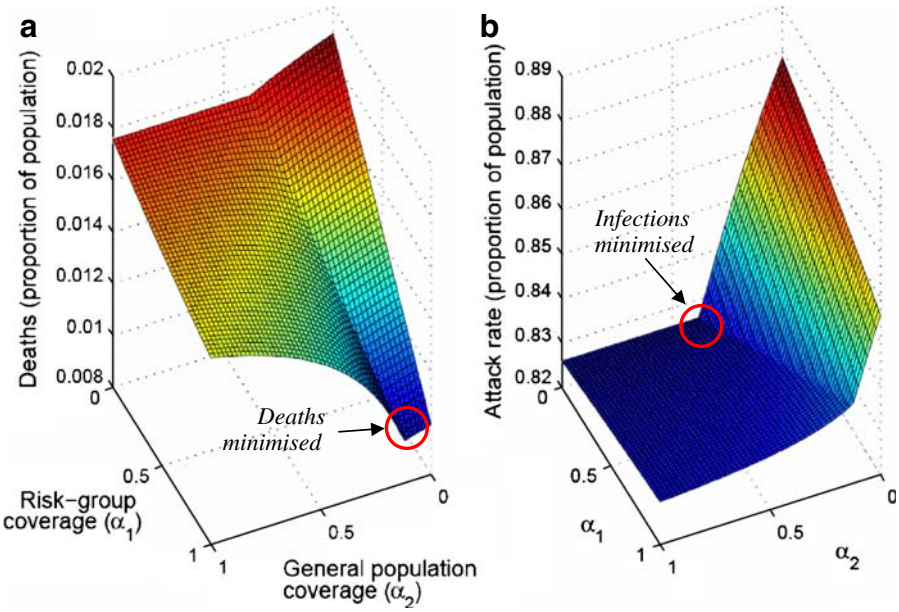


**Fig. 3** **a** Total deaths and **b** infections (attack rate) vs antiviral coverage policy, in a scenario where the drug is effective in both groups, in reducing infection and mortality. Red circles indicate where deaths are minimised (figure a) and numbers of infections are minimised (figure b). Assuming here that 20% of the population is 'at risk'. Further parameter details are given in the Appendix

minimise overall *mortality* should take precedence over the policy to minimise numbers *infected*.

Consider, however, the situation depicted in Fig. 4, where the drug works well at reducing transmission as well as mortality risk in the general population, but offers only very weak protection against mortality in the risk group. This situation is not implausible: clinical features of serious human cases of H5N1 have raised questions about the potential efficacy of oseltamivir for these cases (WHO 2007). Here, minimising mortality agrees with minimising overall numbers of infections: prioritise treatment for the general population, and spend any remaining drugs on the risk group cases. It must be stressed that this is not merely a matter of "abandoning" the risk group as a result of their poor response to treatment: this policy also offers indirect protection for risk group members. Specifically, because the drug performs so poorly in the risk group, rather than aiming to protect these cases against mortality through direct treatment, it

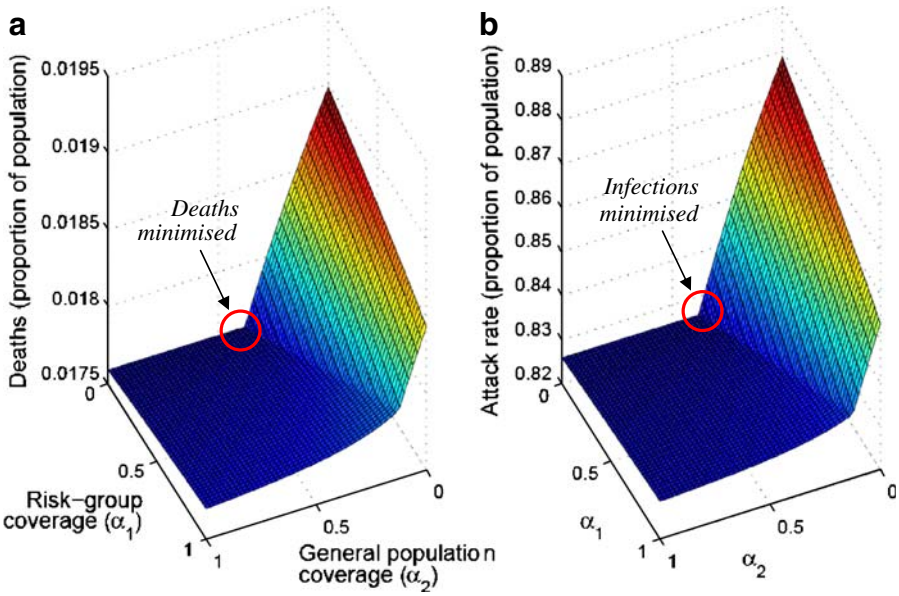


**Fig. 4** **a** Total deaths and **b** infections (attack rate) vs antiviral coverage policy. Here the drug has some effect in the general population, but very limited effect in the risk-group. Minimising mortality agrees with minimising numbers of infections

becomes more important to protect them against *infection*. This is achieved by investing the drugs in the general population, where treatment has the strongest effect in reducing disease spread. Evidence of this dynamic is seen in the fact that the policy for minimising mortality coincides with that for minimising numbers of infections.

Overall, therefore, in deciding which population groups should be prioritised for treatment with a limited stockpile, the effect of the drug in the different groups can be as significant a factor as the disease itself. Consequently, a rational approach to an objective as straightforward as minimising mortality can lead to unexpected conclusions.

## Discussion

The problem of resource allocation for control of infectious diseases has some subtle elements not observed in other healthcare settings. Rather than merely reacting to symptoms, antiviral drugs can in fact fundamentally affect the course of an epidemic. If treatment has any therapeutic effect on the individual level, it also reduces transmissibility, and thus can play a role in limiting the spread of disease in the community.

Take, for example, the objective of devoting resources to the worst off, a central tenet of the Rawlsian perspective of distributive justice (Rawls 1971). At first glance it seems clear that this favours prioritising symptomatic treatment for those most at risk. However, we have seen that a policy to minimise mortality should be guided not only by the effect of the disease itself, but also by the drug efficacy in different groups of the population. As we have shown, in cases in which antivirals have low efficacy in high risk populations, it is possible for the community-wide effect of treatment in the general population to offer more protection than direct treatment of high risk-group members. In this case, is it more "just" to prioritise the general population, if necessary even denying treatment to those hardest hit by a pandemic? There are two reasons to think that denial of treatment of the worst off is consistent with a Rawlsian "maximin" theory of justice of prioritizing the worst off. Firstly, control of infection spread might be regarded as being as much a "public good" as availability of the drugs themselves. Secondly, by denying low efficacy treatment of high risk symptomatic individuals, drugs can be used to maximally reduce the spread of disease and so *indirectly* benefit those most at risk (though not those symptomatic) by reducing their chances of contracting the disease. Under such constraints, justice paradoxically requires *denial* of treatment of the worst off, in favour of preventing infection of those most at risk.

Similarly, in the absence of a sizeable risk group, an intuitive approach aimed at minimising morbidity and mortality might be to dispense drugs aggressively at first, subsequently rationing if supplies run low. However, our simple model suggests, under certain constraints, that both consequentialism (aimed at reducing deaths to a minimum) and Rawlsian justice (aimed at benefitting the worst off, in this case, those most at risk) require maintaining an aggressive policy throughout (regardless of the risk of exhausting the stockpile). This would minimise the overall number of cases, and reduce spread, as well as broadening and delaying the epidemic peak.

Such policies based either on consequentialism or Rawlsian egalitarianism raise other ethical questions about the equity of drug distribution. Both policies would discriminate against infections late in the epidemic, probably including those who have been most compliant with infection-prevention measures and are least responsible for contracting the illness. Should some of the drug stockpile be preserved for these late cases, at the cost of greater numbers of cases, and the greater pressure on health services, that would otherwise result? Both consequentialism and egalitarian justice again seem to require denying some people the opportunity of a chance of treatment. Or should everyone have an equal chance of accessing treatment at all stages of the epidemic, regardless of their individual chance of benefit or the consequences for others?

The stated goal of distributors of antivirals is to reduce deaths. This may require denial of access to either symptomatic high risk individuals or those contracting the disease late in an epidemic.

Some notes of caution are in order. First, a problem with this analysis, as with many resource problems in healthcare, is uncertainty. The optimum strategy for antiviral deployment can only be known once we have the relevant data for drug efficacy in different parts of the population. However, until a pandemic-capable virus emerges, and starts to spread widely, we

will not know which groups might be at risk, nor the drug parameters needed to guide these strategies. Nevertheless, if a virus should emerge in South-East Asia, effective and rapid case analysis during this time could well provide valuable data with which to guide antiviral deployment in other countries. Our discussion does not offer direct solutions for this uncertainty; nonetheless, it highlights the need for continuous, accurate surveillance, and illustrates how this information could usefully inform an antiviral deployment strategy.

Second, the models presented here are necessarily gross simplifications: in reality many other factors will play a role, including stochasticity, and heterogeneities in the population. Moreover, not all clinical cases will start the treatment on time, and not all will finish it, reducing the effective stockpile size and potentially increasing the chances of emergence of a drug-resistant strain. Nor have we considered the possibility of presymptomatic postexposure prophylaxis and its impact on spread and overall mortality. In any case, the strength of the modelling approach presented here lies not in its quantitative predictions, but its capacity for providing heuristic insights, and these are likely to remain valid in yet more detailed models. Moreover, the analysis presented here demonstrates the fundamental effect that disease dynamics can have, on traditional debates about ethical resource allocation.

Pandemic planning is continually under review, and we suggest here that it would be beneficial to move away from regarding drug treatment as a purely reactive strategy, to an appreciation that it can also shape the course of an epidemic. A closer understanding of this behaviour could well provide valuable input for informing strategic priorities and their ethical implications.

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## Appendix

### The Basic Model

We consider a single wave of infection in a closed population, neglecting births and deaths. The population is divided into 5 groups: a proportion S is susceptible to infection; a proportion $I_T$ is infected and receiving treatment; a proportion $I_N$ is infected without treatment; a proportion $R_T$ is removed through treatment, and a proportion $R_N$ is removed without having received treatment. ("Removed" applies here equally well to recovery, or death.) Moreover, assume that a proportion $\alpha$ of infected cases receive treatment.

Infected cases recover in an average of $1/\gamma_T$ days and $1/\gamma_N$ days with and without treatment, respectively. We denote $\beta$ as the rate of infection.

The governing equations are as follows:

$$\dot{S} = -\lambda S,$$
$$\dot{I}_T = \alpha\lambda S - \gamma_T I_T,$$
$$\dot{I}_N = (1-\alpha)\lambda S - \gamma_N I_N,$$
$$\dot{R}_T = \gamma_T I_T; \quad \dot{R}_N = \gamma_N I_N.$$

where $\lambda=\beta\ (I_T+I_N)$, and the dot denotes a time-derivative. Now, the total number of drugs that have been dispensed at any given time is $(I_T+R_T)$, a non-decreasing function of time. If there is a stockpile of drugs sufficient to treat a proportion $M$ of the population, then the stockpile is depleted when $(I_T+R_T)=M$, and we set $\alpha=0$ for all subsequent time in the calculation.

The following parameter values were used to prepare Figs. 1 and 2:

| Parameter | $\gamma_N$ | $\gamma_T$ | $M$ |
|---|---|---|---|
| Value | 1/5 | 1/3.5 | 0.25 |

Finally, the value of beta was chosen to give the correct value of $R_0$, according to the expression: $R_0=\beta/\gamma_N$.

### The Extended Model: Risk Group

Assume that a certain proportion $p$ of the population is "at-risk", that is suffering a higher case fatality rate than the general population. Denoting members of the general population with superscript (g) and the risk group with superscript (r). Write $C_T^{(r)}$ and $C_N^{(r)}$ for the case fatality rates in the risk group with and without treatment, respectively. Corresponding quantities in the general population are obtained by substituting superscripts (g) for (r). Hence, by assumption, we have $C_N^{(r)}>C_N^{(g)}$.

Now, adopt the notation of the basic model for the two population groups so that, for example, $S^{(r)}$ denotes the proportion of the total initial population that is susceptible, in the risk-group. To these classes we add $D^{(r)}$ and $D^{(g)}$, the numbers dead from the risk group and from the general population respectively, written as proportions of the total initial population. Then we have two sets of governing equations: for the risk-group,

$$\dot{S}^{(r)} = -\lambda^{(r)} S^{(r)},$$
$$\dot{I}_T^{(r)} = \alpha^{(r)}\lambda^{(r)} S^{(r)} - \left(\gamma_T + \mu_T^{(r)}\right) I_T^{(r)},$$
$$\dot{I}_N^{(r)} = (1-\alpha^{(r)})\lambda^{(r)} S^{(r)} - \left(\gamma_N + \mu_N^{(r)}\right) I_N^{(r)},$$
$$\dot{R}_T^{(r)} = \gamma_T I_T^{(r)}; \quad \dot{R}_N^{(r)} = \gamma_N I_N^{(r)},$$
$$\dot{D}_T^{(r)} = \mu_T^{(r)} I_T^{(r)}; \quad \dot{D}_N^{(r)} = \mu_N^{(r)} I_N^{(r)},$$

Where

$$\lambda^{(r)} = \beta^{(rr)}\left(I_T^{(r)} + I_N^{(r)}\right) + \beta^{(gr)}\left(I_T^{(g)} + I_N^{(g)}\right)$$

and $\beta^{(gr)}$ is defined as the numbers of secondary infections arising per day in a completely susceptible risk group, due to one infected member of the general population. Corresponding equations for the general population are obtained by interchanging superscripts (r) and (g). Note that this model involves a twofold coverage policy, where drugs are dispensed to a proportion $\alpha^{(r)}$ of risk-group cases and a proportion $\alpha^{(g)}$ of the general population.

The mortality terms $\mu^{(r)}$, $\mu^{(g)}$ are chosen to give the appropriate case fatality rates, according to the expressions

$$C_T^{(r)} = \frac{\mu_T^{(r)}}{\gamma_T + \mu_T^{(r)}}; \quad C_N^{(r)} = \frac{\mu_N^{(g)}}{\gamma_N + \mu_N^{(g)}},$$

and correspondingly for the general population.

The following parameter values were used to prepare Fig. 3:

| Parameter | $p$ | $\gamma_N$ | $\gamma_T$ | $C_N^{(r)}$ | $C_T^{(r)}$ | $C_N^{(g)}$ | $C_T^{(g)}$ | $M$ |
|---|---|---|---|---|---|---|---|---|
| Value | 0.2 | 1/5 | 1/3.5 | 0.1 | 0.05 | 0.001 | 0.002 | 0.25 |

The same values were used for Fig. 4, except for the risk-group case fatality rate with treatment $C_T^{(r)}$, which had the value 0.1.

All case fatality rates (terms in C) are given as proportions.

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