

Drivers and consequences of influenza antiviral resistant-strain emergence in a capacity-constrained pandemic response

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ABSTRACT

Antiviral agents remain a key component of most pandemic influenza preparedness plans, but there is considerable uncertainty regarding their optimal use. In particular, concerns exist regarding the likelihood of wide-scale distribution to select for drug-resistant variants. We used a model that considers the influence of logistical constraints on diagnosis and drug delivery to consider achievable 'reach' of alternative antiviral intervention strategies targeted at cases of varying severity, with or without pre-exposure prophylaxis of contacts. To identify key drivers of epidemic mitigation and resistance emergence, we used Latin hypercube sampling to explore plausible ranges of parameters describing characteristics of wild type and resistant viruses, along with intervention efficacy, target coverage and distribution capacity. Within our model framework, 'real world' constraints substantially reduced achievable drug coverage below stated targets as the epidemic progressed. In consequence, predictions of both intervention impact and selection for resistance were more modest than earlier work that did not consider such limitations. Definitive containment of transmission was unlikely but, where observed, achieved through early liberal post-exposure prophylaxis of known contacts of treated cases. Predictors of resistant strain dominance were high intrinsic fitness relative to the wild type virus, and early emergence in the course of the epidemic into a largely susceptible population, even when drug use was restricted to severe case treatment. Our work demonstrates the importance of consideration of 'real world' constraints in scenario analysis modeling, and highlights the utility of models to guide surveillance activities in preparedness and response.

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Introduction

A number of novel antiviral agents against influenza are presently in development, spurred by awareness of existing limitations of current therapies, including the emergence of viable drug-resistant influenza variants (Hayden, 2009). Notably, seasonal H1N1 influenza viruses resistant to oseltamivir, the most widely available neuraminidase inhibitor (NAI), arose in Northern Europe during the 2007/2008 influenza season (Lackenby et al., 2008) and spread rapidly around the globe (Hurt et al., 2009) before being replaced by the A(H1N1)pdm09 strain that emerged in 2009 (Blyth et al., 2010). Since that time, reports of sporadic cases (Hurt et al., 2011a) and community-transmitted strains (Hurt et al., 2011b) of oseltamivir resistant H1N1pdm09 have become more frequent,

although sustained transmission has not yet been observed. Resistance to zanamivir, an alternative NAI, has to date been associated with severely reduced viral fitness. Based on the 2007/2008 experience – and recent virological analyses indicating the acquisition of so called 'compensatory mutations' which offset the negative effect of the mutation(s) that confer resistance – there is increasing concern that oseltamivir resistant H1N1pdm09 may yet still emerge to become the dominant circulating H1N1 strain (Kelso and Hurt, 2012). Lessons learned regarding best use of the NAI class of agents to limit resistance will be of relevance to application of novel agents in public health practice as they become available.

To date, outbreaks of transmissible NAI resistant viruses have not typically arisen in settings of widespread antiviral use (Hurt et al., 2011b). However, it is reasonable to anticipate that extensive drug distribution should promote selection for such strains (Morlighem et al., 2011). Concerns regarding development of resistance prompted some clinicians to call for restricted drug use during the 2009 H1N1 pandemic response in order to avoid a 'nightmare scenario' with few treatment options for severe cases (Grayson and Johnson, 2009). In reality, drug distribution was very

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limited in most settings (Leung and Nicoll, 2010), commensurate with a proportionate response to mild disease (Bishop et al., 2009), but precluding the ability to document anticipated tradeoffs of resistance versus mitigation.

Several published models exploring optimal application of antiviral agents in a pandemic response have foreshadowed the prospect of dominance of resistant strains in the context of combined treatment and prophylaxis strategies (Lipsitch et al., 2007). With others (Wessel et al., 2011; Qiu and Feng, 2010; Handel et al., 2007) we have demonstrated that the likelihood of resistant strain dominance in these frameworks depends critically upon mutant strain fitness and the proportion of the virus population that can be influenced by the intervention (McCaw et al., 2008). This latter figure depends on (i) the proportion of all infections that exhibit symptoms (and hence may come to medical attention), (ii) achievable drug delivery, particularly early in the epidemic and (iii) the duration of drug distribution which, in our model system, is constrained by a finite therapeutic stockpile (McCaw et al., 2008).

In light of the ‘real world’ constraints experienced during the 2009 H1N1 pandemic response in Australia, we have previously considered the additional limitations of finite diagnostic and drug distribution capacity on the likely mitigating impact of alternative proposed response measures (Moss et al., 2011). Given our finding of considerably reduced ‘reach’ of many interventions beyond previously proposed targets, we here reconsider the possible selective pressure of antiviral strategies focused either exclusively on case treatment, or treatment and prophylaxis, on antiviral resistance emergence. In addition, we seek evidence of key determinants of intervention outcomes that might be amenable to early epidemiological investigation, to support resource allocation decisions during a pandemic response.

Methods

Model structure and capabilities

Our model is based on the classic deterministic susceptible-exposed-infectious-recovered (SEIR) paradigm, with a stochastic component to account for the emergence of a drug resistant strain. All individuals are assumed fully susceptible (S) at the outset of the epidemic and vulnerable to acquiring infection upon contact with an infectious (I) case, entering the exposed class (E). Once recovered (R), individuals are assumed to be fully resistant to reinfection.

To allow for the consideration of community based targeted post-exposure prophylaxis, the model incorporates a dynamic ‘contact’ label (McCaw and McVernon, 2007), applied to a fixed number of individuals drawn from the whole population each time a new infectious case appears. We define these contacts and parameterize our model following the definition and findings of Edmunds et al.’s sociological studies (Edmunds et al., 2006): contacts are those people who have been sufficiently close to an infected individual to conceivably contract infection. Only contacts of an infectious case may proceed to the exposed and infectious classes, however the majority of contacts escape unscathed, returning to their original state within 72 h of exposure.

Epidemic scenario analysis within the model

Model parameters are summarized and referenced in Table S1 and described further below.

Transmissibility assumptions

Transmissibility of the wild type strain depends on both the initial reproduction number (R) and the mean serial interval ($1/\gamma + 1/\omega$), which comprises the exposed and infectious periods

(Roberts and Heesterbeek, 2007). The reproduction number determines the final attack rate (given our assumed homogeneously mixing population), negligible if $R < 1$ and monotone increasing with increasing $R > 1$. For a given R the serial interval determines the time course of the epidemic.

Severity assumptions

A campaign of widespread antiviral distribution is only likely to be justifiably sustained in a ‘severe’ pandemic scenario. Moreover, the proportion of infected individuals presenting for medical care has a substantial impact on the ability of an antiviral intervention to exert influence on the epidemic (Moss et al., 2011). For these reasons, we constrain our simulations in the main text to a ‘severe’ scenario, in which 10% of infected individuals require hospitalization (η). The corresponding proportion of all infections presenting to hospital or community-based medical providers (α_m) is allowed to range from 25 to 75%. Less severe scenarios are explored in the supplementary material (Section 1).

Resistance assumptions

We allow stochastic emergence of a drug resistant strain, modeled as a per-infection probability. Consistent with others, we assume that case treatment selects for the emergence of drug resistant influenza (ρ_r) more strongly than post-exposure prophylaxis (ρ_p) (Lipsitch et al., 2007). This assumption reflects the higher viral load upon which the drug exerts selective pressure when commenced during an established infection, increasing the likelihood that a resistant strain is already present. For simplicity, we do not allow for differences in selection between severe and mild cases, but note that severe (hospitalized) cases may have longer infections and so be more likely to initiate transmission of drug resistant strains. We further consider the possibility that a drug resistant mutant may emerge spontaneously (ρ_n) in the population, parameterized as of lesser likelihood than under either intervention case. With limited empirical evidence to guide parameter assignment, the rate of emergence of drug-resistance at the population level is varied across several orders of magnitude.

Once established, transmissibility of the resistant mutant relative to wild-type (ϕ) determines its spread – this parameter is considered within the range 0–1. While it is plausible that a resistant virus may exhibit fitness in excess of the wild type strain ($\phi > 1$), it may be intuitively supposed that such a virus will inevitably dominate regardless of drug selective effects.

Intervention scenario analysis within the model

Presentation to health care settings

Severe cases present to hospitals and are treated in a timely way. Non-severe (mild, moderate) infected individuals may present to two kinds of community health care settings; general practitioners or designated ‘flu clinics’. Antiviral provision in the community is subject to diagnostic and drug delivery constraints, described below.

Antiviral treatment and prophylaxis

Previous work has identified an optimal diagnostic strategy to ensure efficient antiviral drug delivery, as follows (Moss et al., 2011). In the initial stages of the epidemic where only a small proportion of illness presentations are due to influenza, a highly specific case diagnosis strategy based on molecular diagnosis is used to assign treatment. We incorporate delays to laboratory diagnosis arising from greater logistic complexity in GP compared with flu-clinics during this phase as a fractional reduction in intervention efficacy (f_{GP}). As the proportion of all ILI presentations attributable to influenza increases, a transition to syndromic-based treatment decisions becomes most efficient. In 2009 in Australia,

this time roughly coincided with the time at which diagnostic capacity (D_c) was exceeded, justifying the model assumption as reasonable (Moss et al., 2011). The model is flexible to consider alternative uses of antiviral agents: treatment of severe cases only, treatment of all ‘diagnosed’ cases, or a combination of case treatment with provision of antiviral prophylaxis to the proportion of contacts that it is estimated can be identified within a timely manner (σ).

Antiviral efficacy assumptions

Based on an analysis of combined clinical trials (Halloran et al., 2007) we allow for a modest reduction in transmission for cases treated in a *timely* fashion ($e_t = 10\%$, range 0–20%), and a substantial reduction in susceptibility for contacts provided with *timely* prophylaxis ($e_s = 50\%$, range 20–80%). Contacts receiving prophylaxis who nonetheless become infected have reduced infectiousness (e_i), conservatively assumed to mirror the effect of primary treatment (10%, range 0–20%).

Diagnostic capacity and drug delivery constraints

The model tracks diagnostic and drug delivery requirements throughout the course of the epidemic, in relation to ‘real world’ capacity constraints in the Australian context, estimated through expert enquiry. These constraints are observed in diagnostic capacity (D_c), delivery of treatment courses (MAX_T) and ability to deliver antiviral prophylaxis (MAX_P). As the epidemic grows exponentially, these constraints limit the actual application of interventions in the majority of scenarios, with implications for both the achievable level of drug delivery in relation to aspirational targets and the overall ‘selective pressure’ able to be placed on the viral population to promote drug-resistance.

Vaccination

Rollout of strain-specific vaccine is simulated several months following onset of the epidemic. Vaccinated individuals exhibit reduced susceptibility to infection, resulting in effective containment of transmission once sufficient coverage is achieved. Inclusion of this definitive intervention, envisaged in Australian pandemic planning (Australian Government Department of Health and Ageing, 2008) and hence included in previous modeling scenario analyses (Moss et al., 2011; McVernon et al., 2010), allows examination of the likely ability of transmission constraining measures to buy sufficient ‘time’ to allow mitigation of the final attack rate.

Population

We nominally consider a population size of 20 million (approximate Australian population size), with diagnostic capacity, drug delivery constraints and vaccine delivery set accordingly. As the emergence of drug-resistant mutants is captured stochastically, we also consider smaller populations (5×10^6 , 1×10^6 and 500,000) in Section 3 of the [supplementary material](#).

Sensitivity analysis and key model outputs

It is essential that presentation of the results capture the significant uncertainty surrounding both epidemic scenarios and the effectiveness of interventions. To that end, we employ a Latin-Hypercube-Sampling (LHS) technique to explore model parameter space. LHS is a statistical sampling method for generating plausible collections of parameter values from multi-dimensional distributions (Hoare et al., 2008).

In this work, we specifically consider the timing of onset and final size of the ‘resistant’ epidemic, and the impact of resistance emergence on the intervention’s effectiveness, within the bounds

of drug delivery capacity constraints. We use partial rank correlation coefficient plots to report on the sensitivity of model conclusions regarding the final attack rate, and the final proportion of cases that are drug resistant, to sampled parameters.

Results

Model behavior

The capacity constraints imposed on our model are critical to its behavior, as they impact substantially on *achievable* drug coverage of the target treatment and prophylaxis population as the epidemic progresses. This phenomenon is depicted in Fig. 1, which demonstrates the proportion of all infections that receive antiviral drugs over time, for a given set of epidemic and capacity assumptions, and a range of treatment and prophylaxis intervention scenarios (see legend for further details). Treatment of severe cases is the only intervention that occurs at a fixed rate, without constraint. Achievable community-based treatment coverage falls sharply from more than 40% to just over 10% with exponential growth of the epidemic, even using a syndromic case definition, as there are simply not enough practitioners to deliver the intervention in a timely manner. The additional *proportional* coverage of the total virus population achieved by prophylaxis is modest, due to the fact that the majority of contacts that receive prophylaxis have not truly been exposed (E) at the time of identification, and would never have developed the infection, given an R_0 of <2 . It is worth noting, however, that the addition of prophylaxis to the antiviral strategy delays the exponential growth phase of the epidemic by several weeks compared with treatment alone. Not surprisingly, increased delivery capacity for both prophylaxis and treatment are associated with a greater ability to reduce the overall attack rate in the population (Fig. S3, [supplementary material](#)).

Selection of informative epidemic scenarios

Fig. 2 depicts achievable reductions in attack rate for simulated interventions compared with the base case, scanning across a plausible starting range of R_0 values from 1.15 to 2.5. Box plots depict the median and interquartile ranges of simulation outputs over the LHS samples. Few positive outcomes are observed for an assumed $R_0 \geq 1.5$ (i.e. the intervention is essentially futile), with the greatest variability in attack rate observed between the ranges 1.25 and 1.45 (i.e. the intervention is *sometimes* useful). Hereafter, we will restrict our considerations to this latter range, in order to identify additional factors associated with successful epidemic constraint, that might support a decision to invest in a wide-scale antiviral deployment strategy, while considering implications for resistance.

Influence of intrinsic virus properties on resistance emergence

Fig. 3a shows exemplar wild-type (blue) and resistant (red) epidemic curves, for a single model simulation run. The inset box demonstrates unsuccessful seeding of a resistant strain at approximately 8 weeks, followed by successful establishment of such a variant approximately one week later. This timing, however, is too late to allow dominance of the mutant over the wild-type strain, making it essentially invisible on the full-scale graph (dominated by blue). Fig. 3b depicts the intuitively logical relationship between the *time* of successful seeding of the resistant epidemic (y -axis) and probability of emergence of a resistant strain under drug treatment (ρ_t) (x -axis). Moreover, resistant mutants of higher intrinsic fitness compared with wild-type (ϕ) (shaded red) are more likely than less fit strains (shaded blue) to arise early, at a time when the population is still highly susceptible.

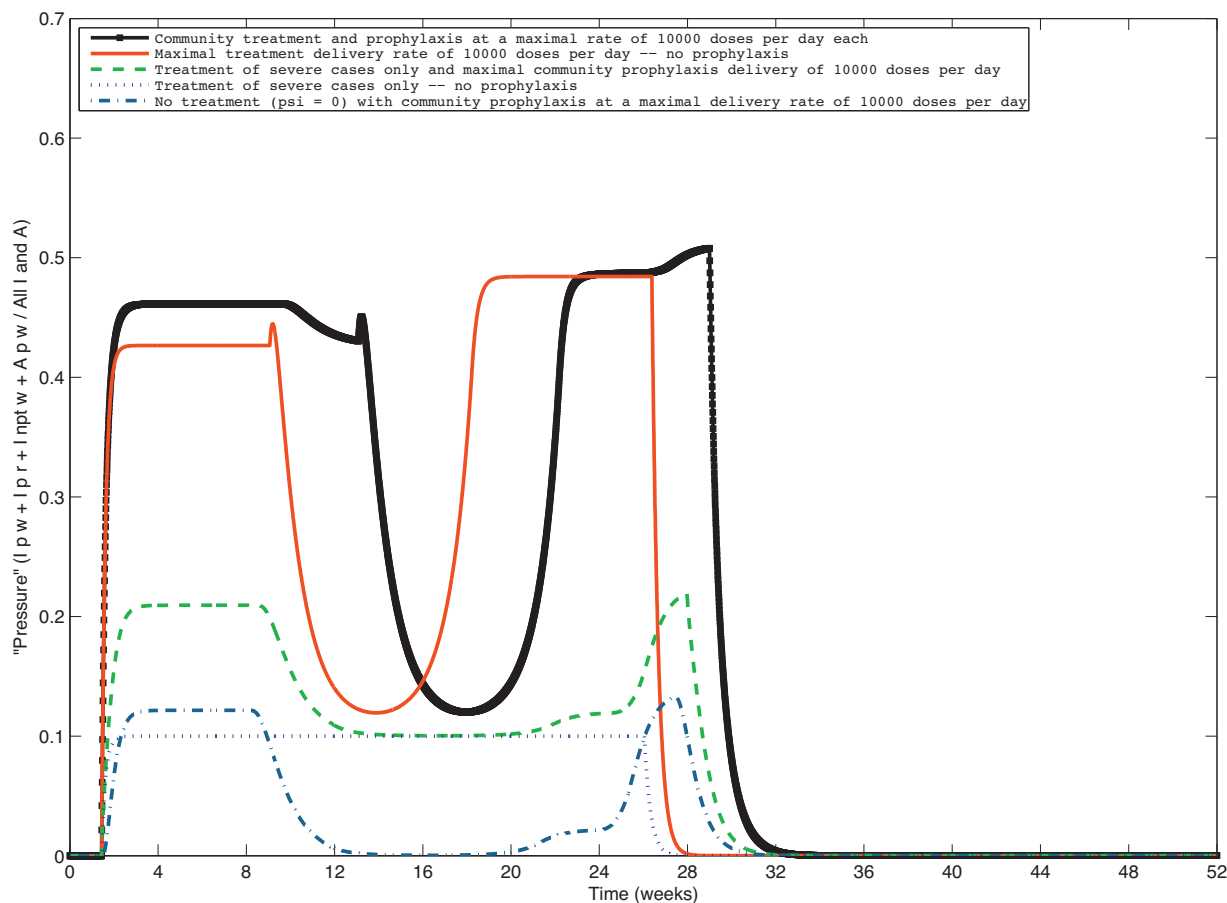


Fig. 1. Proportional coverage of the total virus population achieved, under alternative intervention strategies. The proportion of all infections that receive antiviral treatment and/or prophylaxis is shown, in relation to all observed and unobserved infections, over the course of the epidemic. The epidemic scenario considered assumes a severity (η) of 10%, with a presenting proportion (α_m) of 48%. The proportion of contacts traced (σ) is 50%, within maximal delivery constraints for each of treatment (MAX_T) and prophylaxis (MAX_P) of 10,000 doses per day. Drug efficacy assumptions include a 10% reduction in ongoing transmission from treated cases ($e_t = 0.9$) and prophylaxis 'breakthroughs' ($e_p = 0.9$) and an effective reduction in susceptibility for individuals receiving prophylaxis of 50% ($e_s = 0.5$). Interventions considered are: prophylaxis only; treatment of severe cases only; treatment of severe cases only with prophylaxis; treatment of all identified cases (severe or community-based) only; treatment of all identified cases (severe or community-based) with provision of post-exposure prophylaxis.

Influence of capacity constraints on resistance emergence

We now consider the influence of capacity constraints to mitigate an epidemic, evidenced by reduction in the overall attack rate, in relation to both the timing of resistant strain emergence and the epidemic growth rate (R_0). Fig. 4a demonstrates that higher levels of delivery capacity (shaded red) are generally associated with more favorable outcomes than the lower capacity case (blue). However, at higher assumed values of R_0 , an extensively applied intervention may bring forward the resistant strain epidemic, with unfavorable consequences for the final attack rate. Fig. 4b explores the drivers of this effect further, reporting on the final proportion of all cases that are drug resistant, relative to timing of resistance emergence, mutant strain fitness and capacity constraints. Here we observe that only very early-emergent strains of near-equivalent fitness to wild-type virus become predominant (back corner of the plot), and then usually only under high-end delivery assumptions (Fig. S4, supplementary material).

Other influences on epidemic outcomes

Fig. 5a shows a tornado plot depicting parameter values that are significantly ($p < 0.05$) associated with the intervention's ability to reduce the final attack rate. Bars to the right depict parameters that are associated with higher attack rates. Bars to the left are parameters that are associated with successful mitigation. Not surprisingly,

epidemics with higher baseline growth rates (higher R_0 , shorter serial interval ($1/\gamma + 1/\omega$)) are harder to control. Lower assumed efficacy of the antiviral intervention ($1 - e_t$, $1 - e_s$) logically also predicts a poor intervention outcome. The importance of achievable coverage for intervention success is demonstrated by inverse attack rate correlations with the presenting case proportion (α_m), prophylaxis uptake (σ) and drug delivery capacity constraints for treatment and prophylaxis (MAX_T , MAX_P).

Fig. 5b reports parameters most influential to determining the final proportion of drug resistant cases. Consistent with Fig. 4b, intrinsic properties of the mutant strain (ρ_t and ϕ), demonstrated through early emergence in the population, are the critical determinants of final outcome. Maximum treatment capacity exerts some effect by influencing achievable selection pressure, and is more influential than prophylaxis capacity. As may be anticipated, a drug that exerts little influence on ongoing transmission ($1 - e_t$) is less likely to select for resistant virus, as mutant strains are afforded relatively little advantage over the largely unconstrained wild-type.

Discussion

Our model incorporates 'real world' capacity constraints that limit the actual reach of a case targeted antiviral intervention. As a result, the level of treatment and prophylaxis simulated is far lower than in many existing models of antiviral resistance (Moghadas et al., 2009; Handel et al., 2009), falling dynamically

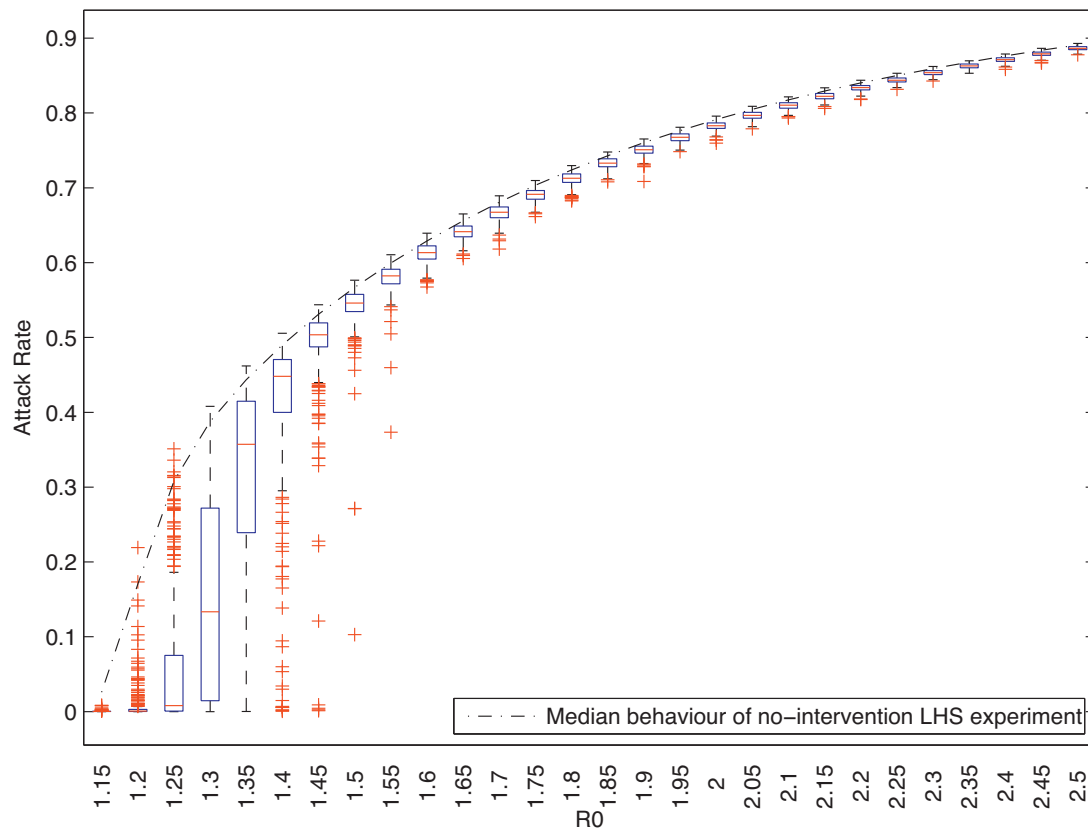


Fig. 2. Achievable reductions in attack rate across a broad range of R_0 assumptions. The dashed line indicates the median final attack rate of the epidemic in the absence of drug intervention. The box plots depict the broad range of outcomes (boxes define interquartile ranges bisected by medians in red, red crosses are outliers) for simulated drug treatment and prophylaxis scenarios, across variable efficacy assumptions and capacity constraints. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

during the period of exponential growth. In consequence, stockpiles as simulated are rarely exhausted and overall impacts of antiviral distribution, including resistance emergence, are more modest than predicted by our earlier work without these constraints (McCaw et al., 2008). With others, we conclude that the relative transmissibility of drug resistant mutants is an influential determinant of intervention outcomes (Moghadas et al., 2009; Handel et al., 2009), as is the timing of their emergence. Of particular note, reserving drugs for treatment alone does little to reduce the likelihood of resistant strain dominance, compared with combined treatment and prophylaxis strategies that have the potential to more effectively constrain transmission.

We consider the incorporation of logistic constraints based on observation of the 2009 pandemic response in Australia to be a key strength of our modeling approach, providing pragmatic upper bounds on likely response capacity and stockpile utilization as the epidemic evolves with clear implications for outcome. In the absence of such limitations, Moghadas and colleagues have proposed strategic moderate use of antivirals for case treatment early in a pandemic response to reduce selection for resistance, scaling up thereafter during the exponential growth phase (Moghadas et al., 2008). However, as Fig. 1 demonstrates, such an approach would be extremely challenging to implement in practice. Instead, with Handel et al. (2009), we suggest that early liberal drug distribution provides the only real (if modest) prospect of effective constraint of virus replication in the population, influencing both wild type and resistant viruses alike, with the caveat that resistance generation is a risk should the attempt at containment fail.

Our implementation of resistance emergence draws from general principles consistent with many previously published model

frameworks, but differs slightly in ways that might be predicted to affect epidemic outcomes. For example, while mutant strains arise stochastically, once established they are transmitted deterministically (and inexorably) through the remaining susceptible population without the prospect of reversion to wild-type (Handel et al., 2009). On the other hand, rather than using a multi-step model of mutant strain evolution that considers increasing fitness due to acquisition of compensatory mutations over time (Moghadas et al., 2008), we have chosen a simple one-step emergence event, which may be predicted to reduce the final size of resistant outbreaks, when they occur (Handel et al., 2009), but is likely to have little bearing on qualitative conclusions of the model.

Properties of the resistant strain are the key determinants of emergence and persistence. Strains of higher intrinsic fitness are more likely to gain sufficient selective advantage from antiviral suppression of wild type to be preferentially transmitted, an intuitive outcome supported by others (Moghadas et al., 2009; Handel et al., 2009). Mutant viruses with transmissibility in excess of the wild type strain may be anticipated to predominate in the absence of drug use, justifying our decision not to include them in scenario analyses. An example of such a virus is the oseltamivir-resistant seasonal H1N1 variant that circulated globally prior to 2009 (Chao et al., 2012). Mutant strains arising early in the epidemic are further advantaged by the relatively large size of the susceptible pool, resulting in a higher final resistant proportion (and potentially total attack rate) as observed elsewhere (Moghadas et al., 2009).

The addition of prophylaxis to our drug delivery strategy has clear benefits for mitigation, without a marked increase in emergence of resistance, in contrast to our own (McCaw et al., 2008) and others' (Moghadas et al., 2009) earlier findings. We attribute this

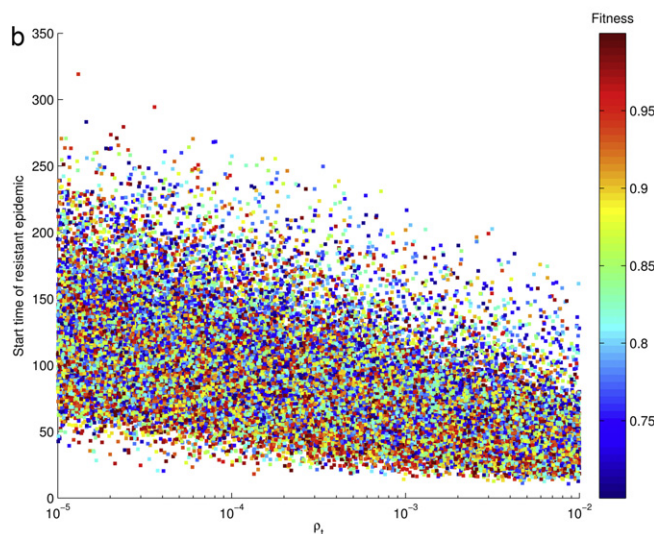
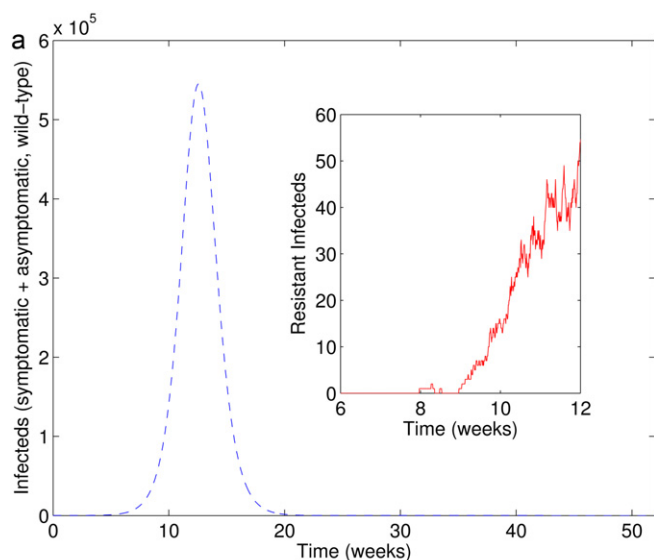


Fig. 3. Time to emergence of drug-resistant mutants. (a) The full-scale figure depicts the overall course of the epidemic, dominated by the wild-type strain (blue). The inset box (note change of scale) shows intermittent seeding of a resistant virus (red), which establishes in the population without predominating. (b) The first successful seeding of a resistant strain in the population is considered in relation to both the probability of resistance emergence under treatment (ρ_t) and intrinsic fitness of the mutant strain (ϕ). As anticipated, earlier emergence is observed for higher assumed resistant virus parameters. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

difference to the reduced virus population size on which antivirals act in early infections ($\rho_p < \rho_t$), the inclusion of capacity constraints and also the very modest proportional increase in coverage of the virus population resulting from post-exposure antiviral use in the present model due to our ‘sociological’ approach to drug distribution (Fig. 1). Moreover, given that our contacts are drawn from the whole population, an increasing proportion will be in the recovered class as the epidemic progresses, further reducing the selective pressure associated with prophylaxis over time. This feature of our model structure differs substantially from most others that apply targeted post-exposure therapy directly to the ‘exposed’ class, resulting in far greater influence on the virus population in such model constructs than may be realistically observed in practice (Moghadas et al., 2009).

All models are necessary simplifications of complex systems and there are many demonstrated features of real world settings

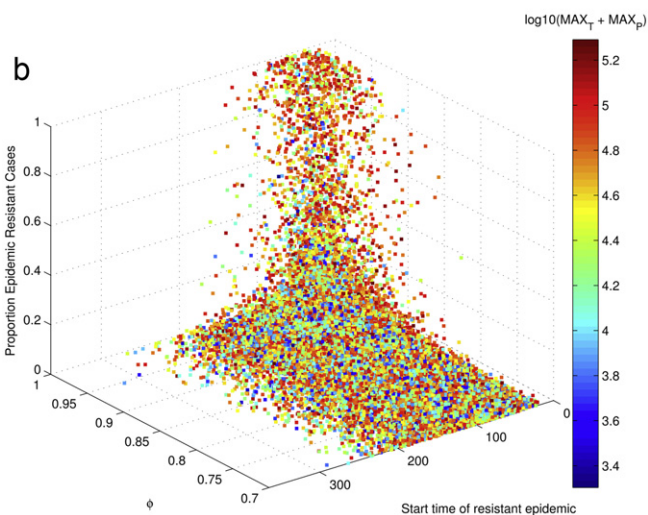
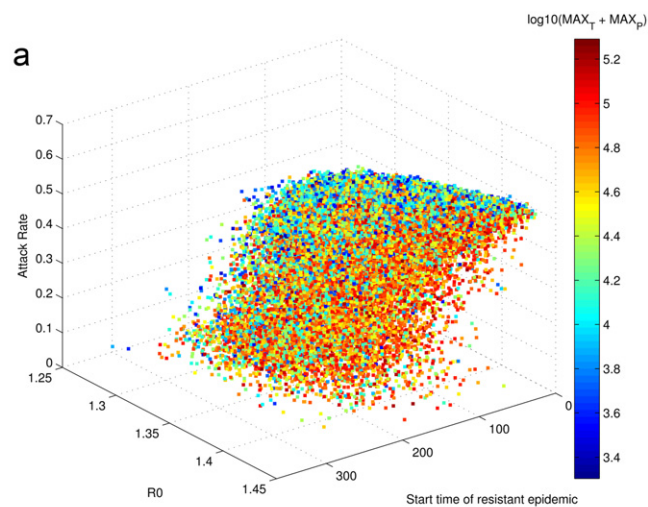


Fig. 4. Influence of capacity constraints on resistance emergence. (a) Final epidemic attack rate is plotted relative to both start time of the resistant epidemic (a proxy for ρ_t) and the baseline epidemic growth rate (R_0). Colors depict drug delivery capacity for both treatment and prophylaxis, ranging from low (blue) to high (red). In general, higher drug delivery is associated with reductions in the final attack rate. However, for higher assumed values of R_0 , extensive drug delivery may fuel early emergence of resistance with negative consequences for intervention impact. (b) The combined influences of drug delivery capacity and resistant strain properties on the final proportion of all infections that are resistant are considered. Resistant strains dominate under a fairly limited set of assumptions, including early time to emergence, near-equivalent fitness with wild-type and high levels of drug delivery. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

that have been omitted from this simple framework. Heterogeneity of population mixing and in particular, the degree of clustering, may drive local resistance emergence at lower treatment thresholds than estimated from homogeneous model systems (Alexander et al., 2007). We have considered smaller population sizes in the supplementary material (Section 3), with consistent findings. The interplay between intervention timing and seasonal variation in transmission has the potential to result in adverse outcomes of early strategies to limit spread (Towers et al., 2011), a challenging finding to incorporate into decision making in the face of uncertainty. Our population is considered fully susceptible at the beginning of the epidemic with vaccination implemented as a ‘terminal’ strategy, ignoring the potential interaction between host immunity and the intervention (Qiu and Feng, 2010) that may be

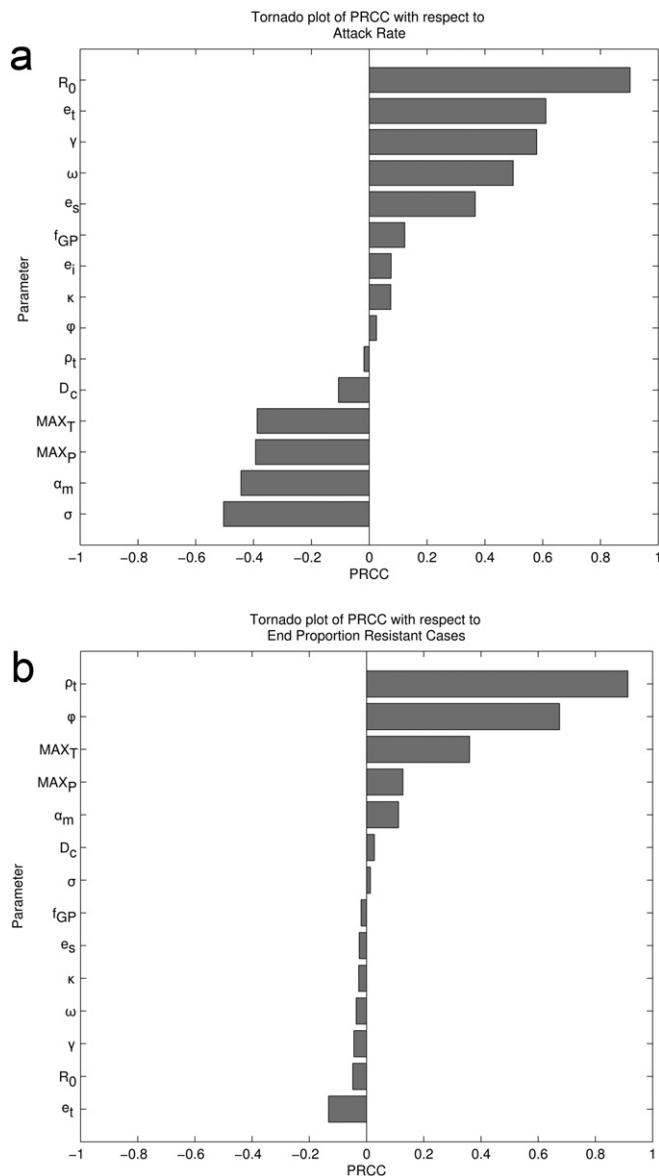


Fig. 5. Partial rank correlation coefficient plots. (a) Epidemic and intervention parameters that are significantly ($p < 0.05$) associated with the epidemic outcome are depicted in the tornado plot. Bars to the right are associated with a higher final attack rate, those to the left with a lower final attack rate. High baseline intrinsic growth rates (higher R_0 , shorter serial interval ($1/\gamma + \omega$)), and low intervention efficacy ($1 - e_t$, $1 - e_s$) are associated with worse outcomes. Achievable coverage of antiviral drugs is a key determinant of the final attack rate, acting through uptake by cases (α_m) and contacts (σ) and drug delivery constraints (MAX_T , MAX_P). (b) The final proportion of cases that is resistant is largely determined by the properties of the mutant itself, including a high likelihood of emergence under treatment pressure (ρ_t) and high fitness relative to wild type (ϕ). Treatment delivery also exerts some influence (MAX_T , $1 - e_t$), in excess of selective pressure due to prophylaxis.

a feature of proposed strategies such as administration of a stockpiled strain-matched ‘pre-pandemic’ vaccine. Of note, an increased prevalence of cross-protective antibody may theoretically be associated with a higher rate of antiviral resistance emergence than would be observed in a fully naïve population, due to the acquisition of complementary mutations in neuraminidase associated with antigenic drift in haemagglutinin (Hensley et al., 2009).

Our model demonstrates that early detection of circulating resistant strains indicates a high likelihood of subsequent dominance. Such a signal in virological surveillance may be the trigger for a shift in strategy to withhold treatment for severe cases alone and/or switch to a different stockpiled agent. Others have

considered ‘switching’ drug strategies and proposed that if two agents have been stockpiled, that the one in smaller supply be delivered first (Hansen et al., 2010). An increasing body of research considers the likely utility of combination therapies to minimize or overcome resistance (Perelson et al., 2012), further supporting strategic stockpiling of more than one agent. Such approaches are more likely to be able to be implemented in practice than our previously proposed ‘split use’ strategy of using one drug for prophylaxis and the other for treatment (McCaw et al., 2008).

Conclusions

Our study highlights the importance of incorporating realistic logistic constraints into scenario analyses for policy decision support, resulting in more moderate predictions of intervention outcomes including resistant strain dominance. By sampling over a broad range of plausible epidemic and intervention assumptions, we have been able to identify key drivers and signals of resistance emergence. Such findings may help to direct early information gathering during a pandemic response, through mechanisms such as the ‘first few hundred’ project undertaken in England in 2009 (McLean et al., 2010). They further reinforce the crucial role of globally co-ordinated active surveillance for transmissible drug-resistant influenza mutants to inform public health decision making (Hurt et al., 2012), supported by basic research to understand the relative transmission fitness of such strains (McCaw et al., 2011).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.epidem.2012.12.002](https://doi.org/10.1016/j.epidem.2012.12.002).

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