USING MATHEMATICAL MODELS TO ASSESS RESPONSES TO AN OUTBREAK OF AN EMERGED VIRAL RESPIRATORY DISEASE

Final report to the Australian Government Department of Health and Ageing by

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PREFACE

This report was commissioned by the Department of Health and Ageing. It uses mathematical transmission models to evaluate the alternative interventions available for the control of an emerged pandemic of influenza. Data from past pandemic and currently circulating influenza strains guide the choice of values for model parameters.

In reading this report it is useful to bear in mind that a glossary of terms is given in Appendix A and values used for the many parameters of the modeling work are given in Appendix B. The latter also contains a discussion of data sources.

The report begins with a brief background statement (Section 1), followed by an introduction to the basic model structures and important concepts used in the report (Section 2). Particular attention is paid to the key concepts of *basic reproduction number* (R_0) and *infectiousness function*, and to the measures used to judge the effectiveness of various public health interventions.

Section 3 evaluates border control measures primarily in terms of their effect on the likely delay between a pandemic being initiated overseas and being imported and gathering momentum in Australia. The additional delay resulting from restricting travel from the infected source region, screening travelers, promoting early presentation of newly-arrived travelers, and instigating partial home quarantine for all arriving travelers is quantified. We also present a method for deciding when Australia should consider implementing border control measures.

Section 4 evaluates interventions aimed at limiting transmission once the infection has been imported. Measures evaluated include early case isolation, personal infection control and distancing, quarantining affected households, closing schools, closing non-essential workplaces, prohibiting mass public gatherings, and the use of antiviral drugs. This section also examines the effect of time-delays in implementing interventions on the subsequent course of the epidemic.

Section 5 evaluates the use of antiviral drugs in greater detail. A range of strategies for the use of the antiviral drugs (who gets the drugs and when) are modeled to assess their contribution to reducing transmission, containment and delaying the epidemic. The implication for the antiviral stockpile is also assessed.

Section 6 assesses the role that health workers may play in spreading disease, and how the extent of this transmission and their risk of infection are reduced by protection through the use of antiviral drugs and personal protective equipment. The likely load on the health-care system in terms of influenza cases requiring hospitalisation is assessed for a range of scenarios.

We discuss limitations of the modeling results, and suggest where further work is needed.

The report concludes with a discussion section in which we comment on the reasons for the main results and their sensitivity to underlying assumptions. Issues that have not yet been addressed adequately are also pointed out.

Many calculations have been conducted for this report. It is hoped that these modeling results will be of help to policy makers. A large number of other calculations could have been conducted, different issues could have been addressed and issues could have been addressed differently. It is hoped that the results obtained so far, and the gaps in these results, will help to identify what other calculations would be particularly useful.

EXECUTIVE SUMMARY

This report uses mathematical models that describe person-to-person transmission of an infectious disease to evaluate the alternative interventions available for the control of an emerged pandemic of influenza. It uses data from past pandemic and currently circulating influenza strains to guide the choice of values for model parameters. However, recognizing that parameter values may be quite different for a newly emerged pandemic influenza strain, the emphasis is on a relative comparison of the effectiveness of interventions and on identifying the circumstances under which measures will be most effective.

Border control

Even with 100% sensitive screening of symptomatic arriving travelers there remains a substantial probability (very roughly, 0.3 when the travel duration is 12 hours) that an infected traveler passes through border screening undetected.

The probability that an outbreak, initiated by a single infected traveler who enters Australia undetected, leads to a major local epidemic can be reduced substantially by

i. actions that promote early presentation of the infected arrival, and
ii. partial home quarantine of travelers arriving from at-risk regions,

making this probability quite small. Nevertheless, such measures delay the time until a local epidemic begins only marginally (several days or, at best, a few weeks), assuming that the epidemic in the source region gathers momentum. Reducing the number of travelers from the source region delays the local epidemic only marginally unless the number of arrivals from the source region is near zero.

Border control is only useful for preventing disease entry, and provides very little further benefit once an epidemic has gathered widespread momentum within Australia. A criterion for initiating the Australian response is suggested in Section 3.3.

Limiting transmission

Calculations indicate that by themselves, the interventions

i. isolating cases upon diagnosis,
ii. closing non-essential workplaces and/or schools, and
iii. restricting travel within Australia,

are only modestly effective at limiting the transmission of influenza-like infections. This means that their effect is modest when the basic reproduction number (R_0) of the infection exceeds 2. However, as R_0 becomes closer to 1 the effectiveness of these interventions, to limit transmission, increases. In particular, the addition of isolating diagnosed cases and closing non-essential workplaces can have a major impact when other interventions bring the effective reproduction number R close to 1. Closing schools does reduce the attack rate in children, and would reduce the overall attack rate effectively if school children were found to have a much higher risk of infection than adults. In combination these interventions can be moderately effective.

By themselves, the interventions

i. personal infection control and distancing (for example: avoiding close contacts, wearing a P2 mask and frequently washing hands),
ii. quarantining affected households, and
iii. use of antiviral drugs for targeted prophylaxis,

have greater potential for limiting transmission. In combination they can be quite effective. This assessment of the use of antiviral drugs for targeted prophylaxis assumes that their effectiveness against the newly emerged strain is as for circulating strains of influenza. A variety of calculations indicates that the effectiveness of each of these interventions decreases rapidly as the delay in introducing it increases.

The intervention of prohibiting mass gatherings is difficult to evaluate. Its effectiveness is sensitive to the probability of attending a mass gathering event during the infectious period and the mean number infected at such gatherings. Unfortunately data are not available to estimate these quantities.

It is encouraging that all of these interventions, used in combination and with good compliance, seem capable of eliminating a newly emerged pandemic influenza infection with a basic reproduction number as high as 10, although the level of compliance required seems difficult to achieve in practice.

Antiviral drugs

Calculations indicate that using antiviral drugs (AVs) only for treatment has a modest effect on transmission. It delays the epidemic peak only when nearly everyone is treated and R_0 is less than 1.5.

The indiscriminate use of AVs for prophylaxis limits transmission minimally, and is simply wasteful. In contrast, providing AVs to individuals who are likely to become exposed, or to have had a recent exposure, can substantially reduce or delay most of the transmissions in a local epidemic if the reproduction number is less than 2. Specifically, calculations suggest that timely prophylaxis for 50% of contacts for every case can delay the peak of a local epidemic by about one year if the basic reproduction number is less than 1.7. This calculation assumes that no other interventions are in place. If the reproduction number is much higher, delays can still be achieved, but a greater fraction of contacts would need to be traced – for example, for a reproduction number of 3.3, 90% of contacts would need to be traced to achieve a six month delay. This strategy delays the central part of the local epidemic (including its peak), but there is little change in the eventual size of the epidemic. Apart from the practical difficulty of distributing the antiviral drugs to the right people, this strategy relies on an effective vaccine becoming available by the time the antiviral stockpile runs out, because transmission will accelerate once the stockpile has been used up.

It is important to note that the majority of the stockpile must be able to be distributed during a short amount of time: in many situations modeled, the most severe part of the epidemic lasts only one month, and therefore the stockpile can only be effectively used if Australia has the capacity to dispense tens of thousands of courses per day.

Note that our calculations have not taken account of the possibility that the virus develops resistance to the antiviral drugs. Moreover, our assumptions concerning the effect of AVs are based on trials with currently circulating strains of influenza A. It is essential that an assessment of the effectiveness of AVs against the new influenza strain be made in the event of a pandemic.

Health care workers

Our calculations indicate that a substantial proportion of infections will be due to health care workers (HCWs) if they are not protected by personal protective equipment (PPE) and AVs when tending infected cases. The number of individuals infected by HCWs is reduced substantially by the use of PPE and prophylactic use of AVs for HCWs.

With targeted prophylaxis of influenza-dedicated health care workers and no use of AVs in the community, our models suggest that the stockpile will last over the course of the first wave of an epidemic. However, this will not delay the peak of the epidemic.

If antivirals are also used to prevent community transmission by giving prophylaxis to contacts of new infectious cases, the stockpile will run out before the peak of the epidemic, unless elimination is successful. However, the peak of the epidemic can be delayed through this strategy for several months, which may facilitate wide-spread distribution of a vaccine before the peak of the epidemic.

The number of cases requiring hospitalisation at any one time rises above 10,000 for a significant period of time for an epidemic with a high attack rate. The peak number of cases requiring hospitalisation can be reduced through treatment of infectious cases, and delayed through prophylaxis of case contacts.

1 BACKGROUND

A glossary of terms used in this report is given in Appendix A.

1.1. Outbreaks of emerged respiratory infections

Outbreaks of newly emerged respiratory infections are a continuing threat. Over the last two centuries pandemics of influenza occurred at the rate of about one in every thirty years [Nguyen-Van-Tam and Hampson (2003)]. There is also a continuing threat of the emergence of new respiratory infections, as is illustrated by the emergence of SARS and its potential re-emergence.

We focus our discussion on pandemic influenza, because the threat of pandemic influenza is currently enhanced due to the global spread of *avian* influenza. We contrast the results with those for SARS, because they essentially represent extremes in terms of when infected individuals show symptoms relative to the start of their infectiousness.

1.2. The use of modeling to evaluate interventions for outbreak control for emerged respiratory infections

It is not ethical, and often not possible, to assess the effect of possible interventions by conducting experiments with real communities. As a result, mathematical models that describe the transmission of infectious diseases are a valuable tool for planning the management and control of infectious diseases.

The use of mathematical models to evaluate an intervention proceeds by first constructing a mathematical model that describes the transmission of the infection. Such a model is necessarily a simplification of the real world, but is a useful basis for the evaluation as long as it contains the essential characteristics of transmission of the infection in the community. One requirement is that the description provided by the model must agree with all relevant empirical data that are available. The next step is to modify the model in a way that reflects the proposed intervention. Then the outcomes predicted by the original model and the modified model are compared, to assess what effect, if any, the proposed intervention has on the outcome of interest.

Applications of transmission models to assess strategies for infectious disease control include the assessment of vaccination strategies [Anderson and May (1991)], predictions of epidemics [see for example Ramsay *et al.* (1994), Roberts and Tobias (2000)], strategies for the control of foot and mouth disease [see Green and Medley (2002) for a review], assessing the effect of interventions used in the control of SARS and recent modeling assessing the potential for controlling an emerged pandemic of influenza [see for example Longini *et al.* (2004, 2005) and Ferguson *et al.* (2005)].

1.3. This report

This report presents results from an assessment of the effectiveness of various responses to an emerged strain of pandemic influenza.

The results on the assessment are presented under the headings of

(a) effectiveness of border control measures (Section 3);
(b) limiting the transmission of imported infection (Section 4);
(c) the role of antiviral drugs (Section 5), and
(d) the role of health workers (Section 6).

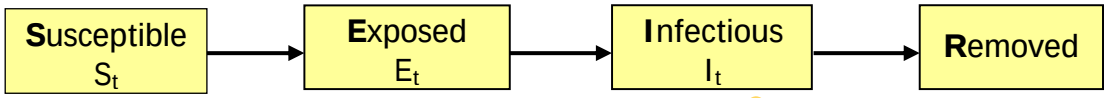
We begin with an outline of the models used.

2 INFECTIOUS DISEASE TRANSMISSION MODELS

2.1. Models used in this project

This work is not based on one comprehensive model that captures all essential features of our community, all plausible characteristics of the infection and all available interventions. Development of such a model and its use to address the numerous aims would be an enormous undertaking, which is quite infeasible in the timeline available for this project. Instead, we have developed a number of models each of which is formulated to contain the essential features needed to address specific issues of interest. There is some overlap in the issues these models can address and this provides a useful check on the results. We now outline some of the features and assumptions that are common to the modeling approaches.

Individuals are assumed to be susceptible at first. Upon infection they are classified as *exposed*, to indicate that they have entered the latent stage of their infection. There follows a period when they are infectious. After this they become removed, by death or recovery with acquired immunity.



Our models of this kind can be classified into two types, referred to as SEIR and $SEIR_H$. In models of the type $SEIR_H$ the community has a household structure, while the simpler SEIR model ignores the household structure. The SEIR model is easier to work with and therefore enables an analysis in a shorter timeframe. Some features of the various modeling approaches are listed below.

First, ordinary differential equations were used to model the transitions between the progression states (Sections 4.9, 5.6, 6.2 and 6.3). Such models are the most common form of infectious disease model found in the literature. This approach models the actual numbers and/or quantities in different categories (e.g. anti-viral stockpile) continuously in time, using equations for the rates of transitions. These are deterministic models (i.e. each run of the model produces the same result) and hence do not capture the variability in outcomes. Such variability may be substantial, especially early in an epidemic.

Second, the transitions between disease states were modeled by difference equations (Sections 4.8 and 5.5), whereby quantities are updated at fixed time steps (e.g. daily). This approach allows complexity to be accommodated (e.g. household size and the disease status of individuals within households on a day-by-day basis) in a conceptually simple manner, using a time scale that is natural for collecting data (e.g. daily incidence). We used deterministic models of this form.

Third, the movement between disease states was modeled using the mean numbers in successive generations (Sections 4.6, 4.11, 5.2–5.4 and 6.1). Generations are defined as follows: The initial case (or cases) makes up the first generation. The second generation consists of all cases that had an infectious contact with a case from the first generation. Similarly for the third, and later, generations. In these models the deletion of susceptibles is ignored, so they are suitable only for studying the effect of interventions on the reproduction number (see Section 2.2) and on the early dynamics. However, the approach can incorporate considerable underlying complexity in transmission between different types of individual in a community (e.g. general public, general practitioners, health care workers), and allows the effect(s) of interventions (e.g. use of AVs, closing schools) either singly or in combination to be easily explored in terms of the effect on the reproduction number (R) and the mean dynamics of the early stages of an epidemic.

Fourth, branching processes were used to incorporate the chance element of transmission between individuals, which is especially relevant in the early stages of an epidemic where chance plays a large role in whether epidemics take off or fade-out (Sections 3.2–3.8). This type of model is most appropriately applied during the early stages of an epidemic when there is little competition for

susceptibles. It is particularly useful for assessing whether an infected individual will successfully initiate an epidemic. We assume that during the early stages of an epidemic, the offspring distribution that describes the number of secondary cases that each infected case generates is Poisson with mean equal to the effective reproduction number operating at the time.

Fifth, a stochastic household model was developed in terms of generations of infected individuals (Sections 4.2-4.5, 4.10, 5.7) that allows for depletion of susceptibles, and so can be used to investigate the size and timing of the outbreak. The model includes adults and schoolchildren as separate types, and was used to consider interventions (such as closing schools) that differentially affect adults and children. The stochastic nature of the model provides insight into the variability in the size and timing of epidemic outbreaks that arises from chance. Transmission within the household follows the Reed-Frost model (Bailey, 1975), while transmission outside the household is according to a mixing matrix that has been calibrated to relative attack rates in adults and children seen in past influenza pandemics.

Finally, stochastic population-based models were used to investigate the spread of infection between cities (Section 4.7). A stochastic approach is valuable in capturing the effects of random variation on the timing of city to city spread. Transmission between cities follows the standard diffusive model, in which the degree of transmission is proportional to the volume of travel between the cities.

For all approaches, the larger structure of the Australian community is not explicitly taken into account (e.g. demographic differences between cities), hence most of the results presented apply at a local level. We have been consistent in the parameters values used in the models (see Appendix B for default parameter values and their justification). Throughout, we allow influenza infected individuals to become symptomatic part of the way through their infectious period. The possibility that individuals may still be susceptible after recovery, due to acquiring only partial immunity is not allowed for, unless explicitly stated.

Assumptions specific to each modeling approach are presented in the sections where they arise.

2.2. The reproduction number

The reproduction number (R) is often used to reflect how infectious a disease is. We will, in part, use this quantity to assess alternative interventions to control an outbreak, because R is changed by control measures. The *basic* reproduction number (R_0) is the reproduction number when there is no immunity from past exposures or vaccination, nor any deliberate intervention in disease transmission. We refer to R as an effective reproduction number when there is some immunity or some intervention measures are in place.

It is useful to recall some of the characteristic of a reproduction number, because its interpretation is not always straightforward.

When individuals are homogeneous and mix uniformly, R is defined as the mean number of infections generated during the infectious period of a single infective. Individuals may differ in the number they infect, due to chance, but the mean number infected is R. Epidemics of an SEIR infection can not occur when R is less than 1 at the start of the outbreak and established outbreaks will fade out if either interventions maintain R below 1 or the susceptible part of the population has been depleted sufficiently to maintain R below 1.

The basic reproduction number may vary across locations because contact rates among people may differ due to differences in population density and cultural differences. The effective reproduction number may vary, as well, because the communities in different locations may differ in their level of immunity.

What *basic* reproduction number should we use in our assessment of proposed interventions against pandemic influenza? It may be that recent exposures to currently circulating strains of influenza, or vaccinations to protect against them, provide some immunity against a newly emerged strain; see Jordan *et al*. (1958), Spicer and Lawrence (1984), Mills *et al*. (2004). Then the appropriate reproduction number, with reference to which we should judge any proposed intervention in our community, is the effective reproduction number corresponding to the population as it is initially, complete with its initial level of immunity arising from exposure to influenza strains that have circulated previously but in the absence of any deliberate interventions. For convenience we shall refer to this baseline reproduction number as the basic reproduction number and denote it by R_0 in this document.

There are two aspects of infectious disease transmission that R does not capture well. One is the rate of transmission in calendar time. To illustrate this, consider two SIR infections with the **same** R_0. Suppose that in one of these infections individuals are highly infectious over a short infectious period. For the other infection individuals are less infectious, but over a longer infectious period. Both will result in the same eventual attack rate, but the former epidemic will take off more quickly, will have a higher incidence at the peak of the epidemic and will be much shorter; see Section 2.4.

The other aspect that R does not capture well in general is q, the probability that an imported outbreak gathers momentum and becomes large, as distinct from fading out after relatively few people are infected. This probability is fundamental to the issues of containment and delaying a local epidemic, so we need to be mindful of this fact when assessing interventions on the basis of R.

2.3. How infectious is an emerged pandemic influenza virus likely to be?

We begin with a discussion of plausible transmissibility of a newly emerged influenza strain, in terms of the basic reproduction number.

Estimates of the basic reproduction number for common SEIR infectious diseases range from 4-7 for diphtheria and poliomyelitis to 14-18 for measles and pertussis; see Anderson and May (1991). In contrast, guided by data on attack rates and excess mortality reported for past pandemics of influenza, recent work on modeling the possible control of a newly emerged strain of influenza in South East Asian [Longini *et al.* (2005), Ferguson *et al.* (2005)] has focused a great deal on values of R_0 in the range of 1.5 to 2.5. Is this a plausible range for R_0?

It is of course possible that the next pandemic strain of influenza will be completely different and will have a very large value of R_0, and we must not ignore such a possible scenario. However, it seems appropriate to focus planning mainly on a range of values judged to be plausible on the basis of past experience. We have focused mainly on the range of values from 1.5 to 3.5, and support this choice with the following observations:

i. The first question we might ask is: Given that most circulating infectious diseases are estimated to have a larger R_0, how can a currently circulating influenza virus with R_0 in the range 1.5-3.5 possibly avoid eradication?

   Three characteristics of influenza help to make this possible. Firstly, it is evident that individuals infected with influenza are infectious before they show symptoms [Fraser *et al.* (2004), Day *et al.* (2006), WHO Writing Group (2006)]. As a result, some infection occurs before the source case is symptomatic. Secondly, the virus (especially the influenza A virus) has the ability to change with the result that immunity wanes [Fox *et al.* (1982)], leaving individuals susceptible to re-infection (in contrast to infections such as measles and chickenpox that confer lasting immunity). Thirdly, the same drift in the virus means that influenza vaccines tend to have an efficacy that is low relative to that of the measles vaccine, for example King *et al.* (1991) and Turner *et al.* (2003).

ii. Data on infections within households, where contacts are considered to be more frequent and 'closer', are not consistent with a large value of R_0. For example, in a study of households from Tecumseh, Michigan [Monto *et al.* (1985)] sera from all members in a large number of

households were tested before and after the influenza epidemic season to see who was susceptible at the beginning and who was infected by the end of the study period. An attractive feature of this study is that asymptomatic infection should be detected by this approach. The observation that among households with at least one primary case the influenza attack rate among the remaining household members was only 24% is not consistent with a large value of R_0.

iii. The reported clinical influenza attack rates in pandemics of the last century are mainly between 25% and 35% [Nguyen-Van-Tam and Hampson (2003)]. There may have been a substantial number of influenza infections that did not meet the case definition used, though a value of R_0 greater than 3.5 is not suggested even if we double the reported clinical attack rates. Admittedly, the 1918 pandemic achieved its moderate attack rate only with substantial efforts aimed at social distancing and without this the attack rate would undoubtedly have been higher.

iv. There are settings in which a much higher influenza attack rate has been observed, specifically in influenza-naïve populations in Alaska [Crosby (1976)] and Tristan da Cunha [Mantle and Tyrrell (1973)]. This suggests that the *basic* reproduction number, corresponding to a completely naïve population, can be much larger and that most populations exposed to pandemic influenza had the good fortune of partial immunity to the newly emerged strain of the virus, presumably as a result of past exposure to circulating influenza viruses. It is, however, the basic reproduction number for a typical community, with some history of exposure to circulating strains of influenza, that is most relevant to planning for the control of pandemic influenza and it is this 'basic' reproduction number that we use here.

v. The current fear of an influenza pandemic stems from avian influenza, specifically that re-assortment might occur if an individual is infected with both the avian influenza virus and a human influenza virus. The possibility that this would lead to a virus that is much more transmissible than a currently circulating human influenza virus seems a less likely scenario.

Individually, each of these observations can be explained in a way that is consistent with a larger value of R_0, but collectively they suggest that the range 1.5-3.5 seems to cover the most plausible range for the basic reproduction number against which interventions ought to be evaluated.

The range of values 1.5-3.5 also covers the range of attack rates that are of greatest concern. In most of our illustrative calculations we used the three values 1.5, 2.5 and 3.5 for R_0. We may view these as the low, medium and high values of R_0 because, for a community consisting of homogeneous individuals who mix uniformly, the SEIR model gives attack rates of influenza infection of 58%, 89% and 97%, respectively, for these values of R_0.

2.4. **The infectiousness function**

The infectiousness function quantifies how infectious an individual is in terms of the time since infection. We focus mainly on two forms of this function. In the first the individual is latent for the first day and has an infectious period of five days. The infectiousness during the infectious period is constant, as in Elveback *et al.* (1976). This *flat* infectiousness function is shown in Figure 2.1(a). The second infectiousness function is depicted in Figure 2.1(b). It is motivated by viral shedding data and the estimate given in Ferguson *et al.* (2005). We refer to this as the *peaked* infectiousness function. For both scenarios we assume that the incubation period is two days [Hayden *et al.* (1998)].

Both R and the shape of the infectiousness function influence the dynamics of the epidemic. To illustrate their effects we show in Table 2.1 the typical progress of an epidemic during the exponential growth phase in terms of R and the two forms of infectiousness functions displayed in Figure 2.1. Note that both infectiousness functions result in the same eventual attack rate for a given R_0, but the epidemic curve is steeper for the peaked infectiousness function.

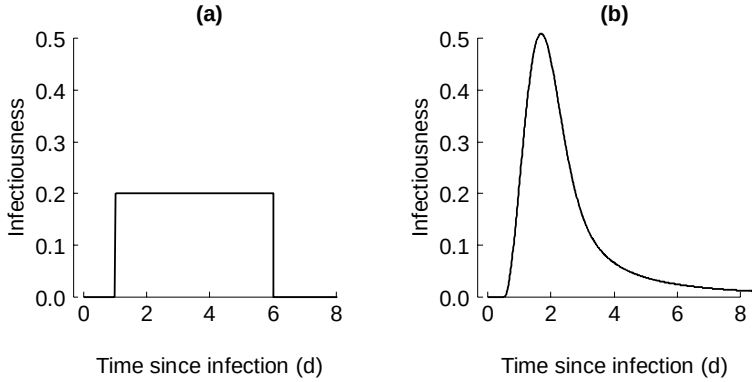


Figure 2.1 The flat and peaked infectiousness functions. The corresponding R for these infectiousness functions is the same when they have the same area under the curve. The two curves depicted above correspond to $R = 1$ in an SEIR model.

	$R_0 = 1.5$		$R_0 = 2.5$		$R_0 = 3.5$	
Infectiousness function	**Flat**	**Peaked**	**Flat**	**Peaked**	**Flat**	**Peaked**
Cases on day 0	20	20	20	20	20	20
Cases on day 10	50	82	179	573	437	2300
Cases on day 20	128	335	1600	16,000	9500	260,000
Cases on day 30	324	1400	14,000	460,000	200,000	1.3 mil*
Doubling time (days)	7.5	4.9	3.2	2.1	2.2	1.46
Eventual attack rate (%)	58	58	89	89	97	97

Table 2.1 Number of infectious cases on days 10, 20 and 30 for the deterministic SEIR model starting with 20 initial infectious cases. The doubling times during this exponential growth phase and the percentage of the population eventually infected (the *attack rate*) are also given.

2.5. Transmission within households

The $SEIR_H$ model requires a specification of how infection is transmitted within households, as well as data on household size and the number of school children in households. Within-household transmission is assumed to proceed according to a Reed-Frost model; see Bailey (1975). When necessary a force of infection from outside the household is added; see Longini and Koopman (1982), Addy *et al.* (1991).

Household data from the Australian 2001 census are used. These are shown in Table 2.2. Note that about 27% of households contain at least one school-age child.

	Number of school children (n_C)						
Household size (n)	**0**	**1**	**2**	**3**	**4**	**5**	**6**
1	236	-	-	-	-	-	-
2	317	18	-	-	-	-	-
3	110	42	14	-	-	-	-
4	51	43	61	5	-	-	-
5	13	15	22	24	1	-	-
6	4	4	7	7	6	0	-

Table 2.2 Number (per 1000) of households that are of size n and include n_C school children.

2.6. Parameters of transmission and progression of disease

By a parameter we mean any constant contained in the model to which a value needs to be assigned to complete the specification of the model. Examples of parameters include

R_0, the basic reproduction number,

θ, the probability that an individual avoids being infected by a specific infected household member during the course of the latter's infectious period, and

f_s, the proportion of between household mixing that occurs during school hours.

The models contain a large number of parameters. A full list of these parameters is given in Appendix B, along with their default values and justifying arguments. We use these default values unless indicated otherwise.

2.7. Three ways of judging the effectiveness of interventions

We compared the effect of interventions on the basis of three different criteria. An intervention was assessed by its effect on the reproduction number (R), its effect on the probability (q) that an outbreak initiated by a single case fades out before becoming an epidemic and its effect on the dynamics of transmission in either calendar-time or in terms of generations. Assessments based on R and q have the advantage that only the mean number infected needs to be modeled, which means that the modeling can incorporate a considerable amount of community structure and a combination of interventions is more easily accommodated for these outcome measures. The information about q contained in the measure R is limited to the fact that $q = 1$ when $R < 1$, so q provides a useful alternative means of comparison when $R > 1$. Describing the complete dynamics of the spread of disease is very much more labour and computer intensive, particularly when community structure and a combination of interventions are accommodated. Time constraints for this work have therefore meant that models to describe the dynamics of transmission are generally based on models with more simplifying assumptions.

To assist with interpreting results on the effect of interventions on R we now point out how R typically relates to the dynamics of an epidemic. Consider four simple SIR models, with R= 10, 5, 2.5 and 1.25. That is, we start with R =10 and successively halve its value. Graphs of the number of infectives and removals over time are shown in Figure 2.2.

Note that halving the reproduction number diminishes and delays the peak of the epidemic, with the greatest gain occurring when R is reduced from a low value (2.5) to an even lower value (1.25). Note also that halving the reproduction numbers has very little effect on the eventual number of people infected when R is large (almost everyone is infected when R = 10, 5, and 2.5). However, reducing a value of R that is already small (<2.5) reduces the eventual number of cases substantially.

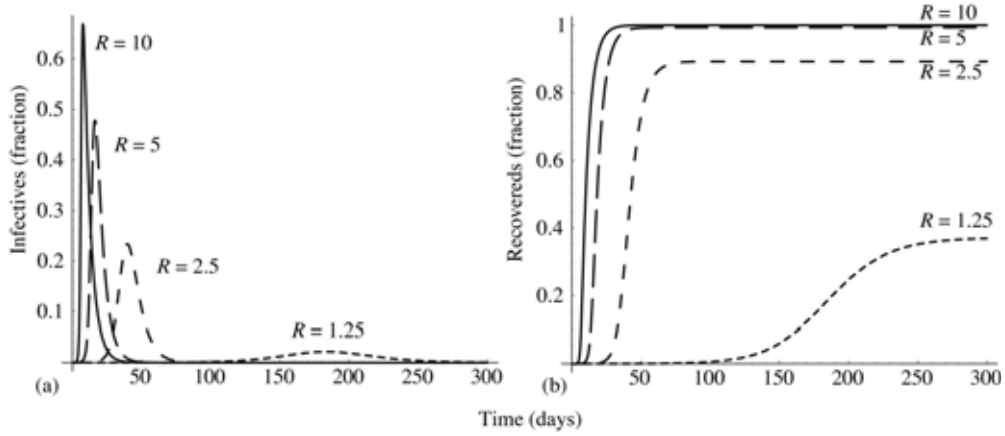


Figure 2.2 The impact of halving the reproduction number in an SIR model
(a) The number of infectives over time. **(b)** The number of removals over time.

3 EFFECTIVENESS OF BORDER CONTROL MEASURES

3.1. Our aims in this section

To perform calculations, and present illustrations of these, to inform us about the questions

a. What is the delay until transmission of the infection gathers momentum in Australia in the absence of border control measures?
b. What is a suitable trigger for the introduction of border control measures?
c. What is the effect of border control measures on the delay until the transmission of the infection gathers momentum in Australia?

There are several reasons for an interest in delay until there is a local epidemic of pandemic influenza.

First, preventing pandemic influenza from entering Australia is included in our concept of delay, although this is thought to be an unlikely event.

Second, the delay may provide time to establish the precise nature of the threat and prepare specific responses. It may give time to estimate (from data in the source region) biological parameters such as R_0 and the effectiveness of various interventions.

Third, it may enable the deployment of a vaccine. This is only a substantial benefit to regions which can hold the epidemic peak off until the vaccine is developed and distributed, and immunity has been able to build up in the vaccinated population.

Fourth, the virulence of a new pandemic virus may decline over time due to adaptation to a new host species, and possibly natural selection. For example, strictly isolating the more severe cases will select for viral variants with milder symptoms. It is believed that this phenomenon occurred in the 1918 influenza pandemic, and can explain the low case-fatality rate in Australia and US Samoa.

3.2. The delay until transmission gathers momentum in Australia, without border control

The delay from the time when WHO declares that a new influenza strain capable of human-to-human transmission has emerged, until an epidemic is established in Australia depends on three components. They are:

i. the delay until a recently-infected person travels to Australia;
ii. the potential delay arising from the fact that not every infected traveler initiates a transmission chain that takes off;
iii. the time it takes for an Australian transmission chain to gather momentum.

We now illustrate the sort of delay one expects when there are no interventions in place, taking each of the above factors into account. For these calculations we used “20 infectious cases on a single day” to indicate that transmission has gathered momentum in Australia. The choice of “20 cases” is made because both the theory of branching processes (Athreya and Ney, 1972) and our simulations indicate that when an outbreak reaches that number of infections on a single day then the growth of the epidemic has almost certainly has reached its exponential growth phase and proceeds deterministically, i.e. without a substantial chance component.

We assume that there are 10 concurrent infected cases in the source region when WHO declares that a new pandemic strain has emerged, and that the epidemic subsequently grows exponentially in the source region. The number of people within the infected source region is assumed reasonably small (5 million) and the number of travelers per day attempting to travel to Australia from the source region is set to 10, 100 and 400 per day unless stated otherwise. It will be seen that the inter-country transmission of infection occurs during the early exponential phase of the epidemic in the source

country, hence the results are reasonably insensitive to the number of people in the source region. We assume a duration of travel between attempted departure and possible arrival of 12 hours, which approximates the travel time from south-east Asia where the next pandemic is considered most likely to be initiated. It is assumed that the aircrafts ventilation and filtration systems are functioning correctly, so although we allow infected travelers to transmit infection during the flight, it is assumed to occur at the same rate as at other times.

Effects of R_0 and traveler numbers

In Figure 3.1 we show the probability distribution for the delay assuming an SEIR epidemic with R_0 =1.5 and 3.5 in both the source region and Australia. The graphs are shown for three volumes of travel, namely 400, 100 and 10 travelers from the source region into Australia per day. A comparison of the graphs for R_0 =1.5 and 3.5 illustrates that the delay decreases as R_0 increases, and that the magnitude of this change is noteworthy.

Comparing the distributions for the three travel volumes indicates how the delay depends on the amount of travel between the source region and Australia and, in particular, indicates the effect that limiting travel has on this delay.

A moderate reduction in the daily number of intending travelers departing the source country has a small though noticeable effect on the delay distribution. For example if we assume that R_0=1.5, then decreasing the numbers of intending travelers originating from the source country from 400 to 100 per day increases the median delay until 20 concurrent cases in Australia from 56 to 65 days. Reducing the number of intending travelers further to 10 per day extends this delay to 81 days (Figure 3.1). For R_0=3.5 the median delay is 17, 19 and 23 days for 400, 100 and 10 travelers per day originating from infected areas, respectively (Figure 3.1).

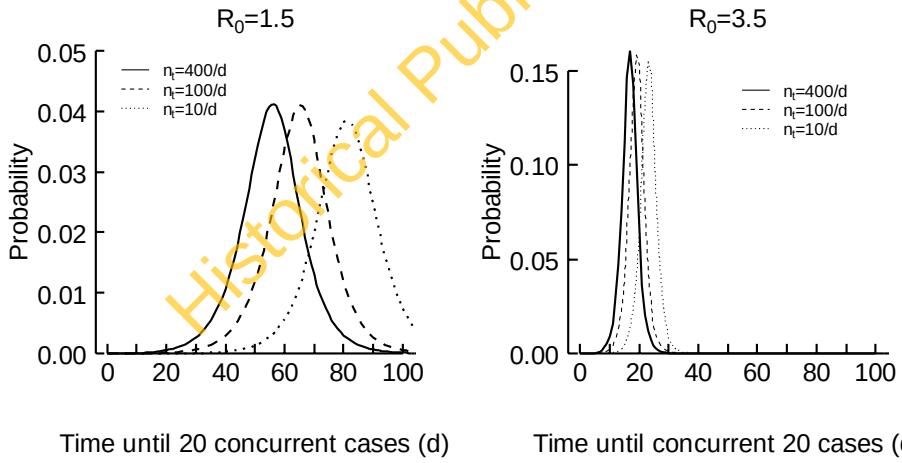


Figure 3.1 The effect of R_0 (1.5, 3.5) and daily traveler numbers (10, 100, 400 per day) on the distribution of the time delay until an epidemic reaches 20 concurrent cases in Australia following identification in the source country (assumed to occur when there are 10 concurrent cases in infected areas). Calculations assume the peaked infectiousness function and no border screening or early presentation.

3.3. When should Australia respond?

It is important to anticipate the importation of the infection into Australia. Suppose Australia has no border control in place when WHO declares that a new influenza strain capable of human-to-human transmission has emerged. A decision on when Australia should respond has a large political component, but it is useful to have a way of assessing the risk of importation objectively. Here is one suggestion of how one might be guided in practice.

Consider a response as soon as overseas disease incidence and travel to Australia are such that

Inequality 1:
Prob(a recently-infected traveler arrives from the source region within the next 14 days) > 0.05.

(The duration **14 days** and probability **0.05** are chosen here for illustration. Alternative values may be preferred, after careful consideration.)

A way to proceed from the daily disease incidence data in the source region to Inequality 1 is as follows: Observe that the number of recently-infected travelers into Australia on day t is random. Its probability distribution may be taken as Poisson with mean $k_t\pi_t$,, where π_t is the prevalence of recently-infected individuals in the source region and k_t is the number of travelers from that region into Australia on day t.

Data on the travel volumes k_t are available for the immediate future. The prevalence π_t can be projected into the immediate future by fitting a model that specifies $\sigma \exp(\rho t)$ for the disease prevalence in the source region on day t. Estimates of σ and ρ can be updated daily, as new data become available, and Australia would initiate response on the first day when σ and ρ are such that Inequality (1) is satisfied.

The set of σ and ρ values that trigger this response are shown in Figure 3.2, on the assumption that 1 per 12,500 of the individuals from the source region travels to Australia per day (e.g. the source region has 5 mil. inhabitants and 400 travel to Australia every day). In other words, Australia's response is triggered on the first day that the point defined by the estimated σ and ρ values falls above the solid curve of Figure 3.2, if a critical probability value of 0.05 is used in Inequality (1). The contour corresponding to a critical probability value of 0.01 is also shown in Figure 3.2 (dashed line).

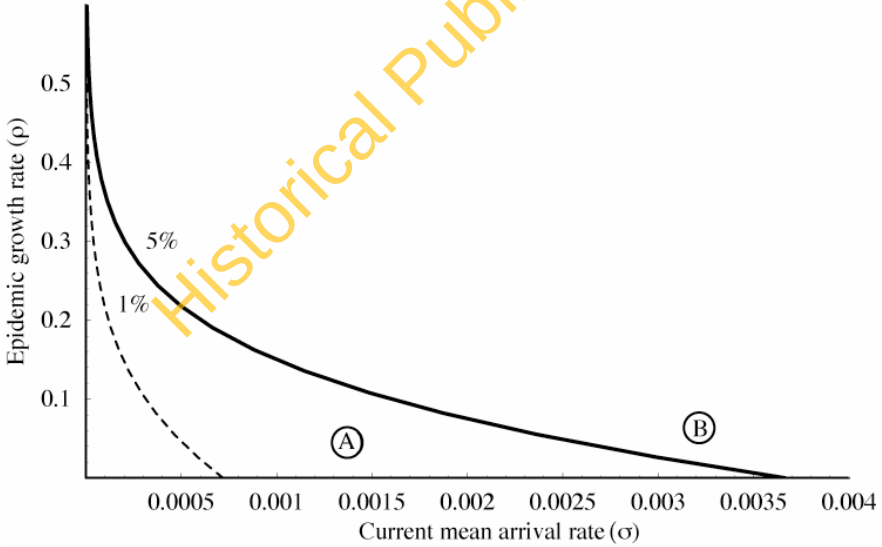


Figure 3.2 The probability that a recently-infected traveler arrives from the source region within the next 14 days exceeds 0.05 if the point (σ,ρ) lies above the solid curve [e.g. the point marked (B) triggers a response], where $\sigma \exp(\rho t)$ describes the growth of the epidemic in the source region. The points (A) and (B) correspond to data in Figure 3.3(a) and Figure 3.3(b), respectively.

Figure 3.3 illustrates how σ and ρ could be estimated in the event of an outbreak. The parameter ρ is obtained by fitting an exponential curve to the incidence data in the source country. From this incidence data, the prevalence is estimated by adding the incidences over the most recent five days, and dividing by the population size. The parameter σ is the mean number of infected people traveling, so σ = prevalence × number of travelers. For the purpose of converting the incidence data in Figure 3.3 into values of σ and ρ that can be used in Figure 3.2, the number of travelers was assumed to be 400/day, and the total size of the population was 5 million.

The number of cases that have occurred overseas at the time when Australia responds is of interest because it indicates how much is known about the pathogen and its disease characteristics at that time. This number depends on the strategy used to trigger response and the number of travelers from the source region to Australia per day. In the above illustration, assuming that day 40 is the day on which response is triggered, there were 110 cases in the source region by the time response is triggered in Australia. A comprehensive study to determine the likely number infected by the time Australia responds would be useful once a criterion for responding, such as Inequality (1), has been chosen.

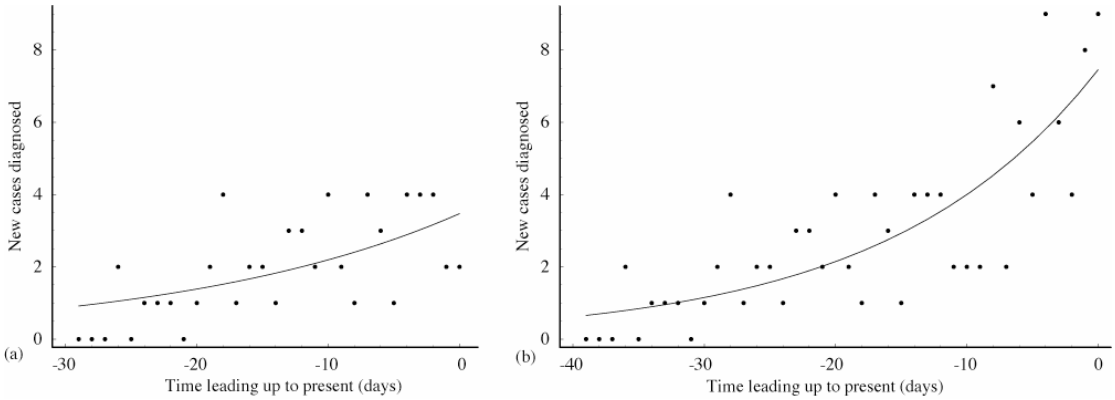


Figure 3.3 Assuming data on incidence is available from the source region for (a) the 30 days preceding the decision point, and (b) the preceding 40 days. Also shown is a curve of the form $\sigma \exp(\rho t)$ fitted to each data set. Prevalence at any time is based on the incidences of new cases over the preceding five days. The estimated parameters for the above two illustrative data sets are

(a) σ=0.00136, ρ=0.0459, and **(b)** σ=0.0032, ρ=0.0623.

The corresponding two points (σ,ρ) = (0.00136, 0.0459) and (σ,ρ) = (0.0032, 0.0623) are marked (A) and (B), respectively, in Figure 3.2.

We now consider the effect of various border control measures on the delay until a local outbreak gathers momentum in Australia.

3.4. What border control strategies are considered?

The probability (p_t) that a recently-infected traveler arrives on day t can be changed by reducing π_t, the prevalence of recently-infected individuals in the source region, and it is in every nation's interest to support this effort. The probability can be further reduced by screening passengers departing from the source region, which includes isolating cases upon diagnosis in the source region. Border interventions under Australian control include

i. Reducing k_t, the number of travelers from the source region to Australia.
ii. Providing all arriving international travelers with information on the disease and common signs of infection and actions to take if symptoms develop after their arrival in Australia.
iii. Requiring all international air travelers to complete a health declaration card on entry into Australia which will include a statement that they have, or do not have, any of the symptoms of the disease.
iv. Requiring crews of all international aircrafts to report any symptoms of illness that they observe among passengers on their aircraft.
v. Applying passive surveillance technology to arriving travelers (e.g. thermal imaging, or direct or indirect body temperature measurement).
vi. Requiring high risk passengers (e.g. those arriving directly from a country affected by the disease) to submit to medical assessment or examination.

vii. Placing all high risk international travelers under surveillance (e.g. reporting for a daily medical examination).

viii. Placing all high risk international travelers into quarantine or partial home quarantine whereby travelers are required to stay at home, though other household members continue to mix in the community.

These measures will reduce Australia's risk of an early local epidemic by reducing incoming travel from at-risk regions (measure i.), identifying some infected travelers at the borders (measures ii.-vi.), leading to early presentation of infected arrivals who are not identified at the borders (particularly measures ii., vi. and vii.) and reducing the mixing of high risk international travelers with community members immediately after arrival (viii.). We incorporated these effects by permitting restrictions on travel into Australia, by including a chance of being identified as a case at the borders (depending on the time since being infected), by including very timely presentation (and subsequent isolation) of infected arrivals and by including partial home quarantine of infected arrivals for measure viii. Clearly the full quarantine of all arriving passengers for a sufficient period should prevent the importation of disease [as was observed with the quarantine of ships arriving into Australia in late 1918; see McCracken and Curson (2003)], but whether this is implemented is a question of policy and logistics, which we don't consider here.

3.5. The effect of restricting travel into Australia

As mentioned, a key determinant of the risk of importing the emerged infection is $k_t\pi_t$, the mean number of recently-infected individuals intending to travel into Australia on day t. The source region will, with help from the international community, attempt to keep π_t, the prevalence of recently-infected individuals, low. Australia has some ability to control k_t, the number of travelers from that region into Australia on day t. For such control one can use methods like that described in Section 3.3 to determine the travel volumes that make the risk of importation acceptable. Such travel restrictions clearly carry considerable economic and political costs.

The effect of restricting travel into Australia from the source region is illustrated in Figure 3.1. When R_0 is large (>3), in both Australia and the source region, it is necessary to restrict such travel into Australia to near zero before the delay is increased appreciably. Even for lower values of R_0 a worthwhile increase in the delay requires travel to be limited to very low levels. For example, with R_0 = 1.5 the median delay until an Australian outbreak gathers momentum is 56 days when 400 travelers arrive from the source region per day. The median is increased by only 9 days when the travel volume is reduced to 100 per day, and by another 16 days when the travel volume is reduced to 10 arrivals per day.

It is important to realise that while stringent travel restrictions into Australia are effective when they are introduced prior to the importation of the infection into Australia, they usually provide very little benefit once the epidemic has gathered momentum in Australia.

3.6. The effect of border screening

Passengers are screened on both departure (exit screening) and entry (arrival screening). We assume that screening is unable to detect infected individuals while they are asymptomatic. That is, during the first two days after being infected. By screening sensitivity we mean the probability that border screening will identify an arriving traveler who is symptomatic. In our calculations we varied the sensitivity of screening from 0 to 1 (perfect symptomatic screening). At the departure border, the probability that a symptomatic individual is detected is s_D, which is zero when there is no border control or isolation of cases in place in the source region. Upon arrival, the probability that a symptomatic individual is detected is s_A.

The results are such that it suffices to illustrate them for the two scenarios $s_D=s_A=0$ (zero, or completely ineffective, screening) and $s_D=s_A=1$ (100% sensitive screening for symptomatic travelers). Symptomatic border screening, even of a very high sensitivity on departure and arrival, has a negligible effect upon the delay until a local epidemic gathers momentum. For example, for a scenario of $R_0=2.5$ and 100 travelers per day attempting to depart the source region, the effect of implementing 100% sensitive screening on both departure and arrival only increases the median delay from 27 to 28 days (Figure 3.4).

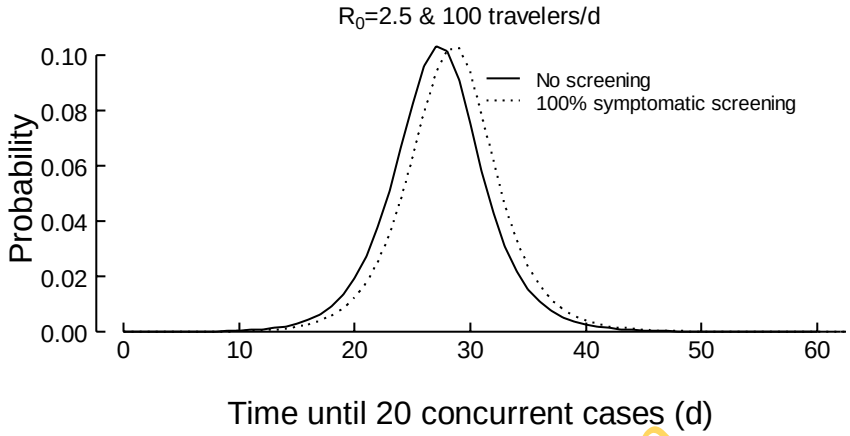


Figure 3.4 The effect of perfect symptomatic border screening (100% sensitivity) on the distribution of the time delay until an epidemic reaches 20 concurrent cases in Australia following identification in the source country (assumed to occur when there are 10 concurrent cases in infected areas).

In order to find a setting where screening does appreciably increase the delay we have looked at very low values of R_0. However, even under the rather benign scenario of $R_0=1.2$ and 100 travelers/day attempting to depart the infected source country, symptomatic screening only increases the delay to an epidemic gathering momentum from 140 to 148 days (Figure 3.5).

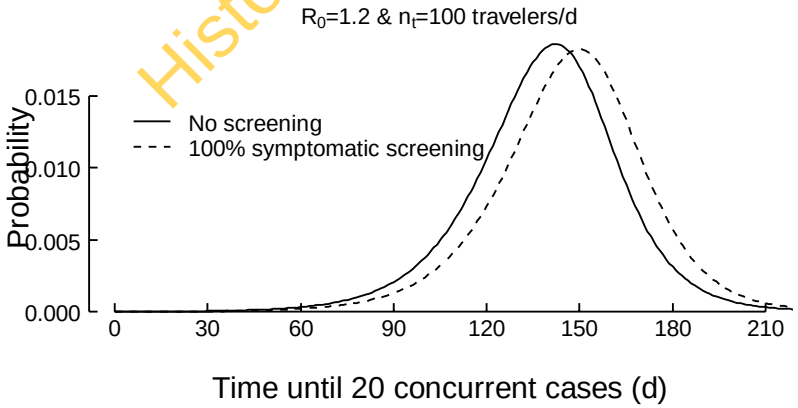


Figure 3.5 The effect of perfect symptomatic border screening (100% sensitivity) on the distribution of the time delay until an epidemic reaches 20 concurrent cases in Australia following identification in the source country. Calculations assume a peaked infectiousness function and no other interventions

The failure of symptomatic border screening, even of perfect sensitivity, to reliably prevent epidemic initiation arises from the two day incubation period acting in concert with short travel times. For example, assuming $R_0=1.5$, the probability of a randomly selected infected traveler disembarking in Australia undetected after a 12 hour journey is 0.29 if screening is 100% sensitive. Increasing R in the source country increases the probability of escaping detection, as it is more likely that an infected

traveler will have been recently infected and be asymptomatic. For example, with R_0 = 3.5 (and other conditions as above) the probability of an infected traveler evading screening increases to 0.48.

The curves in Figures 3.1, 3.4 and 3.5 illustrate that the delay decreases substantially as R increases, particularly in the range $1 < R < 2$. Specifically, the median delays in the absence of screening, assuming 100 travelers per day from the infected source region, are given by

R	1.2	1.5	2.5	3.5
Median delay (days)	140	65	27	19

This highlights again the benefit of seeking to make R as low as possible in the source region, and to quantify the transmission parameters of the newly emerged viral strain as early as possible.

3.7. The effect of early presentation of arriving travelers

Early presentation of an infected traveler increases the probability that this traveler's chain of transmission becomes extinct, although even immediate presentation at onset of symptoms fails to ensure that an epidemic is not initiated, as is shown in Figure 3.6.

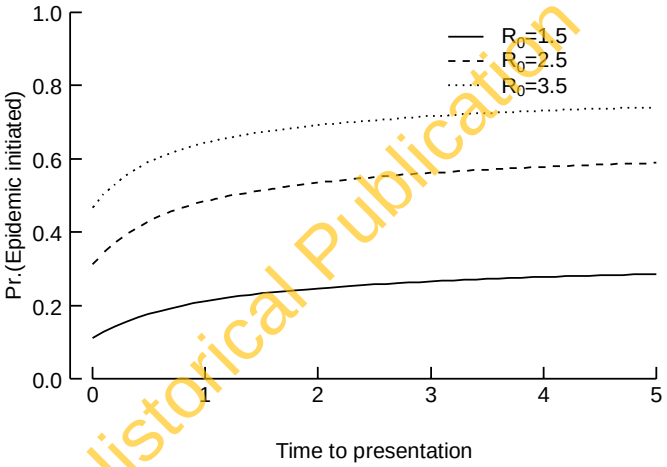


Figure 3.6 The effects of R_0 and the time (days) from the onset of symptoms to presentation at a medical centre on the probability that an undetected infected arrival initiates an epidemic.

Nevertheless, decreasing the time from the appearance of symptoms to seeking medical help, with subsequent isolation, has a relatively small effect on the delay distribution. For example, compared with typical presentation and subsequent isolation, having infected travelers present 6 hours following the onset of symptoms increases the median delay from 56 to 60 days, when 400 travelers arrive from the source region per day. Reducing the delay to presentation to 0 (clearly for illustrative purposes only) only increases the delay a further 2 days (Figure 3.7).

Combining perfect symptomatic border screening, presentation at 6 hours following symptom onset with a drastic reduction in traveler numbers (10 per day) produces no substantial synergies. Assuming R_0=1.5, the median delay increases from 56 to 85 days, with most of this delay attributable to the reduction in traveler numbers alone, as shown in Figure 3.1.

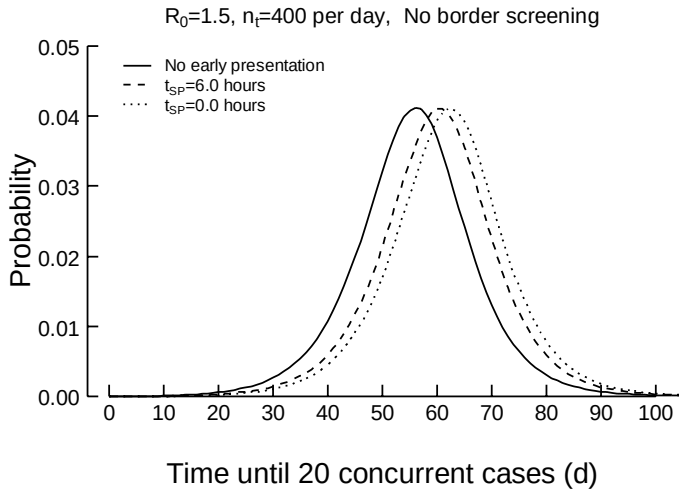


Figure 3.7 The effect of the time from symptoms to presentation (t_{SP}) on the distribution of the time delay until an epidemic reaches 20 concurrent cases in Australia following identification in the source country (assumed to occur when there are 10 concurrent cases in infected areas). Calculations assume R_0=1.5, a peaked infectiousness function, 400 travelers/day attempting to depart the source country, and no other interventions.

3.8. The effect of quarantining arriving travelers

If quarantining means complete isolation of arriving travelers from at-risk regions with full compliance, there is no chance of the infection getting into the community. However, this option is very costly and only likely to be acceptable when the infection is known to have a very high case-fatality rate.

For our calculations we looked at home-quarantining arrival passengers for two days, i.e. long enough for all infected travelers to become symptomatic. We assumed 100% compliance and that infected arrival passengers are able to infect only their household members. Household members of incoming travelers mix, as usual, in the community until the incoming household member shows symptoms (if ever). Figure 3.8 shows the effect of these interventions on the probability that an infected traveler initiates an epidemic upon arrival.

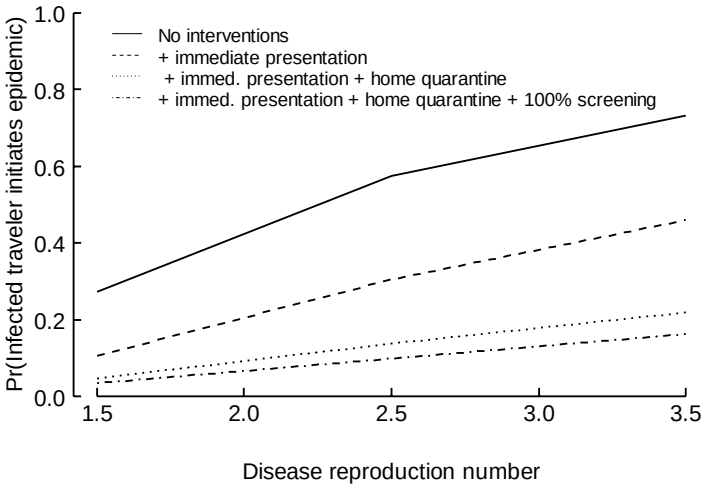


Figure 3.8 The cumulative effects of immediate presentation, partial home quarantine and border screening for different basic reproduction numbers on the probability that an infected traveler is not detected by screening and initiates an epidemic upon arrival. Calculations assume a flight

duration of 12 hours, a peaked infectiousness function, that household members are infected immediately upon the traveler returning home, that household members mix normally in the community up until the infected traveler develops symptoms, and that the proportion of within household transmission is approximately 0.35, 0.25 and 0.22 for R_0 equal to 1.5, 2.5 and 3.5, respectively.

3.9. **Conclusions**

The following summarise the implications of our modeling of the effectiveness of border control measures.

Delay in the absence of travel interventions

The likely delay from a pandemic strain of influenza being recognised overseas and an epidemic taking hold in Australia in the absence of interventions ranges from a few weeks to several months, depending on the disease reproduction number and the number traveling from the infected region to Australia.

Effects of the disease reproduction number on the delay

A large reproduction number in the source region usually means that the epidemic starts with a period of rapid exponential growth, which shortens the delay until an Australian epidemic in two ways. First, the exponential growth increases the prevalence of infectious individuals, and therefore the expected number of recently-infected travelers rises rapidly. Second, at times during this period of rapid exponential growth, the time since infection among recently-infected individuals is considerably weighted towards short times, with the consequence that an infected traveler is more likely to be asymptomatic during travel and therefore escape border screening.

Effects of border screening on the delay

If $R > 1$ in the source region, then border screening cannot be relied upon to delay introduction of the infection into Australia, even if screening is 100% effective for individuals who are symptomatic at entry. The only conditions under which border screening can appreciably delay the initiation of the epidemic in Australia are so benign (e.g. low R_0) that preventing the entry of such a disease may not be the most cost effective way to manage the threat.

Effects of reducing the number traveling

Severely curtailing the number of travelers (e.g. reducing it to 5% of the typical number) may delay the start of an Australian epidemic by several weeks, although the effectiveness of this intervention dissipates as the number of cases in the source country rises.

Effects of early presentation following symptoms

Like screening, attempts to achieve the earliest possible presentation of infected arriving passengers do not delay a local epidemic appreciably. In the absence of a complete halt to international travel, all forms of preventative interventions are eventually overwhelmed by the exponential rise in the cumulative number of infected arriving passengers.

When to initiate a response

Short of preventing international travel altogether or extremely effective quarantine of arrivals from source regions, eliminating a nascent pandemic in the source country appears to be the only reliable method of preventing the importation of a pandemic strain of influenza into Australia. It is therefore important to monitor the risk of importation into Australia, which can be done on the basis of data on the daily incidence of the cases in the source region and travel volumes from the source region into Australia, using methods outlined above.

3.10. Discussion

The above results take other local interventions into account only in that the reproduction number in Australia is assumed to be the same as in the source region. That is, Australian interventions other than border control measures are assumed to be the same as in the source region.

i. Limitations

The results are strongly influenced by the assumption of a fixed 2 day incubation period. This, in combination with the peaked infectiousness function, results in nearly half an infected person's offspring being generated before the onset of symptoms. This puts upper bounds on the effectiveness of both border screening and early presentation in preventing an epidemic being initiated. In slight contrast, Ferguson *et al.* (2005) assume a variable incubation period, with a mean of 1.5 days, and infectiousness spiking immediately following this, though rapidly declining thereafter. Under their model, very early presentation (i.e. several hours or less) following symptom onset reduces transmission more effectively, although border screening will remain similarly ineffective. If the incubation period is variable, partial home quarantine of arriving travelers may not be as effective because, for some infected individuals, the quarantine period may be over before onset of their symptoms.

ii. Further work needed

One important aspect that has not yet been included in our calculations, is the fact that resources available in States and Territories can target cases very effectively while the number of cases is small, but much less effectively when the number is large. In other words, achievable intervention can reduce R effectively (most likely bringing it below 1) during the very early stages while the number cases is small, but such a level of intervention can not be achieved once transmission gathers momentum. Calculations that incorporate this real-world constraint should be conducted.

iii. Contrasting the results with those for SARS

Border control measures, such as border screening and active surveillance of arrivals from at-risk regions, have greater potential to delay a local epidemic for any respiratory infection with a very short incubation period and for which infectiousness is not appreciable prior to the onset of symptoms. The latter is true for SARS, but border screening is not effective for SARS because its asymptomatic latent period lasted for several days. Empirical evidence that border control measures were not particularly effective for SARS are given by Wilder-Smith *et al* (2004) and Samaan *et al* (2004).

4 LIMITING THE TRANSMISSION OF IMPORTED INFECTION

Once the infection enters Australia interest turns to limiting transmission, with the aim of delaying the time until the epidemic gathers momentum and, failing that, reducing the rate of subsequent spread so as to

i. reduce the overall attack rate prior to a vaccine becoming available, and
ii. flatten the epidemic, whereby the peak burden on the health care service is lowered and disruption to other essential services reduced.

4.1. Our aims in this section

To perform calculations, and present illustrations of these, to inform us about the relative effectiveness of

a. isolating cases as early as possible after diagnosis,
b. personal infection control and distancing measures such as avoiding close contacts with people, wearing a P2 mask and frequently washing hands,
c. closing schools,
d. reducing interstate travel,
e. quarantining affected households, and
f. use of antiviral drugs for treatment and prophylaxis to limit transmission.

We will evaluate the relative effectiveness of the above interventions according to their effect on the reproduction number, their ability to achieve the highest probability of elimination, their ability to delay the peak of the epidemic and lower this peak, and their effect on the number infected over the initial months of the epidemic.

4.2. Isolating cases soon after diagnosis

A major reason for the successful elimination of SARS was the early isolation of diagnosed cases. This intervention is likely to be much less effective for influenza since transmission can occur prior to showing symptoms, and the infectious period is generally much shorter. For the SEIR model, isolation at day four of their infection, two days after the time when symptoms start (as was eventually achieved for SARS in Singapore), leaves the infective with an effective reproduction number of $0.6*R_0$ for the flat infectiousness function, and with $0.86*R_0$ for the peaked infectiousness function. This intervention is sufficient to eliminate infection if R_0 is 1.5 and infectivity is flat, but if infectivity is peaked, a local epidemic can still occur. Figure 4.1 shows the epidemic curves produced using the $SEIR_H$ model with isolation (blue) and without isolation (red) for R_0 values of 2.5 and 3.5, assuming flat or peaked infectivity. The epidemics take off sooner when infectivity is peaked as more infections take place early in the case's infectious period. For the same reason, isolating individuals early has much more effect if infectivity is flat than if it is peaked. Similar results for the relative effect of these measures for flat infectivity are obtained when using the SEIR model.

We also observe that the effectiveness of isolation depends critically on the mean time from infection until isolation. Figure 4.2 shows the probability that a single case will start an outbreak that takes off and the effective reproduction number according to the days from infection until isolation, when each case is isolated in the SEIR model. The left-hand plots show the probability that an outbreak takes off, and the right-hand plots show the reproduction number. As mentioned above, if individuals are isolated after 4 days, this is sufficient to prevent a major outbreak if R_0 = 1.5 and the infectivity is flat. If infectivity is peaked, there is about a 40% chance of a major outbreak. In order to ensure that a major outbreak does not occur for R_0 values of 2.5 and 3.5, individuals would need to be isolated

between 2 and 3 days after infection, and perhaps sooner if isolation is the only intervention used. As individuals will only start to show symptoms at this time, this strategy is unlikely to be practical.

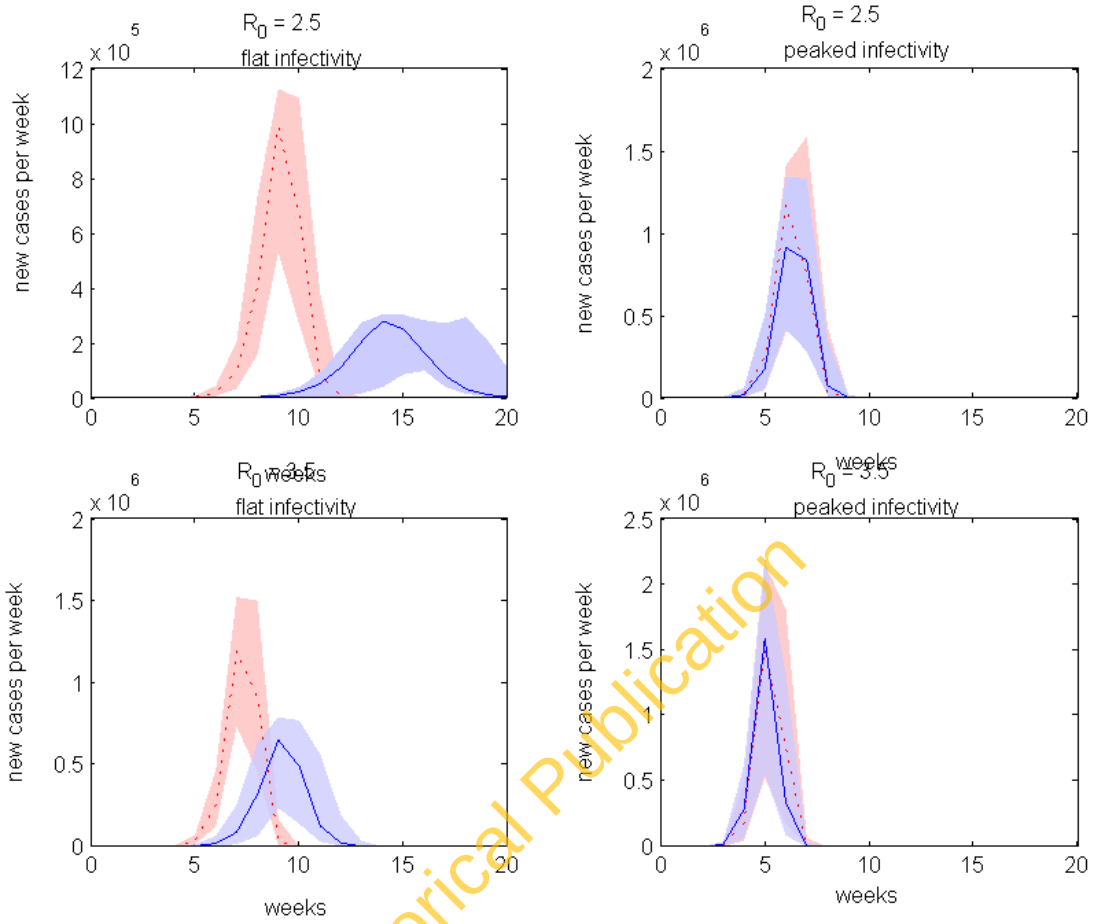


Figure 4.1 The number of new cases per week in the $SEIR_H$ model with a population of 1 million households with R_0 = 2.5 and 3.5 and with flat and peaked infectivity. Each graph shows the median number of cases per day with (blue solid line) and without (red dotted line) isolating cases two days after onset of symptoms. The shaded region represents 90% of the stochastic simulations.

We have indicated that isolation by itself tends to be an effective intervention when R is near 1. While this means that it is not very effective by itself, it can be an effective additional intervention when other interventions have succeeded in bringing R close to 1.

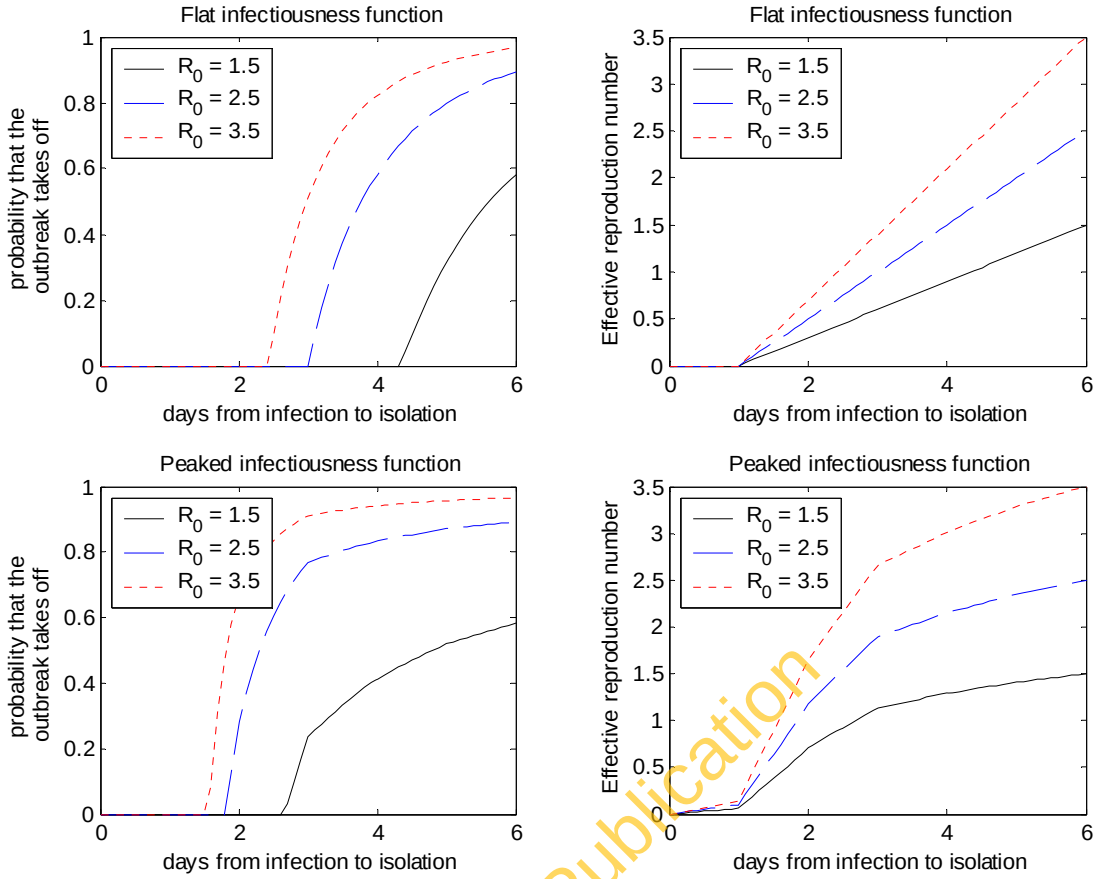


Figure 4.2 The probability that a single infected individual starts an outbreak that takes off and the effective reproduction number of the SEIR model depending on the time from infection until isolation of cases. The top plots assume that the infectivity function is flat, and the lower plots assume that the infectivity function is peaked.

4.3. **Personal Infection Control and Distancing**

In this section, we include all non-pharmacological steps an individual can take to prevent an infectious contact, such as avoiding close contacts with people, wearing a mask and frequent hand washing. The effect of these measures is modeled by decreasing the rate at which an individual makes infectious contacts.

By practicing personal infection control and distancing, a susceptible person reduces their rate of making infectious contacts by a factor denoted λ_S. For example, a susceptible individual may chose to meet fewer people by going shopping less frequently and/or wear a P2 mask when in a public place and/or makes an effort to wash hands more frequently. If the combined effort of this changed personal behaviour by a susceptible reduces the mean number of infectious contacts, i.e. contacts sufficiently close for infection to occur if the contact is with a fully infectious person, by 30% (say) then $\lambda_S = 0.7$.

Similarly, by practicing personal infection control and distancing,, an infectious person reduces their rate of making contacts with susceptible people by a factor denoted λ_I. For example, suppose that when infected an individual continues the practice of meeting fewer people by going shopping less frequently and/or wearing a P2 mask when in a public place and/or making an effort to wash hands frequently. If the combined effort of this changed personal behaviour by an infective reduces the

mean number of infectious contacts, i.e. contacts sufficiently close for infection to occur if the contact is with a fully susceptible person, by 30% (say) then $\lambda_I = 0.7$.

As infections occur essentially as a result of person-to-person contacts between susceptible and infectious individuals we model the combined effect of susceptible and infectious individuals practicing personal infection control and distancing by reducing the rate of infectious contacts occurring by a factor $\lambda_S \times \lambda_I$.

We consider the case where people practice personal infection control and distancing only outside the household and where they practice this within the household as well.

Although the baseline and intervention epidemic curves depend on the form of the infectiousness function, the relative effectiveness of this intervention is similar for flat and peaked infectivity, so we show plots with flat infectivity only. Figure 4.3 shows the epidemic curve with (blue) and without (red) the intervention, assuming that all individuals reduce their rate of making contacts by 30% - that is, $\lambda_S = \lambda_I = 0.7$.

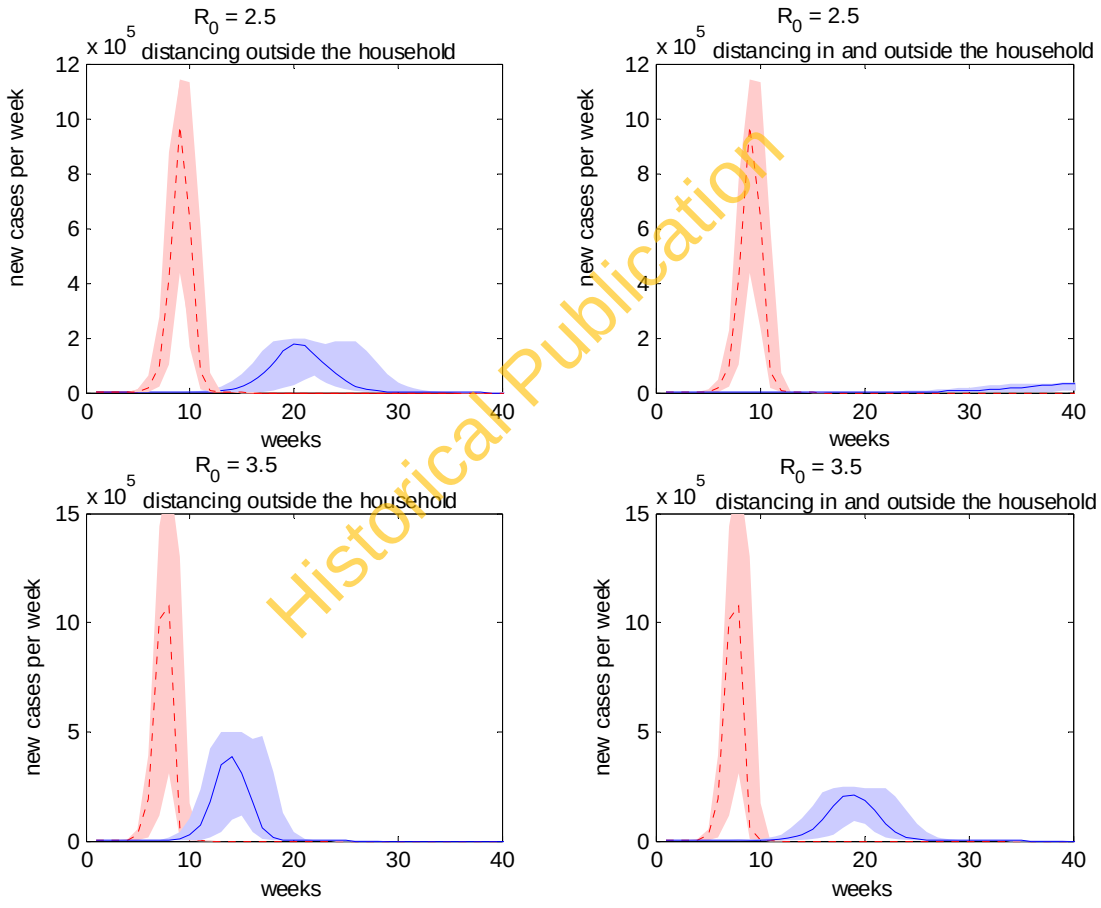


Figure 4.3 The number of new cases per week in a population of 1 million households with R_0 = 2.5 and 3.5 and with personal infection control and distancing (referred to as 'distancing') outside only or both inside and outside the household in the $SEIR_H$ model. Each graph shows the median cases per day with (blue solid line) and without (red dotted line) distancing measures that reduce susceptibility and infectivity by 30%. The shaded region represents 90% of the stochastic simulations.

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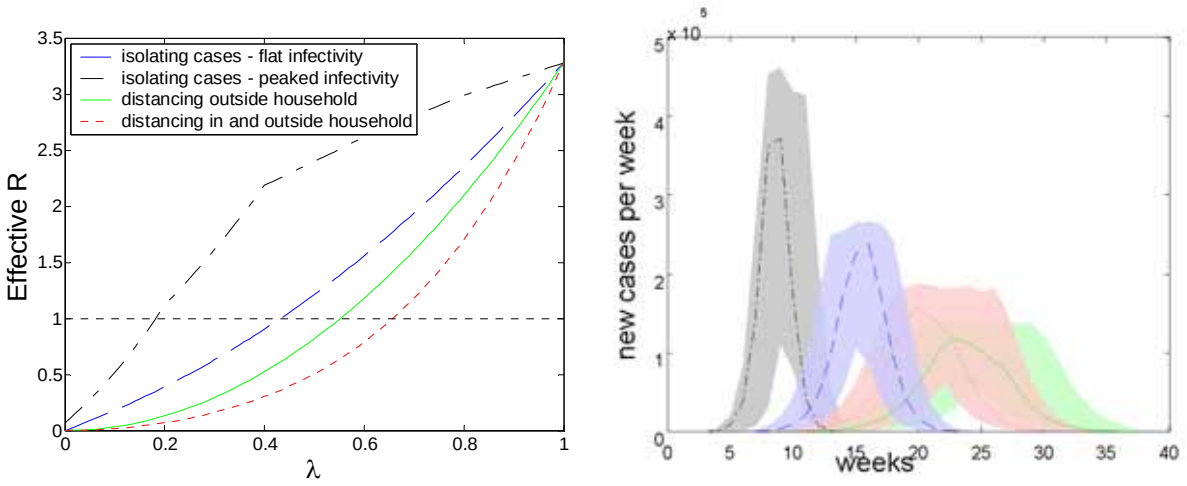

Figure 4.4 A comparison of the effects of personal infection control and distancing and isolation in the $SEIR_H$ model. The left-hand plot compares the effective reproduction number as a function of the level of intervention, λ, for four interventions – isolating cases with flat infectivity (blue dashed line), isolating cases with peaked infectivity (black dot-dashed line), distancing outside the household with flat infectivity (green solid line) and distancing both inside and outside the household with flat infectivity (red dotted line). For personal infection control and distancing measures, $\lambda = \lambda_S = \lambda_I$, while for isolating cases, λ is the fraction of the infectious period before isolation. The right hand plot compares the epidemic curves for each of these interventions with λ chosen for each intervention so that the effective reproduction number is equal to 1.5.

These graphs show the cases where the distancing measures are practiced outside the household only, and where this is practiced both outside and inside the household for R_0 = 2.5 and 3.5. These interventions are sufficient to eliminate the disease if R_0 is 1.5, and reduce the effective reproduction number very close to 1 if R_0 = 2.5 and personal infection control and distancing is practiced within and outside the household.

We can also calculate the impact of these interventions on the effective reproduction number. Figure 4.4 compares the effective reproduction number for isolation and personal infection control and distancing as a function of the degree of intervention (λ). In the case of personal distancing, this λ is λ_S and λ_I. In the case of isolation, λ is the fraction of the infectious period that is spent before isolation. We see that isolation requires a greater reduction in the intervention parameter (λ) to achieve the same decrease in R. The right hand figure shows the resulting epidemic curves if λ is set for each intervention to result in an effective R of 1.5. Although the reproduction numbers (and the total number of cases) are the same for all four curves, the epidemic peak is higher and occurs sooner under isolation than under personal infection control and distancing

It is clear that, for influenza, personal infection control and distancing has much greater potential to reduce transmission than does isolating cases soon after diagnosis. The effectiveness of personal distancing measures are not influenced by the form of the infectiousness function, and is more effective at delaying the peak of the outbreak. In contrast, isolating cases soon after diagnosis has minimal effect when the infectiousness function is peaked, and is much less effective at slowing the spread of disease.

It should be noted, however, that the extent to which personal infection control and distancing is practiced by uninfected and asymptomatic infected individuals may vary considerably between individuals and is likely to change according to the level of community concern.

4.4. **Closing schools**

For some infectious diseases spread by person-to-person, school children are responsible for a disproportionate amount of disease transmission, and opening or closing schools can have a considerable impact on the spread of infection. This is particularly the case for existing highly infectious diseases that confer lasting immunity, where the adult population is almost entirely immune. It is not clear whether school children are responsible for a disproportionate amount of disease transmission of pandemic influenza. A recent review of pandemic influenza interventions [WHO (2006)] noted that 'data on the effectiveness of school closures are limited', and cited examples where it was believed to have been beneficial, in addition to examples where it appears to have been detrimental.

We model the effect of school transmission in the $SEIR_H$ model by assuming that all individuals spend time in three different venues, namely (i) at work or school, (ii) in the community, and (iii) at home. We assume different mixing patterns in each of these venues, and allow for a larger transmission rate between children at school. We also allow for different levels of immunity between adults and school children. To calibrate the model, we use age-specific influenza attack rates measured for south west high-school families in the US during the 1968/69 and 1957 pandemics [Davis (1970)]. In the 1957 pandemic, the influenza attack rate in school children was around 46% compared to 23% in adults. In 1968/69, the influenza attack rate in school children was 42%, while that of adults was 37%. We assume that the mixing patterns in these communities did not vary considerably between the two pandemics, but that there was a higher level of immunity in adults in the 1957 pandemic, and that the reproduction numbers of the two pandemics may have differed.

We assume that the effect of closing schools is that children spend no mixing time within the school, and instead spend all this time within the household. The fraction of time spent mixing in the community is unchanged. This represents the 'best case' scenario for closing schools – in reality, some children may continue to mix with individuals outside the household during school time. Initially, we assume that only school children change their behaviour, and then we consider the effect of some parents staying home to care for their children. As the form of the infectivity function does not change the relative effectiveness of the measures, we assume a flat infectiousness function. Figure 4.5 shows the epidemic curves under these interventions for the model calibrated to 1968/69 age-specific attack rates with R_0 = 1.5, 2.5 and 3.5. In order to reproduce the age-specific attack rates seen in 1957, it is necessary to assume relatively high levels of immunity in adults, which is then not consistent with high estimates of R_0. In Figure 4.6, we show the epidemic curves for the model calibrated to 1957 age-specific attack rates with R_0 = 1.5 only.

The results suggest that school closure could assist in reducing the epidemic size if the reproduction number is relatively low, and if children stay at home when schools are closed. For higher values of the reproduction number, there is much less effect. However, it should be noted that closing schools will assist in reducing the attack rates *in school children* even when it has a limited effect on the overall attack rate. For example, with an R_0 of 3.5 and flat infectivity, closing schools reduces the overall attack rate from 94% to 91%, largely by reducing the attack rate in school children from 97% to 84%. It appears that 'parents staying home to care for their children' does not have a noticeable impact on the outbreak.

The impact of school closure, with a proportion of parents caring for them, on conditions under which the effective R is 1, is illustrated by Strategy D of Figure 4.18 (see below). While not as effective as alternative strategies shown in Figure 4.18, this strategy does have a moderate impact.

Roughly speaking, the effectiveness of closing schools is similar to the effectiveness of isolating cases soon after diagnosis. Closing school has the advantage that its effectiveness is relatively robust against alternative forms of the infectiousness function, in contrast to isolating cases.

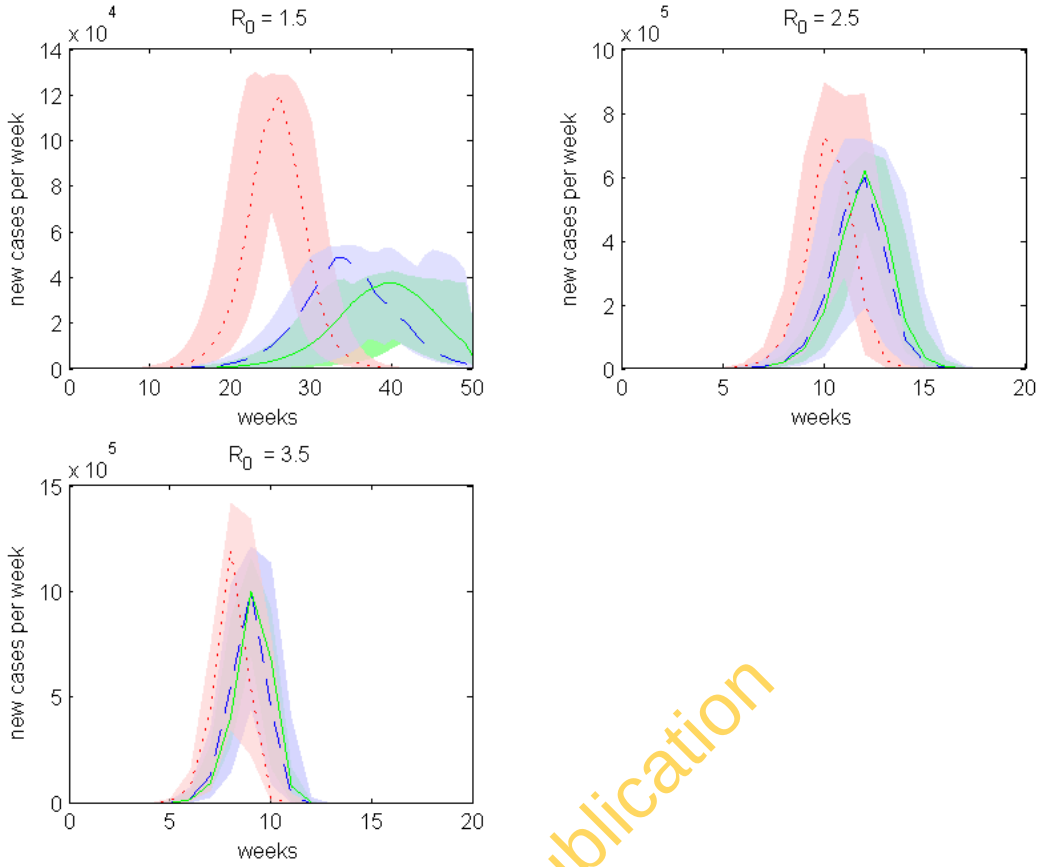

Figure 4.5 Epidemic curves for the $SEIR_H$ model with flat infectivity calibrated to the age-specific influenza attack rates of 1968/69, with R_0 = 1.5, 2.5 and 3.5. Each figure compares: no intervention (red dotted line), schools closed (blue dashed line), and schools closed and some parents staying home from work (green solid line). Solid lines show the median, and shaded regions contain 90% of the simulations.

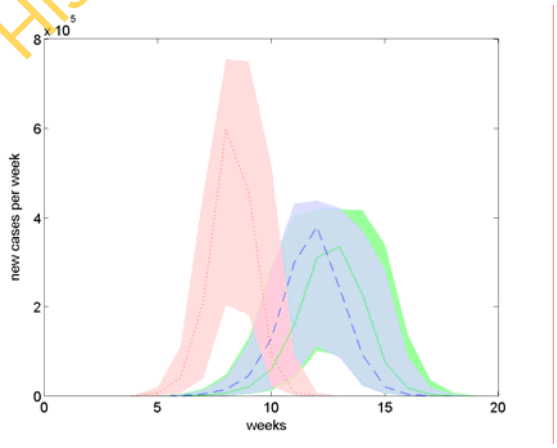

Figure 4.6 Epidemic curves for the $SEIR_H$ model with flat infectivity calibrated to the age-specific influenza attack rates of 1957, with R_0 = 1.5. The figure compares: no intervention (red dotted line), schools closed (blue dashed line), and schools closed and some parents staying home from work (green solid line). Solid lines show the median, and shaded regions contain 90% of the simulations.

4.5. **Closing non-essential workplaces**

We can use the same framework to consider the effect of closing workplaces. As with closing schools, we assume that individuals who are not at work spend their former work-time at home, while time spent circulating in the community is unchanged. Figure 4.7 shows the epidemic curve under no intervention (red), with schools closed (blue), and with 50% of workplaces closed in addition to all schools (green). Closing schools and 50% of workplaces is sufficient to prevent spread of infection for R_0 equal to 1.5.

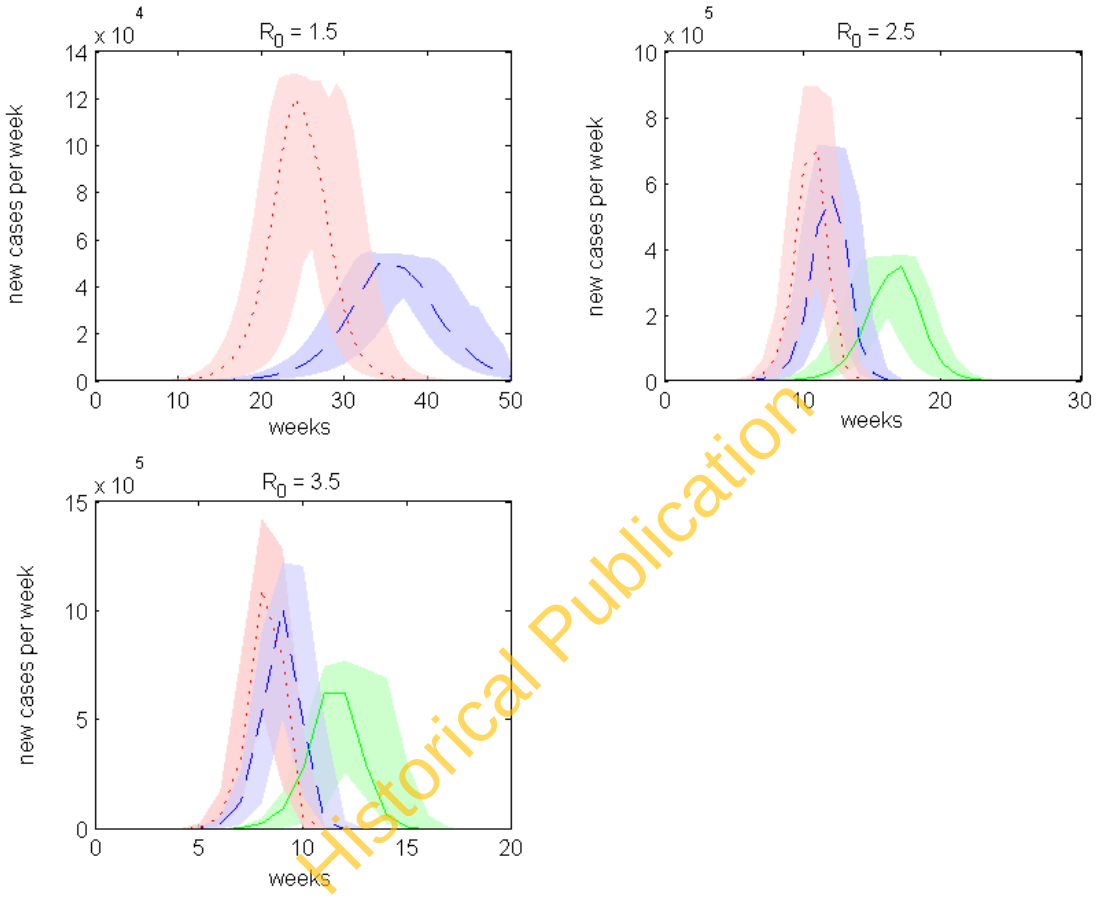

Figure 4.7 The epidemic curves for the $SEIR_H$ with no intervention (red dotted line), closing schools (blue dashed line) and also closing 50% of workplaces (green solid line) for R_0 values of 1.5, 2.5 and 3.5 and assuming influenza attack rates as in 1968-69. The graph corresponding to R_0 = 1.5 and the intervention 'closing schools and 50% of workplaces' is not shown in the top left plot as this intervention is sufficient to eliminate the infection.

The impact that school closure together with the closure of non-essential workplaces has on the *R*, is illustrated in Figure 4.18 (see below). This combination of interventions reduces the effective *R* considerably. Specifically, by adding closure of schools and 50% of workplaces to the default antiviral strategy (whereby diagnosed patients get AVs for treatment, while doctors and flu-dedicated HCWs get AVs for prophylaxis, with the latter using PPE as well), disease elimination is achieved for values of R_0 that are double those that are able to eliminate the infection with the default strategy alone.

The effectiveness of closing schools and workplaces depends on the age-specific attack rates, but shows similar relative effects across reproduction numbers of 1.5 to 3.5. When the attack rates across age classes are relatively flat (as in 1968-69), closing schools reduces the reproduction number to around 85% of its base value. Additionally closing 50% of workplaces reduces the reproduction to

approximately 70% of the base value, and when *all* workplaces are closed, the reproduction number is reduced to around 55% of its base value. In contrast, if the attack rates in school children are particularly high (as in 1957), closing schools reduces the reproduction number to approximately 68% of its base value, while closing workplaces reduces this further to around 58% with half workplaces closed, and 48% with all workplaces closed. The benefit of closing schools is greater when children are particularly at risk of infection, but in this case, closing workplaces provides less additional benefit than when attack rates are similar across age groups.

4.6. **Prohibiting mass public gatherings**

Mass gatherings were prohibited during some stages of previous pandemics in an attempt to reduce disease transmission. To assess how effective this is we can think of the number of 'offspring' an infective produces as consisting of a mixture of regular contacts and close contacts that arise when the individual attends a mass gathering event during the infectious period. Such events include attending a concert, a major sporting event or the cinema.

As an illustration, suppose that R_0=2.5. This means that the mean number infected during the infectious period, including infectious contacts made in the course of everyday life and those made at a mass gathering, is 2.5. We assume that for each infective the probability of attending a mass gathering event during the infectious period is ω, and that if a mass gathering event is attended then the mean number infected at the event is m_G. Figure 4.8(a) illustrates a probability distribution for the number infected by a single infective if R_0=2.5, ω=0.1 and m_G=10. Nearly all of the probability mass near 10 arises from infections at a mass gathering. One way to view this is to say that the mean R_0=2.5 is made up of a mean of ω×m_G=1.0 attributable to mass gathering events and a mean of 1.5 attributable to everyday contacts. When mass gatherings are banned, the part attributable to mass gatherings is removed

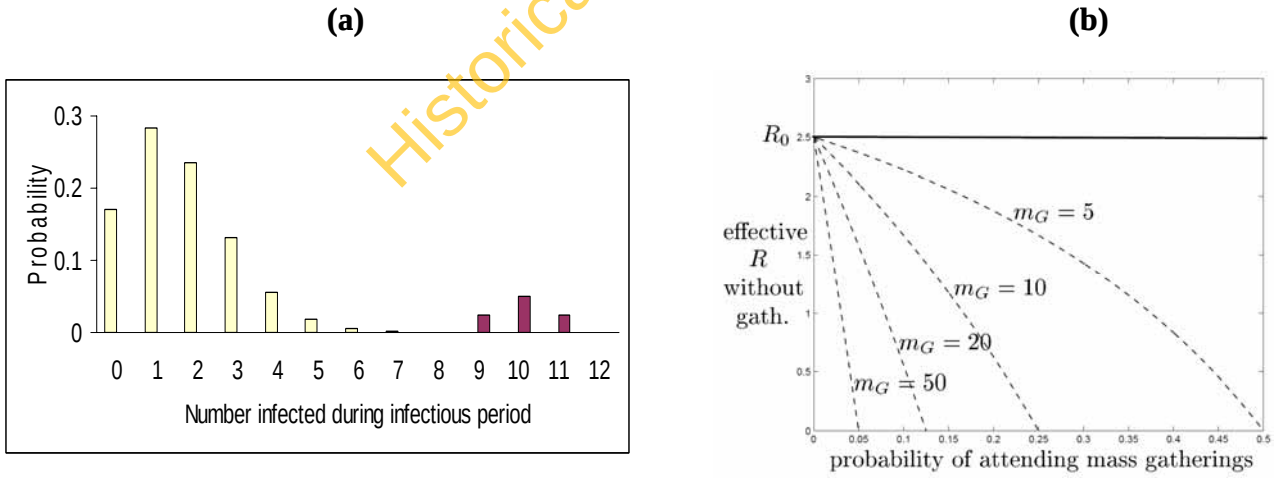

Figure 4.8 For R_0=2.5, the impact of mass gatherings on the effective R is illustrated. The solid line shows R for the case when gatherings are allowed, and the dashed curves the reduction in the effective R when such gatherings are prohibited. Parameter m_G is the mean number of infections at a gathering.

In Figure 4.8(b) we show the effect of banning mass gathering events for various values of m_G over the range of values [0, 0.5] for ω. It is evident that the prohibition of mass gatherings reduces the effective R significantly, but is highly dependent on the values of ω and m_G. Data to guide us on plausible values for ω and m_G are scarce.

4.7. Restricting travel within Australia

During the 1918-1919 pandemic border restrictions were established between states. It seems that today border restrictions between major cities would at best delay the geographic spread of the epidemic. However, it is useful to know how long it might be for an importation in one location to establish itself in another location. One reason is that this can assist in planning a co-operative response, another is that some regions of Australia might try to isolate themselves.

Travel restrictions between regions in Australia will delay the geographic spread of the epidemic. To illustrate this we consider the effect of travel restrictions on the time delay before an outbreak initiated in Sydney gathers momentum in Melbourne. The results of simulations using the model depicted schematically in Figure 4.9 are presented in Figure 4.10, for four scenarios: (a) R_0 = 1.5, with a flat infectiousness function (b) R_0=1.5, with a peaked infectiousness function, (c) R_0=2.5, with a flat infectiousness function and (d) R_0=2.5 with a peaked infectiousness function. The red dotted lines show the time taken for the epidemic to spread from Sydney to Melbourne in the absence of travel restrictions, which are 46, 31, 22 and 15 days for scenarios (a), (b), (c) and (d) respectively. Data on rates of travel are sourced from surveys of domestic visitor nights spent in Sydney and Melbourne (see Tourism Victoria 2005 and Tourism New South Wales 2005), as well as air-travel volumes between the two cities [Australian Bureau of Transport and Regional Economics 2005], and all individuals are assumed to be equally likely to travel.

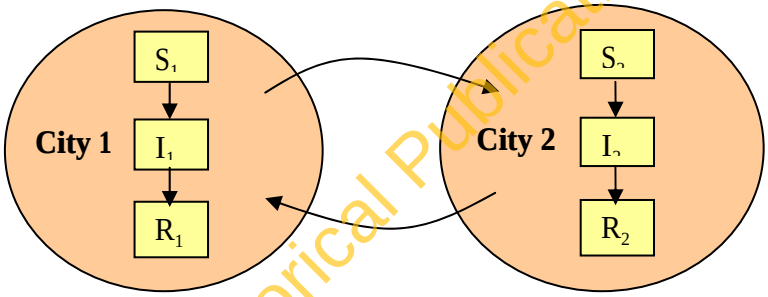

Figure 4.9 Schematic of the model used to simulate the effects of travel restrictions. The epidemic growth in each city is described by an SIR model. Travel between cities has been incorporated, so that an epidemic initiated in City 1 can spread to City 2 and vice-versa. The model also contains stochastic effects, so that chance variation in the early stages of an epidemic is taken into account.

The results show that a median delay of up to 50 days in the spread of the epidemic from Sydney to Melbourne can be achieved with scenario (a), which decreases to 33 days in scenario (b), 21 days in scenario (c) and 13 days in scenario (d). However, these median delays require that 99% of travel between Sydney and Melbourne is prevented, and that these restrictions are initiated when there are 20 currently-infectious people in Sydney. If travel restrictions only stop 90% or 80% of travel, respectively, then the delay is reduced to 25 or 18 days in scenario (a), 16 or 11 days in scenario (b), 11 or 7 days in scenario (c) and 7 or 4 days in scenario (d).

To have an appreciable effect it is necessary to apply travel restrictions quite early in the epidemic. The grey panes in Figure 4.10 show the period of time over which the epidemic in Sydney grows from 20 to 1000 currently-infectious people. All travel restrictions have a minimal effect when implemented at a time when Sydney has 1000 infectious cases.

The above results illustrate the effect of internal border control on the spread of epidemic between major centres within Australia, a situation that is also affected by international travel. Unless international borders are also closed, it is likely that the first case in Melbourne would arrive from

overseas rather than from Sydney. It is, however, possible that restrictions on travel to and from smaller towns could be used to delay or even stop the spread of an epidemic to more remote areas.

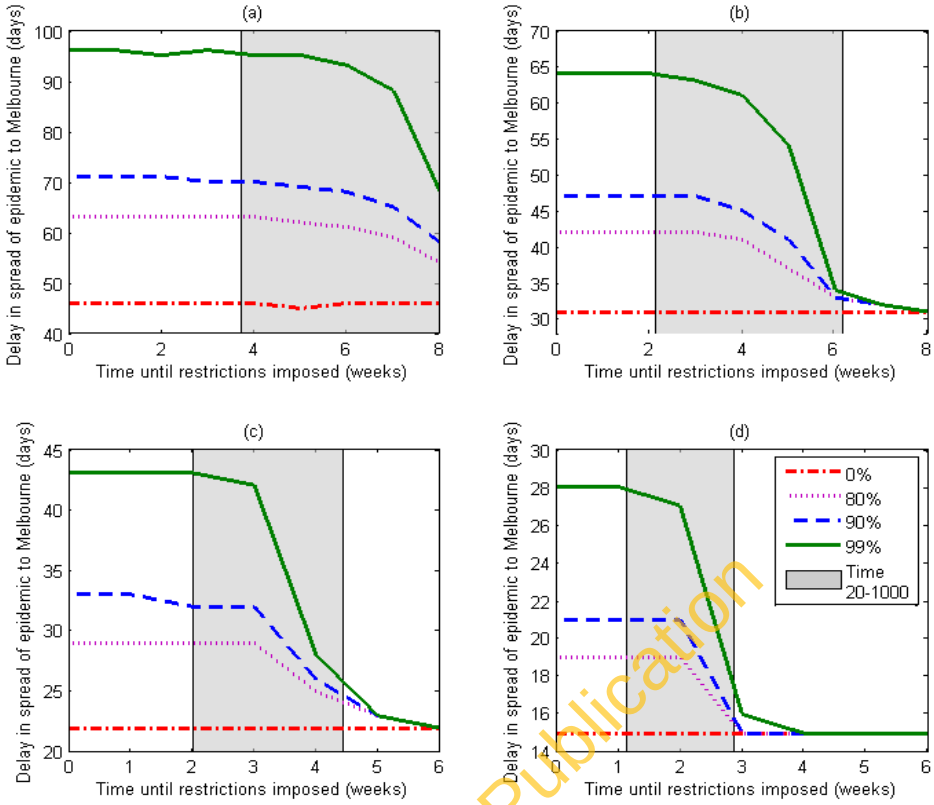

Figure 4.10 The median delay between the time when a Sydney outbreak reaches 20 current infectives (and there are no cases in Melbourne) and the time when the infection is transmitted to Melbourne and reaches 20 current infectives there.

(a) R_0=1.5 and a flat infectiousness function is used,
(b) R_0=1.5 and a peaked infectiousness function is used.
(c) R_0=2.5 and a flat infectiousness function is used.
(d) R_0=2.5 and a peaked infectiousness function is used.

The time at which the travel restrictions are imposed, measured from the arrival of the initial case in Sydney, is varied along horizontal axis. The curves correspond to different percentages of intending travelers prevented from traveling.

The grey shaded region shows the median time between 20 current infectives in Sydney and 1000 current infectives in Sydney.

4.8. Quarantining households

We have seen that isolating cases soon after diagnosis is not a particularly effective way to reduce transmission. Quarantining all members of a household with a diagnosed case presents a way to remove both the diagnosed case and (more importantly) some newly-infected individuals from circulation before they have become symptomatic, or even infectious.

The most favourable results are achieved when the diagnosis is made as early as possible and the quarantine imposed immediately following diagnosis. We examine situations where the household is diagnosed and quarantined either 3 or 4 days after infection of the primary case. It seems unlikely that quarantine could be imposed less than 3 days after the primary infection, as the primary case will typically not become symptomatic until 48 hours after infection.

For our calculations with household quarantine we assume that household members complying with quarantine have no infectious contacts with other community members after the quarantine starts. There is likely to be a problem with compliance: household quarantine intrinsically involves asking people to stay at home with (presumably) infectious family members, thus placing themselves and their children at relatively higher risk than they would experience in the community. For this reason, we examine the results for different levels of compliance.

The model used

Transmission of infection is divided into intra-household and inter-household components. We estimate the force of infection acting within each household according to the number of infectives inside the household, and the total number of infectives in the wider community.

The population is divided into households of sizes between 1 and 6, in accordance with data from the Australian 2001 Census (Table 2.2).

The force of infection acting in the wider community is computed by counting the total number of infectives in the community. Infectives are divided into two categories depending on whether or not they come from a house that could be quarantined (i.e. whether someone in their household has been infected for long enough to be diagnosed). Infectives who come from a household that is potentially quarantined contribute a diminished force of infection, which adjusts for compliance. The force of infection is reduced to 0.8 × (original value) if households are 20% compliant with quarantine. Infectives from households that could not be quarantined are allocated their full force of infection until someone in their household has been diagnosed.

We present scenarios in which there is 0%, 20%, 50% and 90% compliance with household quarantine, for reproduction numbers of 1.5 and 2.5.

When the reproduction number is R = 1.5, household quarantine implemented three days after the primary case is infected is an effective intervention. Figure 4.11(a) demonstrates how even a low level (20%) of compliance brings about a substantial reduction in epidemic peak height, as well as delaying it in time. A level of 90% compliance is able to suppress the epidemic entirely. However, if quarantine is delayed until the fourth day, see Fig 4.11(b), its benefit is significantly reduced.

If the reproduction number is R = 2.5, quarantine on day 3 after infection conveys some benefit if the compliance is very high (90%), but is almost useless if it is imposed on day 4 after infection or if compliance is low, see Figure 4.11(c) and Figure 4.11(d).

In short, household quarantine by itself is a moderately effective intervention. It is more effective the earlier it is imposed, and therefore depends on early diagnosis of patients.

In Section 4.9 we demonstrate how combining household quarantine and prophylaxis of household members is far more effective. It is natural that these two interventions go together, because a combined approach is socially more acceptable, since it provides prophylactic protection to household members who stay at home with patients.

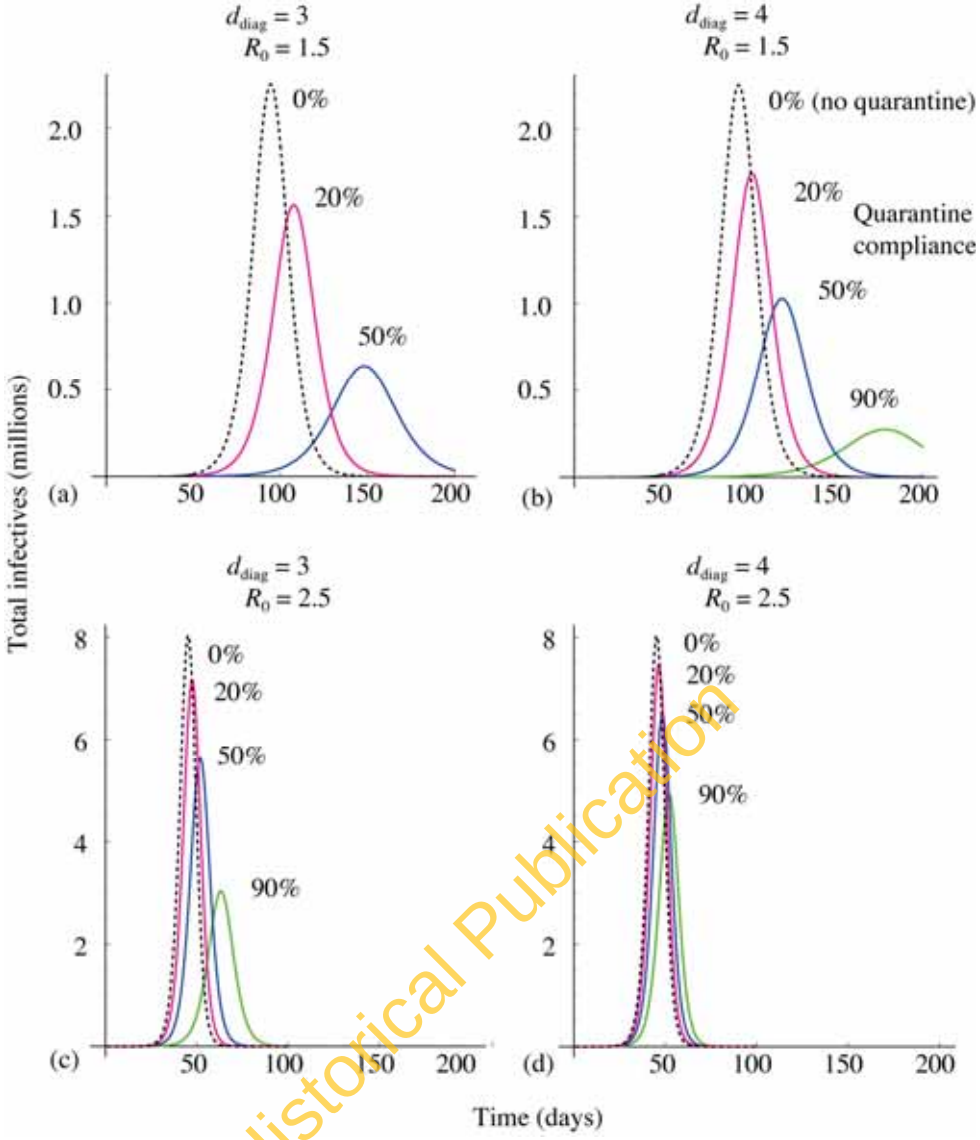

Figure 4. 11 Epidemic curves for different levels of compliance with household quarantine. d_{diag} is the day on which the primary case in each household is diagnosed, and subsequently quarantine is implemented starting at the end of that day.
(a) R = 1.5, quarantine implemented on day 3
(b) R = 1.5, quarantine implemented on day 4
(c) R = 2.5, quarantine implemented on day 3
(d) R = 2.5, quarantine implemented on day 4

4.9. The effect of using antiviral drugs (AVs) to reduce transmission

The role of antiviral drugs is the theme of Section 5. However, as antiviral drugs also play a role in reducing transmission we present some of the results for the effect of using antiviral drugs here. The model used to derive the graphs in Figure 4.12 and 4.13 is described in greater detail in Section 5.4. Note that the model used for these calculations is a deterministic model, which means that it does not take chance fluctuations into account. In particular, this means is that it will indicate elimination only when the intervention is adequate to bring R below 1. The probability (q) of achieving elimination by chance, during the early stages, when R exceeds 1 is dealt with in Section 5.3.

Figure 4.12 and Figure 4.13 illustrate that the use of antiviral drugs for treatment affects transmission quite differently than their use for prophylaxis. Treatment use tends to flatten the epidemic curve while prophylaxis use delays the epidemic with little change to its shape when it occurs. For higher values of the reproduction number, treatment strategies become ineffective, failing to significantly reduce the overall attack rate and the height of the epidemic peak. In contrast, prophylaxis strategies continue to be effective in delaying the onset of the epidemic, although the ensuing epidemic remains of about the same size. Use of antiviral drugs for prophylaxis is an effective way of postponing the peak of the epidemic and may, depending on the value of R, provide enough time for a vaccine to be developed and distributed.

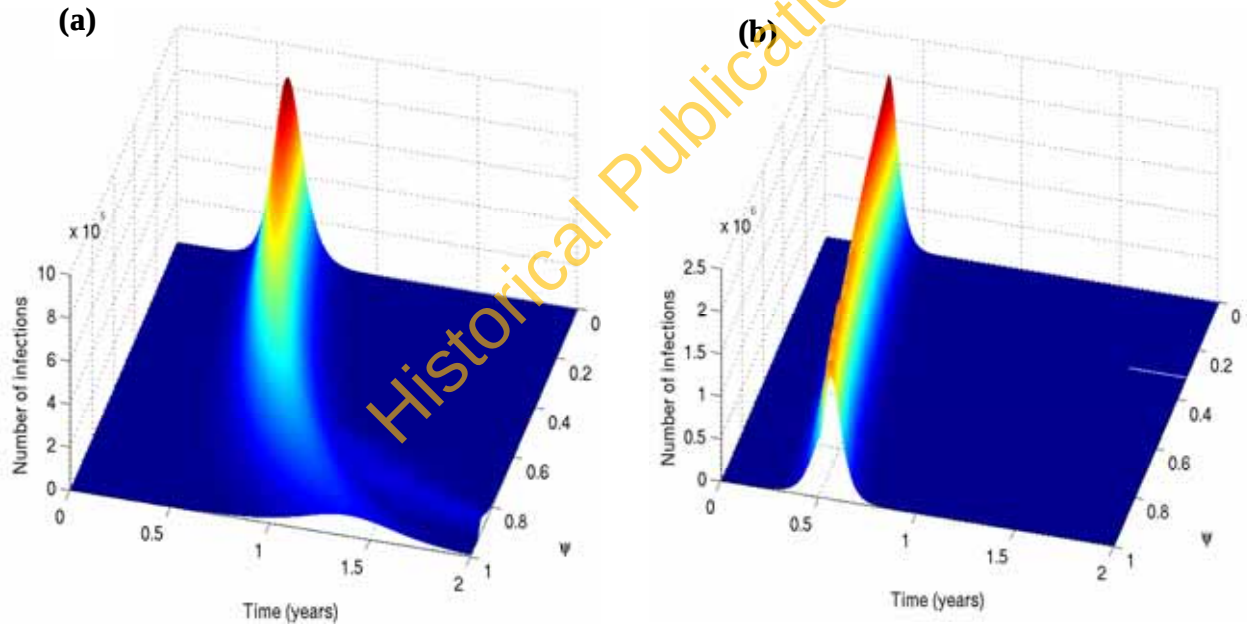

Figure 4.12 Epidemic curves as a function of treatment.

(a) As the proportion of cases treated (ψ) increases, the epidemic curve is reduced in size, but the peak is delayed only marginally, except for extremely high treatment coverage scenarios. The baseline attack rate is 50% ($R \approx 1.4$) and the infectious period is 6 days.

(b) As for **(a)**, but for a baseline attack rate of 70% ($R \approx 1.7$). Treatment is ineffective in either reducing the attack rate or delaying the epidemic.

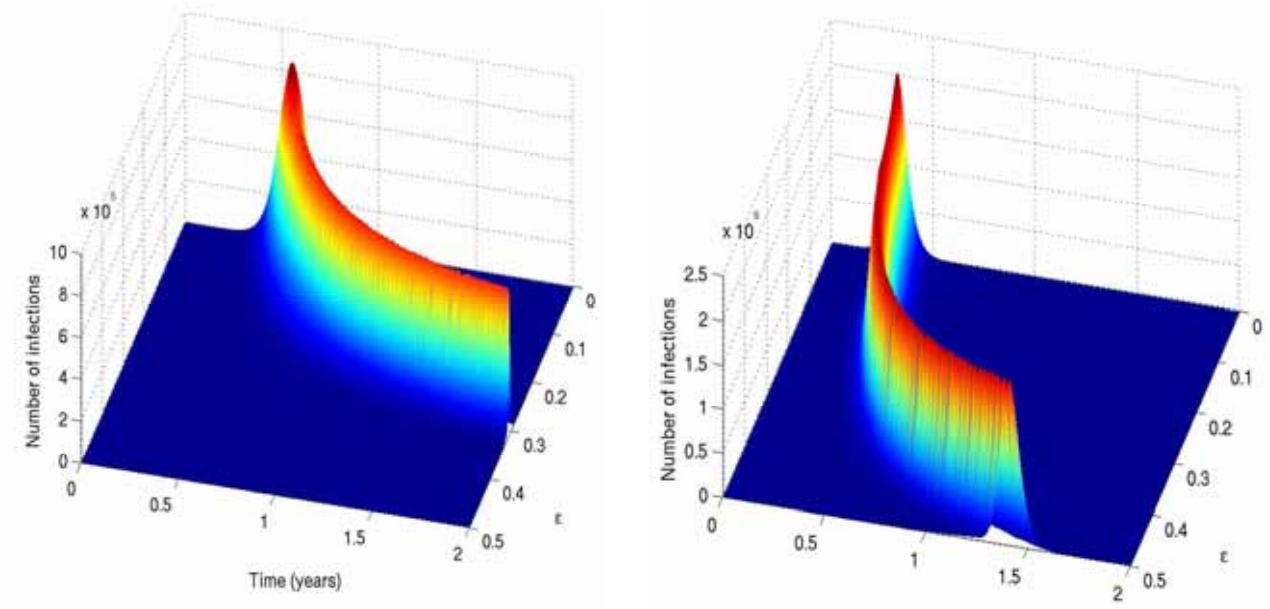

Figure 4.13 Epidemic curves as a function of prophylaxis. As the proportion provided with prophylaxis (ε) increases, the epidemic curve is delayed significantly, while its peak size is only marginally reduced. The graph is shown for $\varepsilon \leq 0.5$, because above this value the intervention delays the epidemic for a very long time. The infectious period is 6 days.

(a) Baseline attack rate of 50% ($R \approx 1.4$). **(b)** Baseline attack rate of 70% ($R \approx 1.7$).

Further results based on this model are given in Section 5.4.

Figure 4.14 shows the effect of combining household-based quarantine and prophylaxis measures in the case where R_0=1.5. The model used for calculation is the same as that described in Section 4.8, with the inclusion of prophylaxis (using the default parameters for effectiveness given in Appendix B).

Early intervention is very effective, and a high level of quarantine compliance, or deployment of prophylaxis is able to suppress the epidemic entirely if R_0 is 1.5. Note that in the case of only 20% compliance with quarantine, even though the epidemic grows exponentially, the size of the epidemic at 60 days is vastly reduced, from 66,500 to 8,100 (Figure 4.14).

Intervention at 3 days after infection is able to suppress the epidemic very well, though a combination of a high level of compliance and prophylaxis are required for complete suppression, or the epidemic continues at a low level.

If intervention cannot be implemented before day 4 after infection, no intervention is able to suppress the epidemic entirely, though a combination of prophylaxis and high level of quarantine compliance greatly reduces the number of cases in the first 60 days.

It may seem infeasible to quarantine infective households early enough to have an effect. The top graph of Figure 4.14 shows that successfully quarantining only 20% of households at day 2 after infection could usefully slow the growth of the epidemic in its early stages

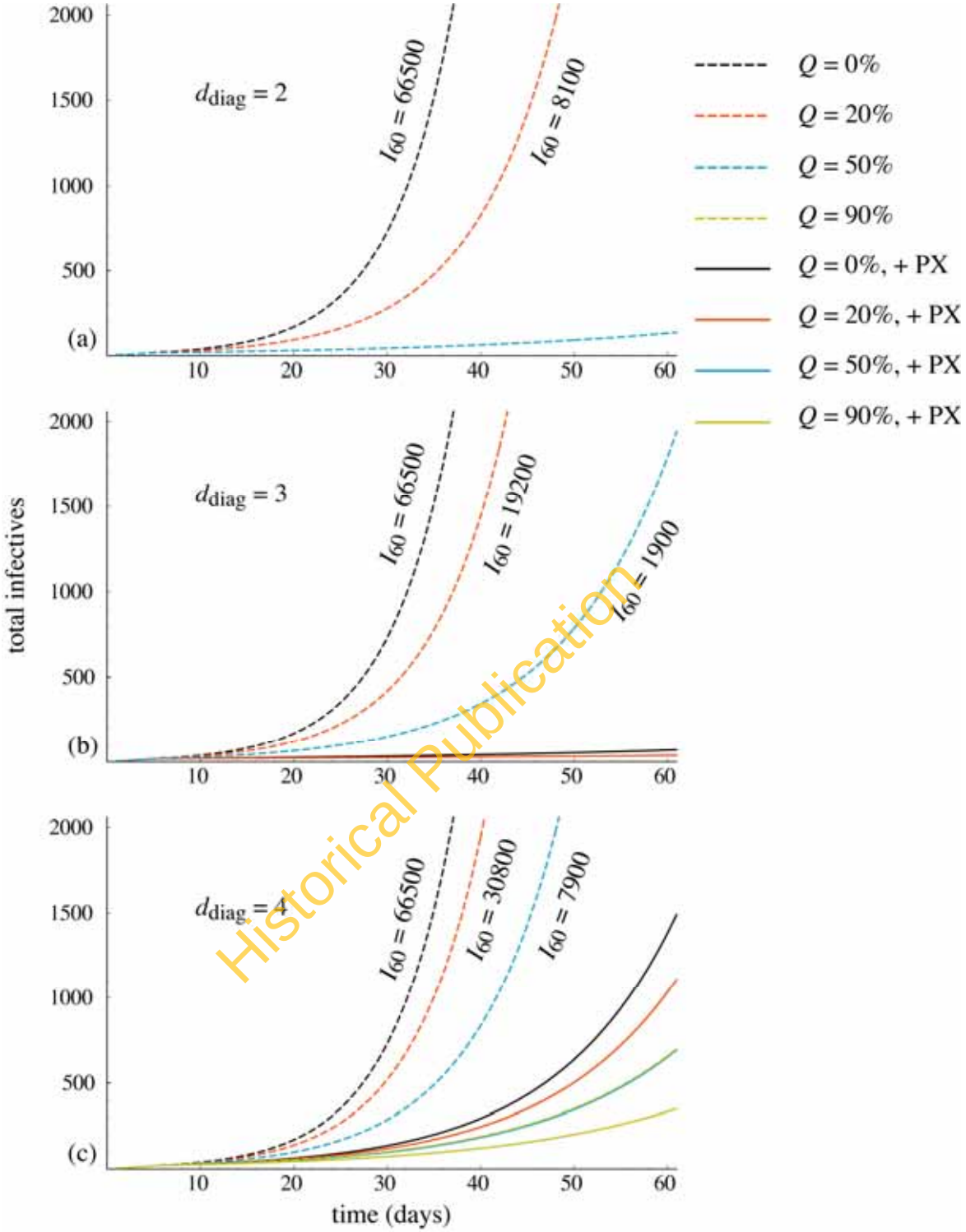

Figure 4.14 The effect of quarantining households on the first 60 days of the epidemic for four levels of compliance and the effect of prophylactic use of antiviral drugs (AVs) for household members. Parameter values: R_0=1.5, peaked infectiousness function.
The black dashed line (the top curve) is equivalent to the situation where there is no intervention.
Top graph: Intervention occurs two days after the primary case is infected
Middle graph: Intervention occurs three days after the primary case is infected
Bottom graph: Intervention occurs four days after the primary case is infected
I_{60} = total number infected on day 60
The order (top to bottom) of the curves in each graph are as in the legend.

These results are relatively sensitive to the largest household size used in the model. In general, if smaller households are used, both the quarantine and prophylaxis interventions are less effective (results not shown). This is because (according to a Reed-Frost model), a substantial fraction of the transmission occurs within larger households. As a result, much of the benefit could be gained by targeting larger households.

The calculations suggest that one should

(a) aim to quarantine and prophylax within 2-3 days of the infection of the primary case, i.e. within one day of onset of symptoms in the primary case;

(b) give priority to prophylaxis and quarantine of larger households.

4.10. **The value of rapid response**

There is much to be gained by responding quickly to the onset of disease spread. In Figure 4.15 we compare the outbreak size when containment is achieved by personal infection control and distancing measures in the $SEIR_H$ model when R_0 is 1.5. We assume that there are no control measures in place at the start of the outbreak, but that after a number of weeks, transmission is reduced to 70% of its original level outside the household. The left hand plot compares the epidemic curve when personal infection control and distancing is introduced 10 (red), 12 (green) and 15 (blue) weeks after the first case. The right hand plot shows the total outbreak size as a function of the number of weeks delay in implementing the measures. This intervention is sufficient to eliminate disease spread once it is implemented, however delays in implementation can lead to many cases. When the delay is less than 5 weeks, the total outbreak size remains below 2000. When the delay reaches 10 weeks, the total size ranges from 2000 to 100,000 cases. With a delay of 15 weeks, the outbreak reaches close to 1 million cases.

The effect on the total outbreak size is less dramatic if the measures that are introduced are not sufficient to eliminate transmission, though rapid response is still of importance. Figure 4.16 presents the epidemic curves for delays of 0, 5 and 10 weeks in introducing personal infection control and distancing measures when R_0 = 2.5.

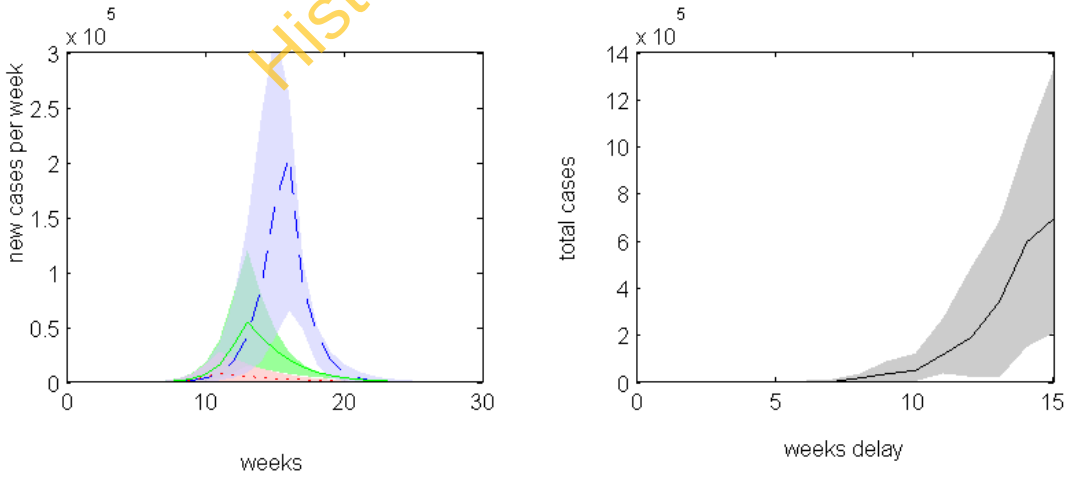

Figure 4.15 The outbreak size when personal infection control and distancing measures are introduced into the $SEIR_H$ model with R_0 = 1.5 after a delay of a number of weeks. The left hand plot shows the epidemic curves for delays of 10 weeks (red dotted line), 12 weeks (green solid line) and 15 weeks (blue dashed line). The right hand plot shows the total cases as a function of the delay in weeks.

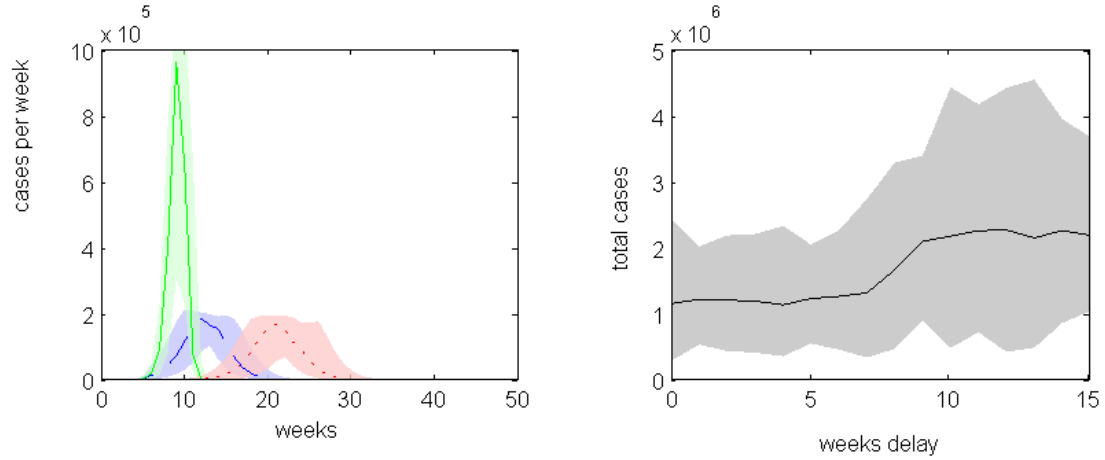

Figure 4.16 The effect of delay in introducing personal infection control and distancing measures on the epidemic curve and final outbreak size in the $SEIR_H$ model with R_0 = 2.5. The left hand plot compares epidemic curves when measures to reduce contacts by 30% are introduced immediately (red dotted line), 5 weeks (blue dashed line) and 10 weeks (green solid line) after arrival of infection. The right hand plot shows the final outbreak size as a function of the delay in introducing these measures.

4.11. **Combining interventions**

Above we considered the impact of different interventions aimed at reducing infection transmission, considering each intervention in isolation. By looking at them separately we get a clear indication of how effective each intervention is, and a comparison of their separate effects shows their relative effectiveness. In practice, however, a combination of such interventions will be used and it is of interest to see how effective this may be. In particular, we might wish to know what combination of interventions can achieve disease elimination and whether such a combination can be achieved in practice.

Here we give illustrative calculations of the effect of some combinations of interventions. We use a model that distinguishes between three types of individual (general population members, general practitioners and influenza-dedicated health care workers). Further details of the model are given in Section 5 (see subsection 5.2), which deals in greater detail with the role of antiviral drugs. Figure 4.17 illustrates how, compared with the case of no intervention (when R_0 obtains), the distribution of AVs to doctors, patients and health care workers, with PPE for the latter, impacts on the effective R. This strategy (Strategy **A**) might be motivated by the need to maintain a sustainable health service. It reduces the transmission of the infection marginally. Further, the figure illustrates the significant impact of Strategy **B**, which combines Strategy **A** with isolation (f =0.75) and personal infection control and distancing ($\lambda_S \times \lambda_I$ =0.25). For values of R_0 as high as about 5.5, this combination of interventions can reduce the effective R to below 1, thereby eliminating the infection.

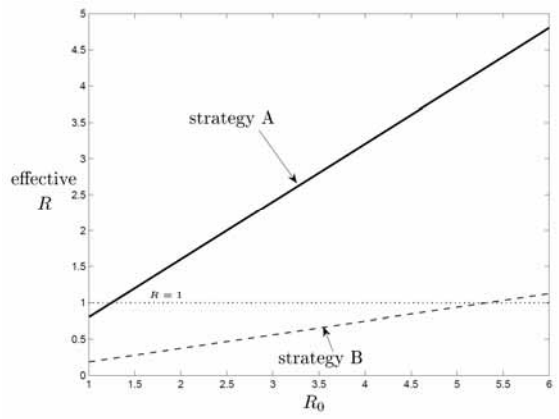

Figure 4.17 The amount by which a combination of strategies changes R, as a function of R_0. Strategy **A**: AVs are distributed to doctors (post-exposure prophylaxis), to patients (treatment) and to influenza-dedicated health care workers (pre-exposure prophylaxis), with the health care workers also using PPE (the default strategy for antiviral use).

Strategy **B**: a combination of Strategy **A**, personal infection control and distancing ($\lambda_S \times \lambda_I = 0.25$) and isolation (spending 75% of infectivity in the community before being isolated, i.e. $f = 0.75$). Clearly, this combination reduces the effective R significantly.

School children are a special group of interest, as they have been found in some disease studies to be responsible for a disproportionate contribution of disease transmission through greater infectivity, less prior immunity and enhanced mixing in school environments. Thus a more general model is considered now, which includes a fourth class, namely school children, as well as a household structure. It includes prior immunity and enhanced school mixing, as well as a structure that allows a proportion of parents to stay home from work and care for children when schools are closed. Figure 4.18 illustrates the impact of a combination of such measures. Strategy **A** is, as in Figure 4.17, aims to maintain a sustainable health care service. Its effect is again shown by the heavy line. This strategy together with closing schools, giving AVs to all school children, as well as closing schools and distributing AVs to all school children as prophylaxis, are the combinations of interventions considered. Also included in this figure is the impact of closing non-essential workplaces, together with closing schools and the default antiviral distribution to protect health care workers. The results indicate that closing 50% of non-essential workplaces is more effective than providing AVs to all school children, when both strategies are in combination with the default antiviral strategy and the closure of schools.

While each combination of strategies has a significant impact on transmission, the results suggest that isolation and personal infection control and distancing, and the closure of schools and workplaces (a means of enforced social distancing) are substantially more effective than the others.

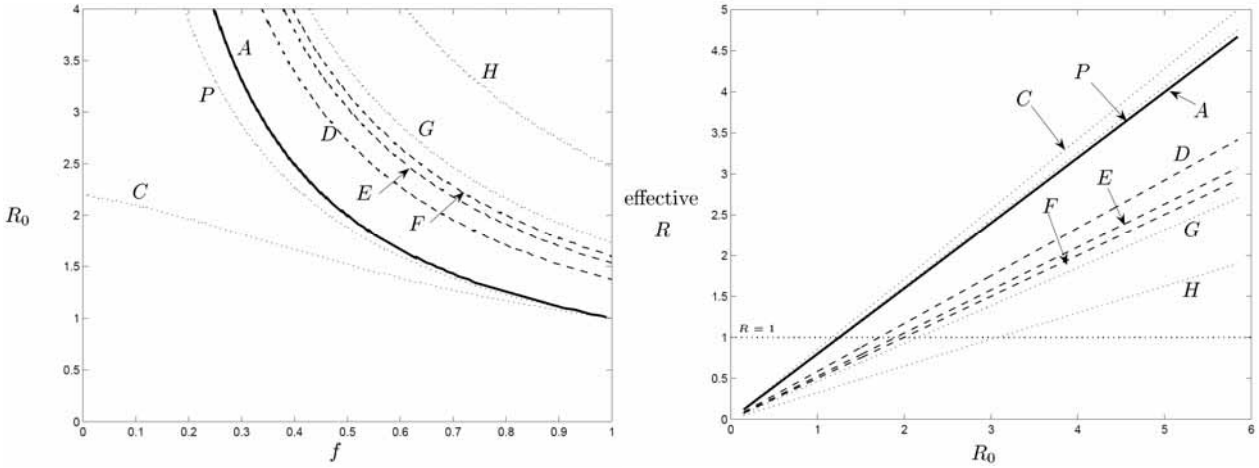

Figure 4.18 The impact on the effective R of closing schools, closing non-essential workplaces and providing school children with antiviral prophylaxis is illustrated. The first graph plots the curves for which the effective R = 1 for a parameter combination of f (the proportion of infectivity spent in the community) and R_0. Note that $R > 1$ above the curve so that a major epidemic may occur, while $R < 1$ below the curve so that the outbreak is contained. The second graph plots the effective R for given R_0 and a particular strategy.

Strategy **A**: AVs are distributed to doctors, patients and health care workers, with the latter using PPE (the default strategy for antiviral use).

Strategy **P**: PPE (only) used for HCWs (no AVs distributed).

Strategy **C**: no intervention.

Strategy **D**: Strategy **A** together with closing schools and a proportion of parents remaining home to care for them.

Strategy **E**: Strategy **A** together with all school children receiving AVs as prophylaxis.

Strategy **F**: Strategy **D** together with all school children receiving AVs as prophylaxis.

Strategies **G** and **H:** Strategy **A** together with closing schools and 50% and 100%, respectively, of all working adults staying at home.

4.12. **Conclusions**

Each of the interventions used alone reduces transmission of the infection, although they reduce transmission by different amounts and differ in the way they affect the dynamics of the local epidemic. Each intervention has its greatest effect when the reproduction number R is close to 1 (say R<1.5), because the total number infected reduced dramatically as R decreases from 1.5 to 1. This effect is similar to the effect known as herd immunity.

Isolating cases

For influenza, isolating diagnosed cases as soon as possible after their diagnosis is not likely to reduce transmission effectively when used by itself. This is seen by both its effect on R and its effect on the eventual number infected. This is because for influenza substantial transmission occurs before isolation can be effected in practice. However, if other interventions are able to reduce R to 1.5 then adding isolation of cases to these interventions will have a worthwhile effect and will possibly bring R below 1, to achieve elimination.

Isolating cases would be an effective intervention if the disease characteristics of the emerged pandemic strain include a long period of high infectivity following the onset of symptoms.

Personal infection control and distancing

The effect of reducing transmission by promoting behaviour that reduces close contacts between individuals depends on the extent to which contacts are reduced. However, the percentage by which contacts can be reduced is potentially higher than the percentage by which isolating cases can reduce the portion of the infectious period spent in the community. As a result, and noting that we get a double effect when reducing contacts (because both susceptible and infectious individuals avoid contacts), personal infection control and distancing is potentially quite effective, in terms of reducing *R* and the total number of cases. Furthermore, if an intervention consisting of isolating cases and an intervention consisting of personal distancing reduce *R* by the same amount, then distancing is preferable because, compared with isolating cases, it produces a flatter local epidemic, which is less disruptive and results in a lower peak burden on the health care system.

Closing schools

Using mixing rates for school children and adults that are consistent with group-specific influenza attack rates observed for school children and adults in previous pandemics of influenza it is found that closing schools has at best a modest benefit on overall transmission although it can assist in reducing the attack rate in children (see Section 4.4 for a discussion of assumptions and findings). If it turns out that the elderly are at greatest risk from the pandemic influenza strain, and closing schools has the effect of increasing the mixing between children and the elderly, then the value of closing schools becomes highly questionable. As with all interventions, closing schools has an appreciable effect when *R* is in the range 1–1.5.

Restricting travel within Australia

Levels of interstate travel are now very high and it is necessary to achieve very high levels of restrictions in movements to see any appreciable delay in the time before the infection moves from one state/territory to another. This is especially true for movement of the infection between state or territory capitals. Isolating a more remote region might be feasible if contact with infected regions can be kept to a very small number.

Quarantining households

Quarantining household members of a diagnosed case separates newly-infected individuals and potentially-infected individuals from the community before they become infectious or earlier in their infectious period. As expected, it is found to have considerably more potential to reduce transmission than merely isolating diagnosed cases, because infected household members have a considerably reduced potential to infect others. The cost is that some individuals who are not infected are also quarantined. The effect of quarantining depends considerably on the level of compliance, and results suggest that 60% compliance can produce a significant impact on transmission, case numbers and possible containment.

Use of antiviral drugs for limiting transmission

Under the default estimates of effectiveness for antiviral drugs calculations suggest that their use for targeted prophylaxis can delay the largest part of the infection incidence by several months. The default estimates of parameters suggest that the current stockpile of antiviral drugs is likely to delay the peak of the epidemic by one year, provided 40-50% of the exposed individuals are reached soon after the source case is symptomatic and the reproduction number is relatively low. As will be discussed in Section 5.6, this strategy is most effective when combined with treatment of symptomatic cases (see Figure 5.8).

Combined interventions

When interventions are used in combination, and assuming that

a. isolating cases reduces the part of the infectious period spent in the community by 20%,

b. personal infection control and distancing reduces the rate of making infectious contacts between susceptible and infectious individuals by 50%,

c. quarantining with 80% compliance, and

d. AVs are used for prophylaxis with 50% coverage,

then we are theoretically able to achieve elimination of the infection even if R_0 is as high 10. To achieve those levels of intervention in practice would require a great deal of community co-operation.

4.13. **Discussion**

i. Limitations

Our calculations have not incorporated all plausible heterogeneities. For example, personal infection control and distancing may not be adopted uniformly. Some individuals will practice it conscientiously, while others may practice it only minimally. Some plausible differential severity in infection, e.g. in the elderly, has not been accommodated.

Some aspects of the structure of the community, e.g. geographic dispersion, are not accommodated.

There are also limitations with regard to the results on AVs. They are given at the end of the next section.

ii. Further work needed

The extent to which we have allowed for heterogeneity among individuals has been severely limited by the tight timelines. It is necessary to check the sensitivity of results to heterogeneities such as those mentioned above.

The models used here do not include the elderly as a separate class. This makes the current suite of models unsuitable for considering interventions that may differentially impact this group, such as quarantining aged care facilities. In future work we will adapt these models to assess the impact interventions targeted at the elderly.

The two forms of infectiousness function we have used, Figure 2.1, are motivated by data on current and past influenza. It seems worthwhile to perform calculations on alternatives that are guided by data from sporadic human cases of avian influenza.

iii. Contrasting the results with those for SARS

Isolating cases and quarantining households have the greatest potential to reduce transmission when there is an appreciable time from infection until the end of infectivity. Isolating cases would be expected to be considerably more effective for SARS than for influenza, as SARS cases show a longer latent period, and are infectious for longer.

5 THE ROLE OF ANTIVIRAL DRUGS

Some assessments of the use of antiviral drugs were included above, under limiting transmission. Here we elaborate on these results, including consideration of the use of AVs (for treatment and prophylaxis) in combination with other interventions, such as who receives antiviral drugs and the number of courses of AVs used over time.

5.1. Our aims in this section

To perform calculations, and present illustrations of these, to inform us about

a. the effect of using antiviral drugs for treatment or prophylaxis on transmission,
b. plausible outcomes if antiviral drugs are distributed primarily to risk groups such as health care workers and children, and
c. the depletion of the stockpile of antiviral drugs over time under different usage strategies.

5.2. Evaluating the use of antiviral drugs by its effect on R

It may be that using antiviral drugs for treatment against illness is very beneficial for the patient. Strategies that take this into account have not yet been investigated. So far we have considered primarily the effect of AVs on transmission of the infection and maintaining the health care services.

The illustrations shown in Figure 4.12 indicate strongly that the use of antiviral drugs for treatment alone reduces transmission only modestly. Specifically, when R is 1.4, as in Figure 4.12(a), we can see a substantial reduction in the size of the epidemic when we are able to treat more than 70% of cases within 48 hours. The peak of the epidemic is then also delayed. However, this effect dissipates rapidly as the infection spreads more easily. Specifically, already with $R = 1.7$ (as in Figure 4.13) we see only a minimal effect on the epidemic, even if all cases can be treated within 48 hours.

In Figure 5.1 we support this conclusion with another calculation. It plots the effective reproduction number assuming a basic reproduction number of 1.5, and that individuals are isolated 2 days after onset of symptoms. The left plot shows the effective reproduction number according to the fraction of cases that are given AVs as treatment upon diagnosis. The right plot shows the effective reproduction number according to the fraction of susceptible individuals that are given prophylaxis. The solid line shows the case where no cases are treated with AVs after diagnosis, and the dotted line assumes that all cases are given AVs as treatment after diagnosis.
The strategy of using AVs as treatment is not sufficient to eliminate disease spread even when the basic reproduction number is 1.5. There is more scope to reduce the effective reproduction number by using AVs as prophylaxis, although this strategy is only likely to be practical while potential contacts are small in number and relatively easy to identify. The relative effects of these measures are identical for larger values of the basic reproduction number.

Consider now calculations based on a model that can allow different usage of AVs for health workers and the general public. We also allow diagnosed cases to be isolated, and denote the fraction of the infectivity spent in the community (before being isolated) by f. Consider an SEIR model with three types of individual, namely general practitioners (who are the first health care contact of pandemic influenza cases), influenza-dedicated health care workers (who tend the isolated cases) and general community members.

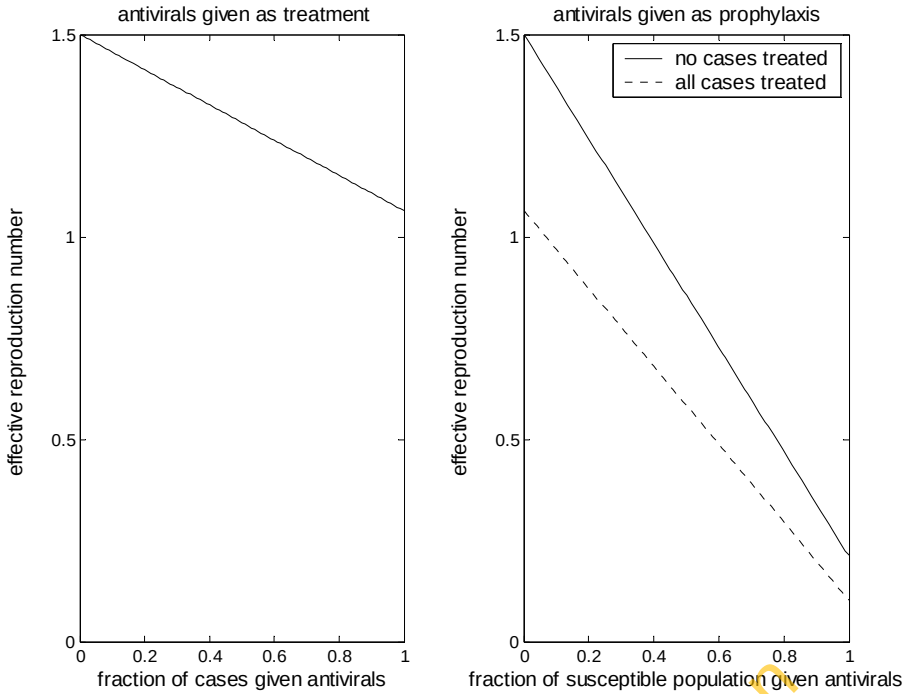

Figure 5.1 The effective reproduction number achieved by using AVs for treatment and prophylaxis, assuming a basic reproduction number of 1.5 and that individuals are isolated 2 days after onset of symptoms.

We define a default strategy for the use of antiviral drugs as follows:

i. Influenza-dedicated health care workers (HCWs) receive antiviral drugs for prophylaxis and use personal protection equipment (PPE),
ii. GPs receive antiviral drugs for prophylaxis following the first time they diagnose a pandemic influenza case, but do not use PPE, and
iii. all individuals are isolated upon diagnosis and treated with AVs.

When an infected person presents to a GP there is a probability p that the case infects the GP, if the latter is susceptible.

Figure 5.2 shows the contours where R =1 as a function of R_0 and f, the fraction of the infectivity an individual spends in the community before being isolated. The six contours, going from the lowest curve to the highest curve, correspond to progressively increasing intervention, namely

a. isolation of symptomatic cases, but no protection for HCWs (labeled 'neither AVs nor PPE' in Figure 5.2)
b. add PPE only for influenza-dedicated HCWs (labeled 'no AVs - with PPE')
c. add the default strategy for use of AVs as well (labeled 'default AVs')
d. add targeted use of AVs achieving 20%, 40% and 65% coverage among contacts of infectives (labeled '20%', '40%' and '65%' respectively)

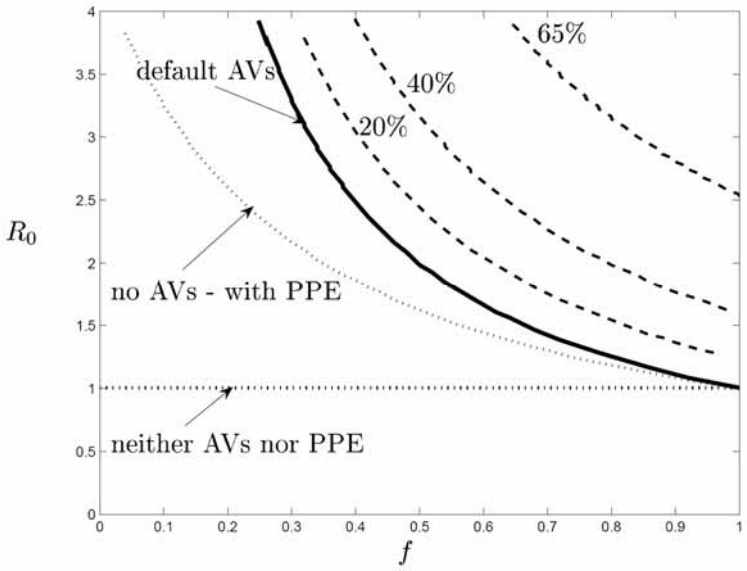

Figure 5.2 Each of the above six curves, corresponding to six different levels of intervention, is a contour for which R=1. For points above the curve (where a point is specified by a value for R_0 and a value for f) the effective R exceeds 1, so the probability that an imported outbreak takes off is positive. In contrast, $R < 1$ for points below the curve, which ensures that an imported outbreak will fade out early.

The lowest curve in Figure 5.2, for which R_0=1, indicates that isolating symptomatic cases will only lead to elimination if $R_0 < 1$. This is because HCWs are offered no protection, so that 'isolated' cases will continue to infect people.

Go now to the curve above this, namely the curve labeled 'no AVs - with PPE'. For the specified intervention, this curve consists of all the points for which R=1. The reason for giving this curve is that it partitions all the potential values of R_0 and f into those (below the curve) for which an outbreak will fade out rapidly and those (above the curve) for which the chance of a major outbreak is positive. From the curve labeled 'no AVs - with PPE' in Figure 5.2 we see that the early isolation of infected individuals and having them tended by HCWs using personal protective equipment enables elimination of the infection for some moderate values of R_0 above 1. For example, if cases spend only 40% of their infectious period in the community, before being isolated, then this isolation strategy is sufficient to achieve elimination as long as $R_0 < 2$.

The third curve from the bottom (labeled 'default AVs') indicates that adding antiviral use for health workers to this strategy enables containment of infection for a larger range of R_0 values. Note however, that most of the additional benefit occurs for early isolation. For influenza one might expect to achieve f = 0.6, at best, and for values of f greater than 0.6 the benefit of the default use of AVs is minimal in terms of its contribution towards eliminating the infection. However, the default strategy for the use of AVs is an important one for maintaining a sustainable health service during a pandemic of influenza.

In contrast, targeted use of AVs for prophylaxis of individuals exposed to diagnosed cases is seen to have a more substantial effect, even when isolation of diagnosed cases is impractical. This follows from the fact that the curves labeled 25%, 40% and 65% are significantly raised above the other contours. Specifically, it suggests that providing protection to 65% of exposed individuals, by prophylactic use of AVs that targets for example contacts, schools or residents of specific geographic locations, one is likely to be able to contain the epidemic. While this does not acknowledge that the AV stockpile may run out, we must remember that elimination, if it occurs, is likely to occur sooner rather than later (as long as we have not delayed the intervention response very long). More on how long the stockpile might last in Section 5.6.

5.3. Evaluating the use of antiviral drugs by its effect on q

We now assess the effect of interventions involving the use of antiviral drugs by a different measure, namely with reference to q, the probability that an outbreak initiated by a single infected individual fades out before gathering momentum. Recall that the information that R contains about q is that R < 1 implies q = 1. For R > 1 we are interested in the value of q, corresponding to different interventions.

In Figure 5.3 we show the value of q for a range of R_0 values corresponding to different interventions. The model and the interventions considered are as in Section 5.2, for the SEIR model with three types of individual (an individual is either a GP, a HCW or a member of the general public).

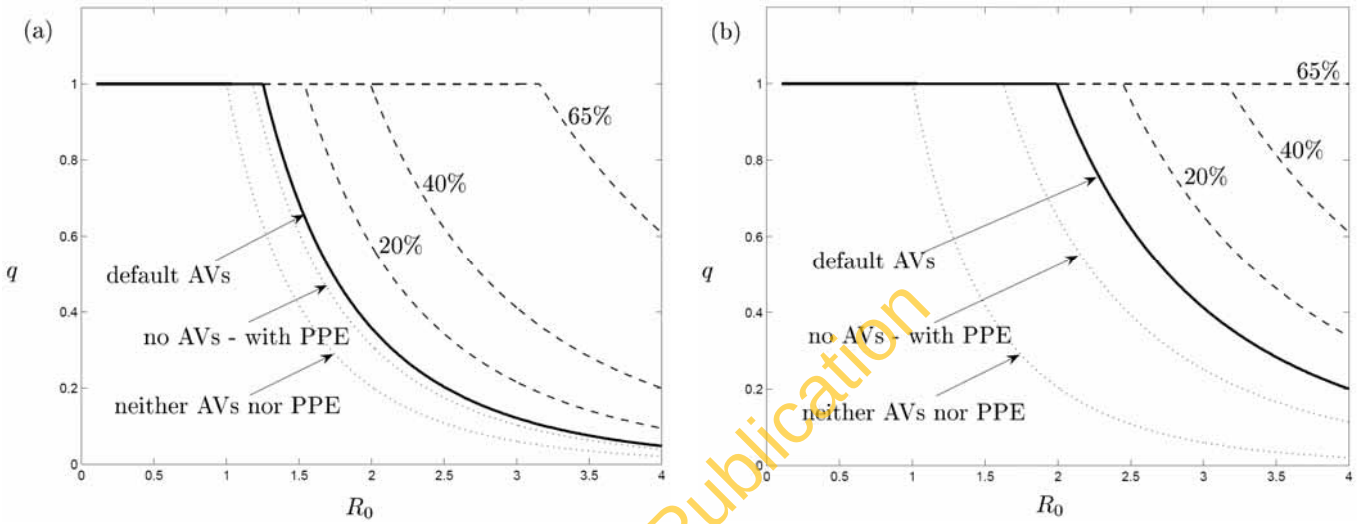

Figure 5.3 The probability q that an outbreak initiated by a single infected individual fails to gather momentum as a function of R_0, for a variety of targeted antiviral coverage.
(a) f =0.8, i.e. late isolation of cases, and
(b) f =0.5, i.e. timely isolation of cases.

The curves in Figure 5.3 are consistent with the results seen in Figure 5.2, in terms of the magnitude that each additional component adds to the effectiveness of the combined intervention. Specifically, if in addition to using the default AV strategy for health care workers it is possible to protect 65% of exposed individuals, by targeted prophylactic use of AVs, one is likely to eliminate the infection.

As the targeted use of antiviral drugs for prophylaxis seems effective it is instructive to show the result over the entire range of coverage that might be achieved. This is done in Figure 5.4, where the horizontal axis is g, the proportion of exposed individuals who are administered AVs for prophylaxis. (Figure 5.2 and Figure 5.3 show results only for g = 0.2, 0.4 and 0.65.) Figure 5.4 illustrates directly the impact of varying g (the proportion of the population successfully targeted) for a low (R_0=1.5), medium (R_0=2.5) and high (R_0=3.5) value of R_0. The results demonstrate that relatively low values of g are adequate for significant increases in the probability of containment. For example, when R_0=2.5 and f =0.8, targeting 50% of the population will achieve elimination.

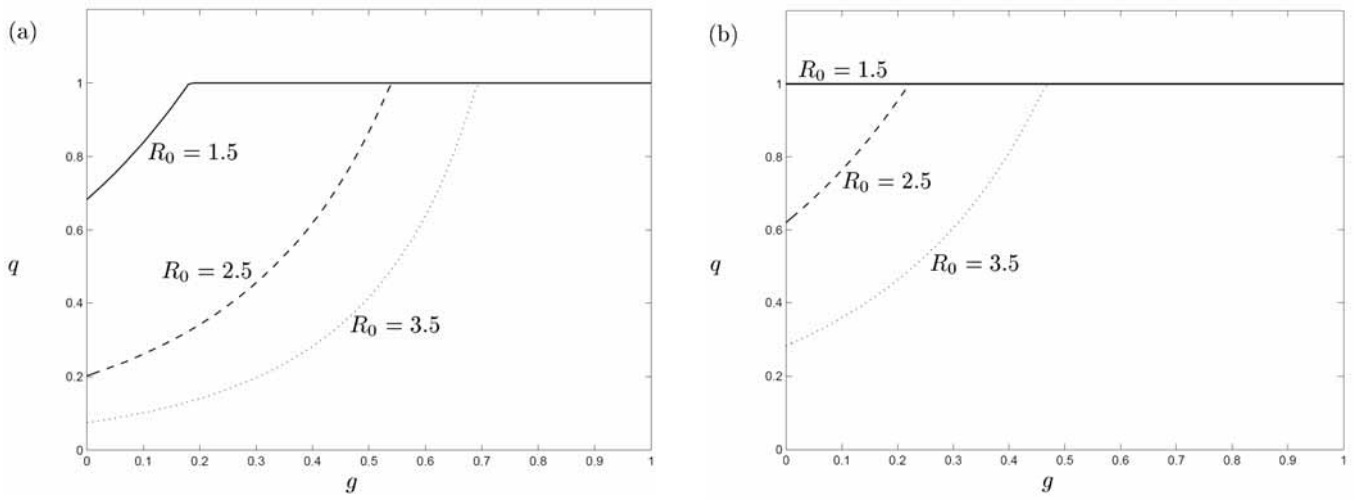

Figure 5.4 The probability q that the infection is eliminated before it establishes itself as a function of g, the proportion of the exposed individuals receiving AVs for prophylaxis, for R_0= 1.5, 2.5 and 3.5.

(a) f =0.8, i.e. late isolation of cases, and **(b)** f =0.5, i.e. timely isolation of cases.

5.4. How much do antiviral drugs reduce early transmission?

The advantage of assessing interventions with respect to R or q is that a considerable amount of community structure can be incorporated into the models with moderate effort. It is, of course, also necessary to look at the calendar-time dynamics of any local epidemic, if it occurs, and we do so in Section 5.6 with an appropriate model. A small step in this direction is possible with the model underlying our calculations for R and q. While this underlying model contains some community structure, it ignores the depletion in the number of susceptible individuals as the epidemic progresses. The latter is of no concern for the calculation of R and q. In terms of number infected, this model can trace the transmission adequately only during the early stages of the outbreak. In Figure 5.5 we depict the way different interventions affect the mean rate of growth over the first four generations.

Figure 5.5(a) gives the mean of the total number of cases over 4 generations. From Figure 5.5(b), one can deduce that the 'default AVs' strategy reduces the number of cases within 4 generations by approximately half, and that by providing AVs prophylactically to 40% of an at-risk group within the population leads to a reduction in the number of cases of between 80% and 90%. Such a reduction would infer a significant reduction in the demand on the health care system.

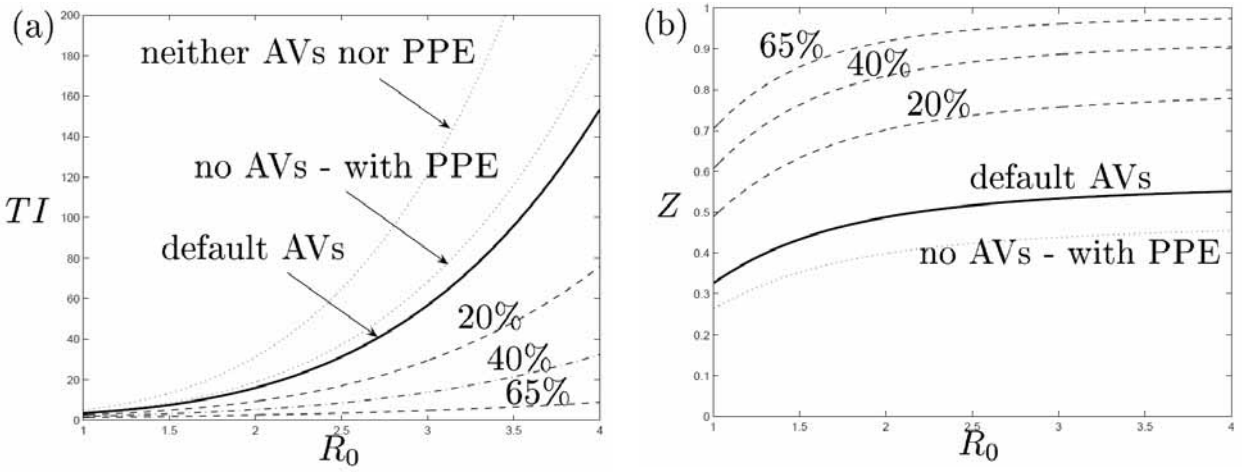

Figure 5.5 Effect of various antiviral strategies on the early spread, for different values of R_0 and f=0.8. **(a)** *TI*, the mean of the total number of cases after 4 generations
(b) *Z*, the proportion by which the mean number of infectives within 4 generations is reduced, compared with the case of no intervention.

5.5. How many courses of AV drugs are used in an attempt at elimination?

Suppose that during elimination attempts, neuraminidase inhibitors are distributed to probable infectious contacts of diagnosed individuals. In such a situation, prophylactics may be relatively generously distributed without having a substantial impact on the stockpile. For practical purposes we may consider that an elimination attempt has failed when 20 or more new infectives are diagnosed on a single day. When the progress of an epidemic reaches that stage it indicates strongly that $R > 1$ and, furthermore, the probability of an outbreak fading out with 20 initial infectives and $R > 1$ is negligible. We say that an elimination attempt has succeeded if number of infections on a single day never reaches 20, in which case the outbreak fades out. With this definition of elimination in mind we simulated 100,000 realisations of an outbreak, starting with one initial case and continuing until there are 20 new infections on a single day or the outbreak fades out, whichever comes first. For example, with R_0=1.5 this produced the frequency distribution shown in Figure 5.6 for the total number of cases by the end of the elimination attempt.

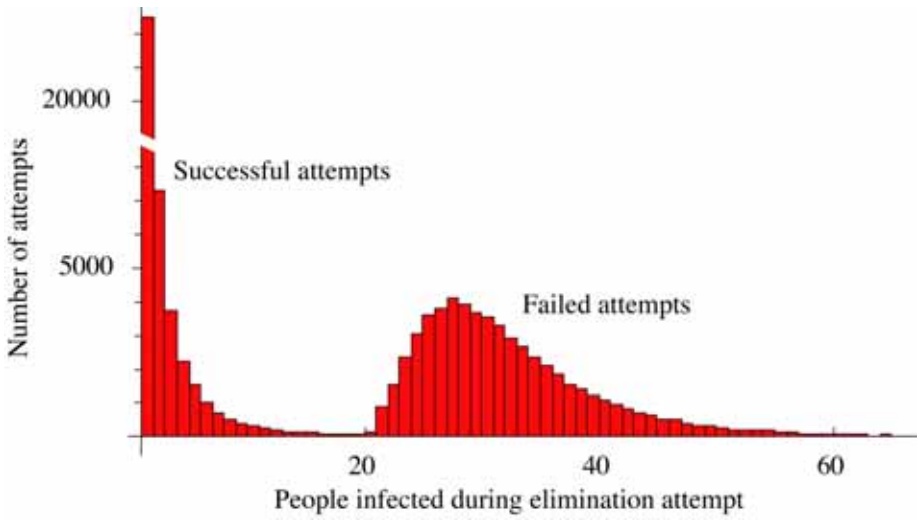

Figure 5.6 Frequency distribution of the total number of cases, in 100,000 simulated outbreaks, up to elimination or 20 new cases on a single day, whichever came first. (R =1.5)

Table 5.1 shows the 50th, 95th and 99th percentile of the total number of cases by the end of an elimination attempt, for R=1.5, 2.5 and 3.5. They range from 25 to 55. In other words, the total number of cases by the end of the elimination attempt is very small relative to the population size and relative to the size of the antiviral stockpile.

	R = 1.5	R = 2.5	R = 3.5
50th percentile (median)	25	25	25
95th percentile	43	33	35
99th percentile	55	36	39

Table 5.1 Percentiles of the total number of cases, in 100,000 simulated outbreaks, up to elimination or 20 new cases on a single day, whichever came first.

Consider now what this might mean in terms of AV use for an elimination attempt. During an elimination attempt, we assume that the number of courses used for prophylaxis will be proportional to the number of cases diagnosed. This number of courses might be low, perhaps 10, for some diagnosed cases, if it only covers family members and close acquaintances. For some diagnosed cases it might be large, say 100, if there is a need to prophylax an entire child care centre, for example. It seems likely that the number of courses used in an elimination attempt, as defined above, will use less than 2,500 courses of AVs. This is a small number relative to the size of the stockpile, particularly in view of the fact that the targeted use of AVs decreases R to a level where the probability of an elimination attempt succeeding becomes substantial.

5.6. The effect of antiviral drug use on the full dynamics of a local epidemic

As mentioned, the advantage of assessing interventions with respect to R or q is that a considerable amount of community structure can be incorporated into the models with moderate effort. However, it is also necessary to look at the full calendar-time dynamics of any local epidemic, if it occurs. Specifically, this provides the total attack rate, the timing of the epidemic peak, the shape of the epidemic and can provide the number of courses of antiviral drugs used as a function of time. It is very time consuming to incorporate extensive community structure into models that describe the transmission dynamics and so here we use an SIR model to make calculations and present illustrations on how AV use affects the full dynamics.

An unusual feature of the use of AVs for individuals thought to have been exposed is that the individuals identified as a contact are administered AVs temporarily and then come off AVs. To accommodate this feature we developed a model depicted schematically in Figure 5.7. This model does not explicitly include a latent phase.

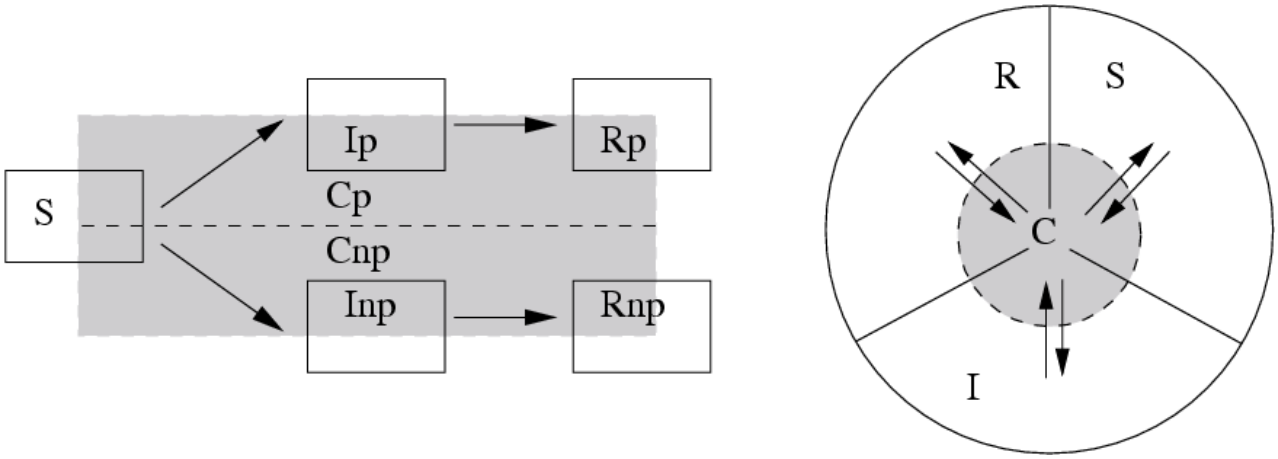

Figure 5.7 Schematic of the modified *SIR*-model. Individuals are in one of five states: *S*, the susceptible population; I_p, individuals on prophlyaxis who became infected ("breakthrough" cases); I_{np}, individuals not on prophylaxis who became infected; R_p, recovered individuals who were on prophylaxis when infected; R_{np}, recovered individuals who were not on prophylaxis when infected. An individual from any of these five states may also be classified as a contact, of which there are two possible types: C_p, individuals who have come into contact with an infectious individual and who have subsequently been administered antiviral drugs for prophylaxis; C_{np}, individuals who have come into contact with an infectious individual and who have not received antiviral drugs. Healthy contacts lose their contact classification after three days.

The model developed assumes the following:

i. On average, an infectious individual makes a meaningful contact with around 20 people over a period of a few days; see Edmunds *et al.* (1997).

ii. A proportion of these contacts are provided with antiviral drugs for prophylaxis. Data (see Edmunds *et al.*, 1997) suggests that up to 85% of contacts should be traceable. We allow for a delay in administering the drugs. Typically we have set this at four days following the onset of symptoms in the case. Two days due to the delay in providing treatment to the initial infective and a couple of days to allow for contact tracing.

iii. A proportion of infectious individuals who were not provided antiviral drugs for prophylaxis receive them for treatment. We allow for a delay until the drug is administered. Typically, we have set this at two days from exposure. It is assumed that breakthrough cases (those becoming sick while receiving prophylaxis) will continue to use the antiviral drugs that they already have, as treatment.

iv. Infectiousness during the infectious period is assumed to be constant so that infectivity is flat.

v. The effect of providing AVs for treatment is to reduce infectiousness to 0.7 (e_t) times baseline infectiousness.

vi. The effect of providing AVs for prophylaxis is to reduce susceptibility to 0.2 (e_s) times baseline susceptibility, and, if infected, to reduce infectiousness to 0.4 (e_i) times baseline infectiousness.

vii. The antiviral stockpile is 4 million doses. The population size is 20 million. Note, however, that the results apply similarly to a smaller population, e.g. Sydney, as long as the available number of AVs courses are reduced proportionately.

viii. An antiviral distribution program is only initiated once 10 new cases are observed on a single day. We examined the sensitivity to this delay.

The main outcomes from this model are illustrated in Figure 4.12 and Figure 4.13. The effect of treatment is to flatten the epidemic. It is noteworthy that this intervention becomes ineffective for reducing transmission when R_0 is 1.7, as seen from Figure 4.12(b). The effect of targeted prophylaxis is markedly different. Prophylaxis has almost no effect on the final attack rate, but consistently delays the bulk of the epidemic for over 6 months. With an effective contact tracing program, delays of over 1 year may be achievable, even for higher values of R_0 [see Figure 4.13(a) and Figure 4.13(b)]. For R_0 of around 3.5, combined prophylaxis and treatment strategies can delay the peak of the epidemic by around six months.

We now examine some aspects of the model in more detail. A central feature of the model is that it allows for the tracing of contacts of infectives. A percentage of contacts are identified, traced and then provided with AVs for prophylaxis. Contacts (both those provided with AVs for prophylaxis and those not traced) may either develop disease or return to the general population.

The model allows for realistic "wastage" of antiviral drugs by acknowledging that many courses of drugs will be provided to contacts who, unknown at the time, will not actually become infected.

Figure 4.12 and Figure 4.13 do not reveal some aspects of the model's outputs. While treatment is not an effective strategy on its own, it can play a significant role in delaying the onset to epidemic peak when used in conjunction with an established prophylaxis strategy. An example of this is seen by comparing Figure 5.8(c) with Figure 5.8(b). As mentioned above, the delay to the epidemic peak is reduced for higher values of R_0.

Results presented in this section assume a flat infectiousness function. Under the assumption of a peaked infectiousness function, the delay to epidemic peak will be reduced for two reasons:

a. the doubling time is shorter under a peaked infectiousness function, as discussed in Section 2.4;
b. contact tracing is less effective with a peaked infectiousness function because infections occur earlier in the infectious period.

A thorough investigation of the effect of peaked infectivity will be considered in future work.

While provision of prophylaxis can provide a delay to the onset of the epidemic, it requires a significant effort on the part of the health system which must contact trace and then deliver the antiviral drugs to an ever increasing number of people over an extended period of time. Figure 5.9(a) shows that, even in a highly effective intervention, as in Figure 5.8(c), there is, in fact, exponential growth in the number of infectives. Figure 5.9(b) shows the doses per day required to be distributed. In fact the doses per day reach a level that may not be achievable in practice.

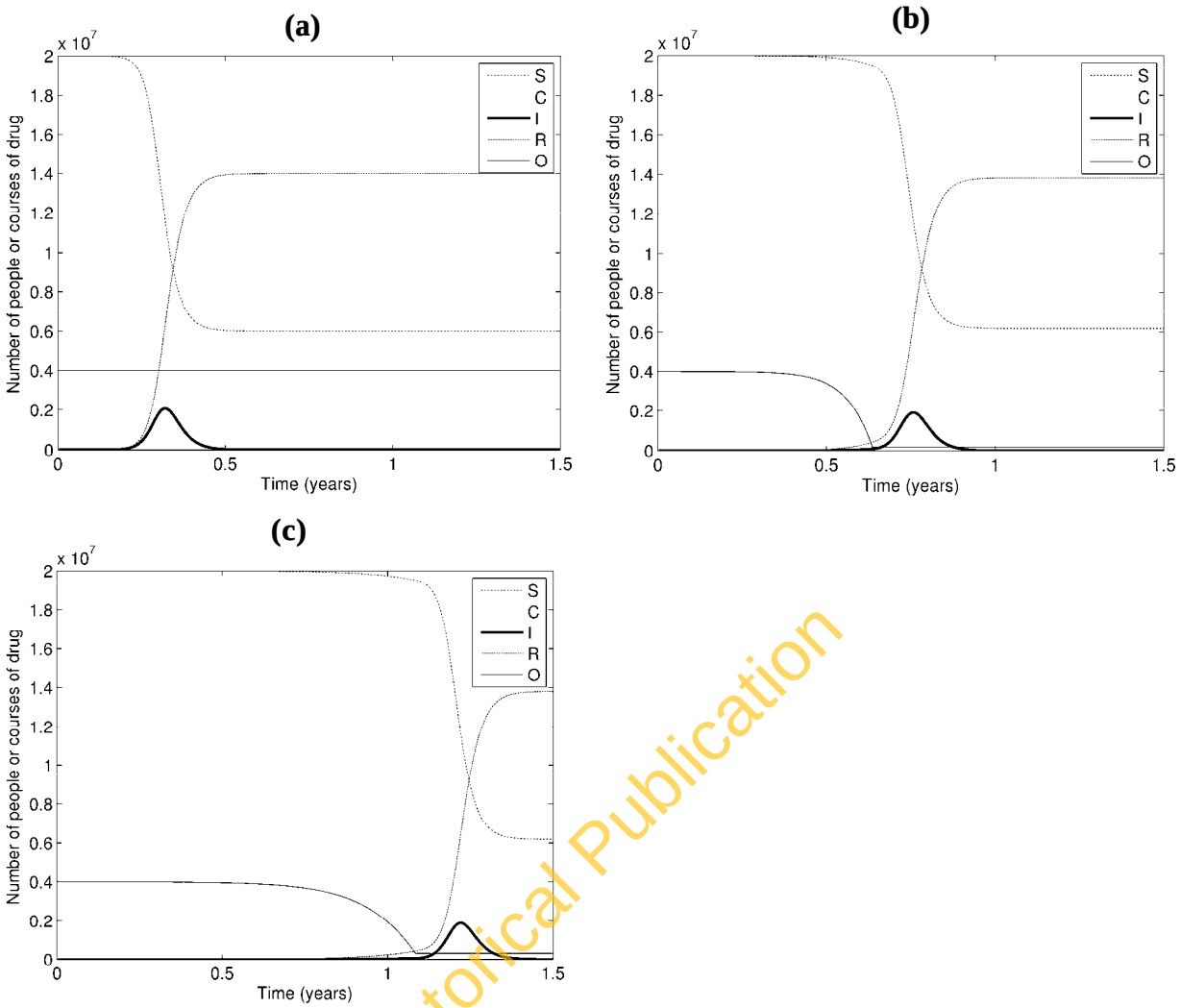

Figure 5.8

(a) Baseline epidemic, i.e. without intervention. The epidemic peak occurs at 0.32 years.
(b) 40% of contacts are provided AVs for prophylaxis. The epidemic peak occurs at 0.76 years.
(c) 50% of non-prophylaxis cases are provided AVs for treatment and 40% of contacts are provided AVs for prophylaxis. The epidemic peak occurs at 1.2 years.

All three graphs show the curves for the susceptibles (S), the traced contacts (C), the infectives (I), the removals (R) and those receiving Oseltamivir (O) for the model with $R_0 = 1.7$.

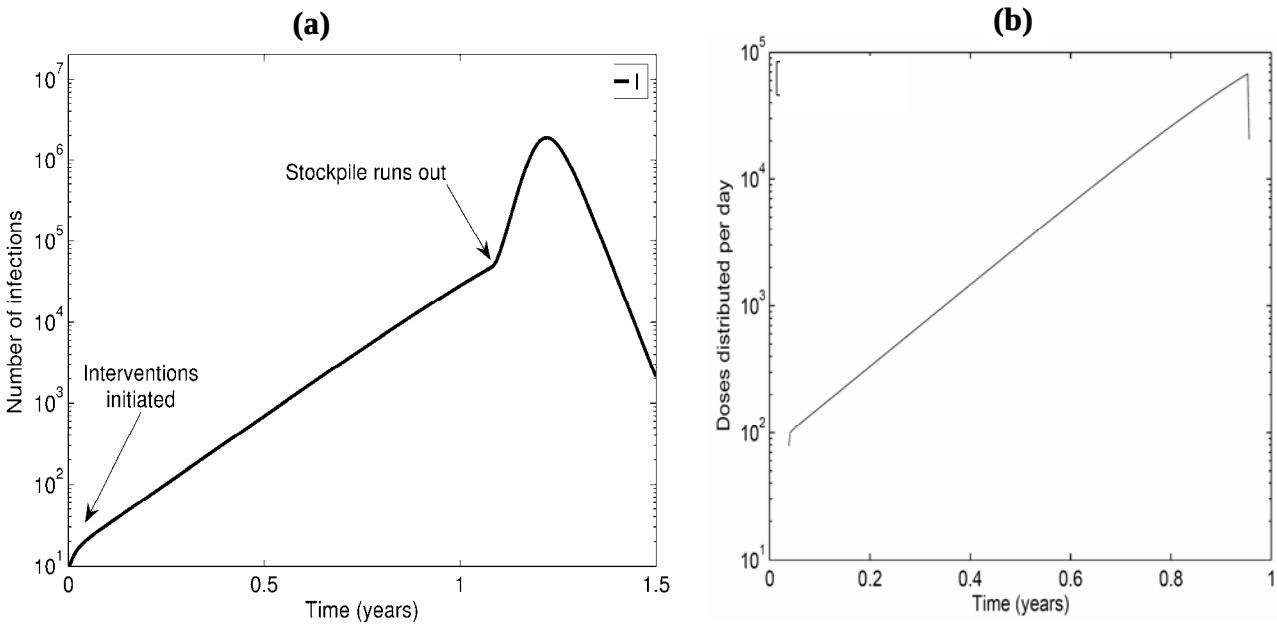

Figure 5.9

(a) A zoom of the epidemic curve presented in Figure 5.8(c), using a log scale on the vertical axis. The epidemic grows exponentially from the very beginning. The first kink shows the correction in growth due to implementation of the interventions. The point at which the stockpile runs out is clearly visible as a kink in the epidemic curve just before the 12 month mark.

(b) Doses distributed per day for the intervention shown in Figure 5.8(c).

Both graphs assume parameters as in Figure 5.8(c); in particular, $R_0 = 1.7$.

If the percentage of contacts traced and provided with prophylaxis is not maintained, the intervention will fail to delay the epidemic. The number of doses per day peaks at around 100,000 for a wide range of scenarios and interventions.

Protecting HCWs and essential services workers will be important during a pandemic. If the health system fails, other interventions such as contact tracing and provision of AVs for treatment and prophylaxis will be unsustainable.

Prophylaxis of HCWs and essential service people can be taken into account, at least partially, by including a constant drain on the AV stockpile. This method does not take into account the effect on dynamics from this intervention.

We assume that individuals spend half of their time taking prophylaxis and half of their time off work, based on a 6 week on, 6 week off rotation.

Table 5.2 is based on the 40% prophylaxis, 50% treatment scenario presented above, with R_0=1.7. With no intervention, the epidemic peaks after 0.32 years and the attack rate is 70%. As the number of persons (HCWs, essential services) provided with AVs increases the benefit of prophylaxis and treatment for the population as a whole is eroded. Providing a small group of HCWs (25,000) with prophylaxis has only a small effect on the delay to peak, reducing it from 1.22 years to 1.20 years. If all 1 million essential service workers in Australia were provided with AVs for prophylaxis, the stockpile would be used up rapidly for virtually no benefit.

Number of persons undergoing non-targeted protection (N_HCW)	Time to peak of epidemic (years)
0	1.22
25,000	1.20
250,000	0.95
1,000,000	0.49

Table 5.2 Time of the peak of the epidemic for different levels of prophylaxis distributed to HCWs**.** The provision of AVs to essential services brings the time to epidemic peak back towards baseline. If a small group of dedicated influenza workers (25,000-50,000) are provided with AVs then the time to epidemic peak can be kept above 1 year. If AVs are distributed on-mass to essential services, they will be largely wasted and provide very little benefit to the population as a whole. Without a constant depletion term, the epidemic peaks at 1.22 years. For baseline (no intervention) the peak is at 0.32 years.

Table 5.2 shows that it is possible to protect a small influenza taskforce and still have an effective intervention. A quick calculation [maximum doses per day from Figure 5.9(b) divided by 25,000] shows that the peak load on the 25,000 strong workforce would be delivering around 5 courses of AVs per day (a couple of families), which seems reasonable. For most of the time, the load would be an order of magnitude or two lower than this.

If however, AVs are provided indiscriminately, their potential to curtail an epidemic will be lost. It must be kept in mind that once the AV stockpile runs out, if the number of susceptibles in the community is still large (as it will be) then the epidemic will run its natural course. Little or no benefit will have been gained by protecting the million or so essential services workers for a couple of months.

The calculation for Table 5.2 is rather crude. A more dynamic and detailed calculation is presented in Section 6.2 where the number of HCWs requiring protection is calculated from the current number of infectives in the population. Table 5.2 simply demonstrates that with careful planning, the lifetime of the stockpile is not compromised by protecting a subset of the HCWs.

5.7. Targeting children for antiviral prophylaxis

In this section, we consider the effect of administering AVs for prophylaxis to school children using the stochastic household model. We assume that all school children at risk of infection are given AVs as prophylaxis, and remain on AVs if infected. The graphs in Figure 5.10 show the epidemic curves without intervention (red) and under this intervention (blue) in the $SEIR_H$ model with a flat infectiousness function. We see that this control measure is not sufficient to prevent major epidemics even with low values of R_0, although it does have a noticeable effect, that weakens as R_0 increases. If all individuals are given prophylaxis, rather than just school children, this is sufficient to eliminate infection for all three values of R_0.

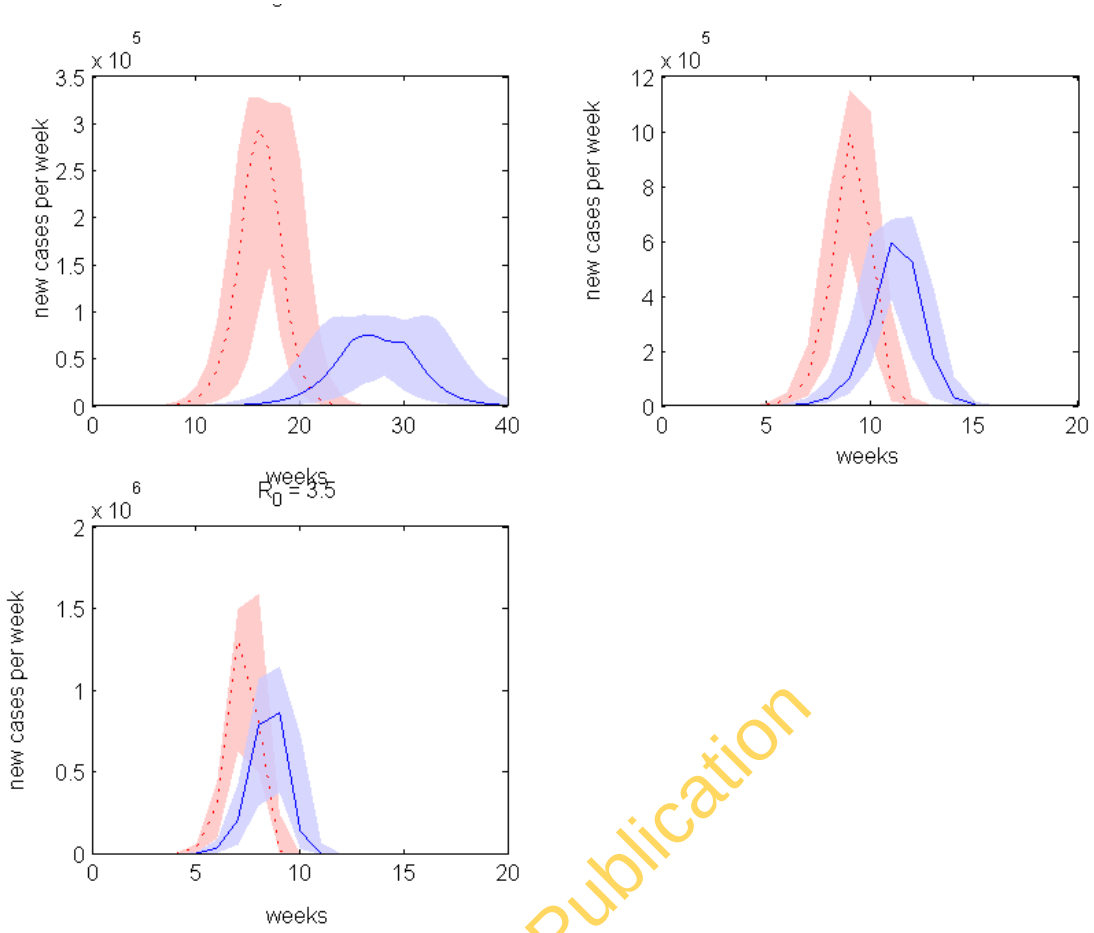

Figure 5.10 The effect of providing AVs as prophylaxis to all exposed school children. The graphs show the epidemic curve with no intervention (red dotted line), and with AVs provided to school children (blue solid line) in the $SEIR_H$ model with flat infectivity.

The effect of giving AVs to children for prophylaxis is also reflected by its effect on *R* as shown in Figure 4.18.

5.8. **Conclusions**

Using antiviral drugs for treatment

Use of antiviral drugs for treatment may be desirable if that prevents some serious illnesses and some mortality. However, such use of antiviral drugs has only a modest effect on reducing transmission. The exception is when other interventions have brought the reproduction number down to near 1. Then the additional reduction in transmission induced by the use of AVs for treatment can be substantial.

Using antiviral drugs for prophylaxis in the general population

The indiscriminate use of antiviral drugs for non-targeted prophylaxis will deplete the stockpile prematurely with minimal reduction in transmission of the infectious disease in the community.

On the other hand, use of antiviral drugs for prophylaxis that rapidly targets likely contacts of diagnosed cases can postpone the bulk of transmission in a local epidemic substantially. Using current estimates of effectiveness, the Australian stockpile is likely to be able to postpone the peak of a local epidemic for up to one year if $R_0 \leq 2$ and the distribution of AVs is able to rapidly target

approximately 50% of contacts. Broadly speaking, if 80% of contacts can be traced, a delay of a year is possible for $R_0 \leq 2.5$.

However a strategy of using AVs for prophylaxis that targets individuals who are likely to have been exposed requires drugs to be dispensed rapidly to community members in increasing quantities, to the extent that this strategy may be difficult to sustain.

5.9. Discussion

i. Limitations

The measures of effectiveness of AVs for reducing susceptibility and infectivity are estimated from data on strains of influenza that are currently circulating. Effectiveness with respect to a newly-emerged strain may be different. It is important to bear this in mind since the results on the use of AVs to reduce transmission are sensitive to the values of AV effectiveness parameters e_s, e_i and e_t.

It is also possible that strains of the virus that are resistant to AVs may emerge and reduce the effectiveness of the available antiviral drugs dramatically. The calculations presented here have not taken the possibility of the emergence of antiviral resistance into account. The impact of a strategy that relies heavily on the use of antiviral drugs for prophylaxis could be greatly reduced if antiviral resistance develops, if the resistant strain is also highly transmissible.

The feasibility of the timely use of AVs for prophylaxis decreases as R_0 increases, because the amount of contact tracing required becomes too onerous.

ii. Further work needed

It is necessary to design studies that are able to estimate the effectiveness of antiviral drugs against the emerged pandemic influenza virus during the early stages of a local epidemic. These studies must be simple so that they are feasible during the hectic early stages of the pandemic.

In our work we have not distinguished between different types of cases. Treatment may avert serious illness or even death. There is then a need to assess whether antiviral drugs should be used for treatment or prophylaxis, with respect to the incidence of severe illness or mortality.

We need to develop alternative strategies for the use of antiviral drugs in the event that the virus develops resistance to them.

6 THE ROLE OF HEALTH WORKERS

Without adequate protection, health care workers will be at high risk of infection if an emerged infectious disease has adverse health outcomes. It is essential to protect health care workers and their families, in the interest of maintaining a sustainable health care service and preventing HCWs from acting as a conduit for the transmission of the infection.

6.1. Extent to which protecting health care workers affects transmission

One way to examine the effect that protecting HCWs has on transmission is to look at its effect on R. Of particular interest is the question of whether $R<1$ can be achieved. Towards this end we present in Figure 6.1 contours where $R=1$, for scenarios in which HCWs are given different levels of protection. These contours are some of those shown in Figure 5.2. We see that, for $f < 0.5$, the intervention consisting of isolating diagnosed cases, as well as PPE and prophylactic use of antiviral drugs for HCWs provides the opportunity for preventing a major epidemic for a substantial range of R_0 values.

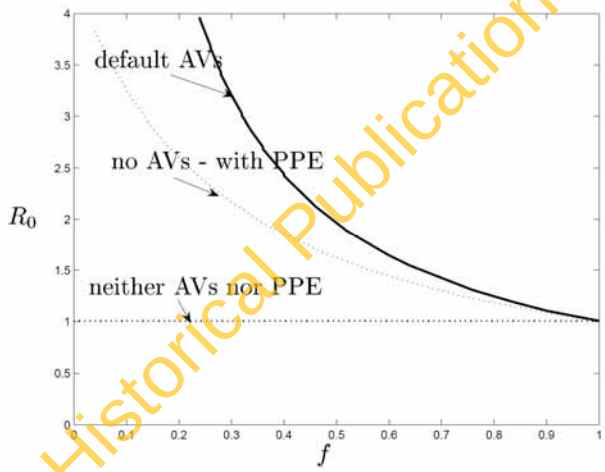

Figure 6.1 Contours of $R=1$ corresponding to different levels of protection for HCWs, over a range of values for R_0 and f. For points above a curves $R>1$, so there is a possibility of a major outbreak. For points below a curve $R<1$, so the infection will fade out.

To explain why protecting HCWs provides a greater opportunity for elimination, we present in Figure 6.2 the graphs of I_H, the proportion of all infectives over the first 4 generations that can be attributed to direct infection from a health care worker, for a range of R_0 values and some alternative interventions. The interventions considered are isolating cases following diagnosis, with f =0.8 achieved, and

(i) no additional intervention,

(ii) PPE for HCWs, and

(iii) default AV and PPE use for HCWs.

We see that when no protection is given to HCWs a substantial number of the infections are attributable to HCWs (top two curves in Figure 6.2). Specifically, after 4 generations without antiviral distribution or PPE to HCWs, and with R_0 in the range 1 to 4, about 30-40% of all infections arise from contacts with health care workers when f =0.6. This is a very large proportion of the infections, bearing in mind that HCWs are only 1% of the population. The infection rate by HCWs is

substantially reduced by the use of PPE for HCWs, and dissipates almost completely when HCWs are also given AVs for prophylaxis.

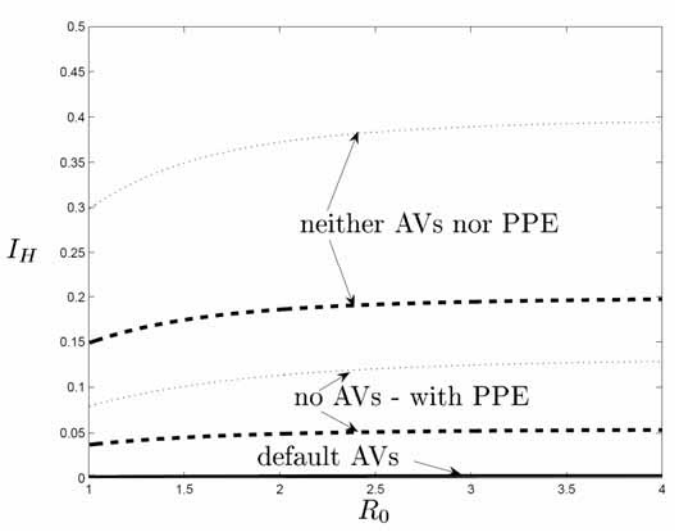

Figure 6.2 Graphs of I_H, the proportion of all infectives over the first 4 generations that can be attributed to direct infection from a health care worker, for a range of R_0 values.
Curves for $f = 0.8$ are shown by heavy dashed lines, and curves for $f = 0.6$ are shown by dotted lines
The outbreak begins with one initial case from the general population.
(Parameters: $p = 0.005$, $e_i = 0.275$, $e_s = 0.25$, $e_p = 0.23$.)

While the model used to create Figure 6.2 does not contain a household structure, such a high percentage of infections due to unprotected HCWs suggests that members of their households are at high risk of infection. Whether this remains true when HCWs are protected by PPE and AVs needs further investigation.

6.2. How many courses of antivirals are needed for health care workers

The role of health care workers (HCWs) will be an important one in several ways during a pandemic. During the early stages, in which elimination of the outbreak is likely to be attempted, various interventions will be needed and HCWs are likely to be involved and subject to exposure in most of these. Antivirals will need to be used for the prophylaxis of health care workers engaged in the implementation of these interventions.

In the early stages of the outbreak, the outbreak will be localised within a small number of regions in Australia. This makes it likely that only a relatively small number of health care workers will need to be taking prophylaxis initially, but that as the number of cases grows large, a greater fraction of the health care workforce will need to receive prophylaxis. Here we model this growth in the number of health care workers requiring prophylaxis in a simple way by assigning a set number of antiviral courses for health care workers' prophylaxis for each new infectious case.

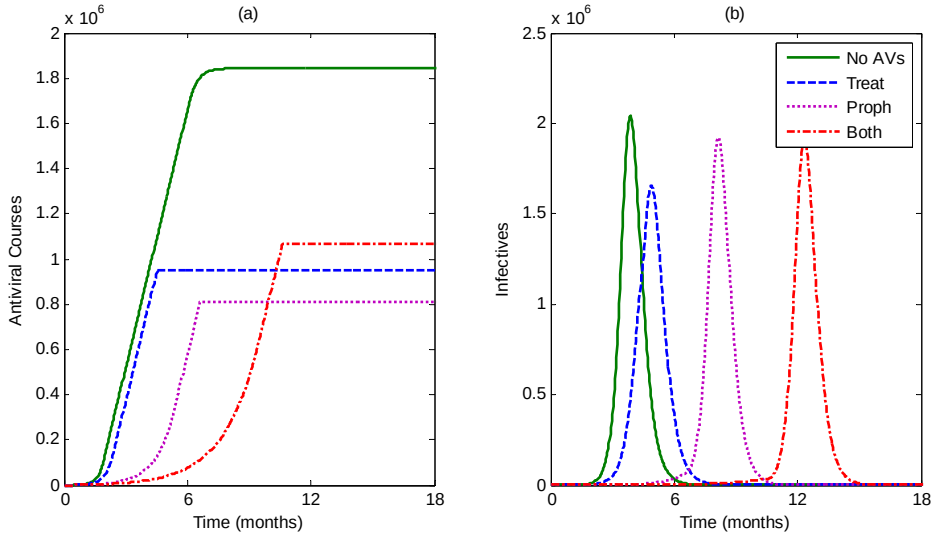

Figure 6.3 Effects of four strategies for targeted use of the AV stockpile for community members on (a) the cumulative use of AVs by HCWs over time and (b) the number of infectives over time for an epidemic with a 70% attack rate in the absence of intervention. The strategies are (i) no AV use, (ii) 50% of cases treated, (iii) 40% of patient contacts prophylaxed, and (iv) 50% of patients treated as well as 40% of patient contacts prophylaxed.

As an example, consider an epidemic which without intervention would lead to an attack rate of 70% and where for each new infective, 5 courses of antiviral drugs would need to be distributed to health care workers, up to the point at which half of the entire health care workforce is placed on prophylaxis (we describe this as a dynamic distribution of AVs). On the basis of these assumptions, the use of AVs by health care workers over the course of an epidemic can be calculated. If AVs are also used to treat a proportion of cases and to prophylax a proportion of case-contacts, then the number used by health care workers will change.

In Figure 6.3(a) we show the use of antiviral courses by HCWs over time for four different strategies of stockpile use, namely using AVs
(i) for HCW prophylaxis only,
(ii) for HCW prophylaxis and to treat 50% of cases,
(iii) for HCW prophylaxis and for prophylaxis of 40% of case contacts, and
(iv) for HCW prophylaxis, to treat 50% of cases and for prophylaxis of 40% of case contacts.

Figure 6.3(a) shows the number of infectives over time for each of these strategies. The amount of the stockpile remaining after 3, 6, 9 and 12 months for these strategies is presented in Table 6.1. These results were generated using the contact-tracing model depicted in Figure 5.7.

If the stockpile is used only to prophylax health care workers, then for this example more than half the stockpile remains after the epidemic has passed, but this has no effect on the course of the epidemic. If 50% of cases are also treated, then the stockpile runs out 4-5 months after the start of the epidemic, and the peak of the epidemic is smaller and delayed by about 1 month. If contact tracing is employed and 40% of case contacts are prophylaxed throughout the course of the epidemic, then the stockpile runs out between 6 and 7 months and the peak of the epidemic is delayed by more than 4 months. Finally, if both treatment and prophylaxis of cases are conducted in addition to protecting HCWs, then the stockpile will last for 10-11 months and the peak of the epidemic will be delayed by at least 8 months.

	No community use		*50% of cases treated*		*40% of case contacts prophylaxed*		*50% treatment and 40% prophylaxis*	
Time (months)	AVs left (mil)	AVs used for HCWs (mil)	AVs left (mil)	AVs used for HCWs (mil)	AVs left (mil)	AVs used for HCWs (mil)	AVs left (mil)	AVs used for HCWs (mil)
3	3.50	0.5	3.6	0.37	3.9	0.0220	3.97	0.0097
6	2.30	1.7	0	0.95	1.9	0.58	3.75	0.076
9	2.10	1.9	0	0.95	0	0.81	2.41	0.483
12	2.10	1.9	0	0.95	0	0.81	0	1.07

Table 6.1 Amount of the AV stockpile remaining, and the number of courses used to protect HCWs at 3, 6, 9 and 12 months after the start of the epidemic for the four strategies of community AV use described in the text

These results might appear counter-intuitive in the sense that by using AVs for community intervention, the number of courses required for HCWs is reduced. The reason for this is that the courses are being distributed to health care workers in proportion to the number of new infectious cases. Since the epidemic peak is delayed and reduced in size by community use for prophylaxis and treatment, there is less use of AVs over time than in the results presented in Table 5.2. A second factor is that the stockpile eventually runs out when used for community treatment and prophylaxis and after that point is no longer available to protect health care workers. This also has the effect of reducing the cumulative use of the stockpile for protection of health care workers.

These results assume that the community prophylaxis and treatment will continue to be used until the stockpile runs out. It would not be difficult to design a strategy that switched from this approach to one of maintaining services at a time that ensured enough courses of AVs remained to protect health care workers through the entire epidemic.

6.3. **Hospitalisations over time**

A second major impact of an emerged pandemic on the health care system will be the number of patients requiring hospitalisation. In particular, if the epidemic cannot be controlled, then there will be a period of time near the peak of the epidemic in which the health care system will have to cope with a large number of extra patients in need of hospitalisation.

The model used above can also calculate the number of cases requiring hospitalisation for the various antiviral strategies described above. Estimates of hospitalisation rates for an emerged pandemic vary considerably in the literature – as an example here, we consider the moderate assumption that 2% of cases will require hospitalisation, and that on average patients are hospitalised for 1 week. The hospitalisation rate is higher than that of Meltzer *et al.* (1999) to allow for the possibility that a future pandemic resembles the 1918 pandemic rather than the 1957 influenza pandemic. Those who become infected while on prophylaxis are assumed to have the same rate of hospitalisation and the same length of stay, although treatment with AVs is assumed to reduce the average stay in hospital from 7 to 5 days. Treatment is not assumed to reduce the rate of hospitalisation in this example.

In Figure 6.4, we graph the number of cases requiring hospitalisation over time for an epidemic that (without intervention) would produce (a) a 50% attack rate (R_0 = 1.4) and (b) a 70% attack rate (R_0 = 1.7), and with use of the antiviral stockpile as outlined in Section 6.2.

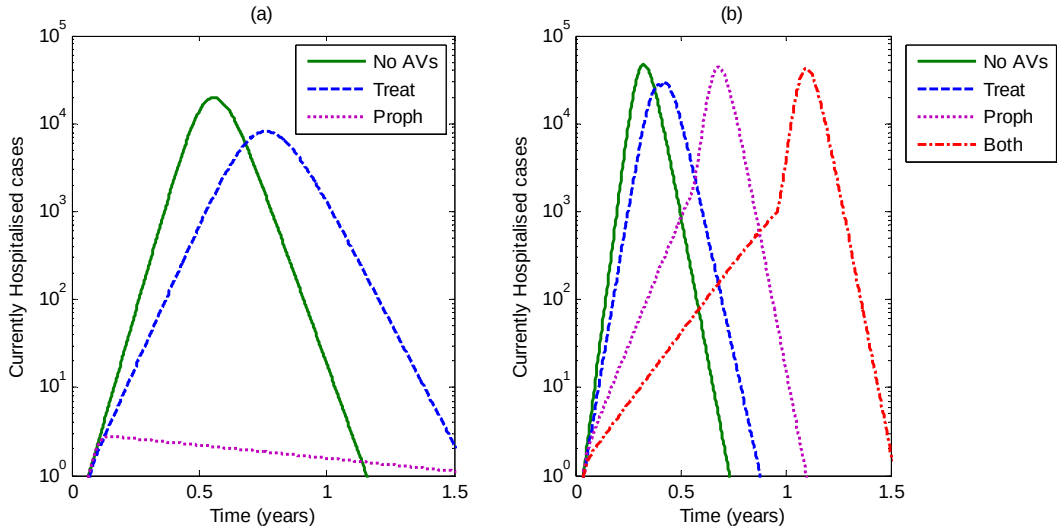

Figure 6.4 Cases in need of hospitalisation over time for a baseline attack rate of **(a)** 50%, and **(b)** 70%, for the four community AV-use strategies described in the text.

In this example we considered 10,000 currently hospitalised cases to be a threshold indicating a high demand on hospital beds, that might have to be met through alternative hospitalisation arrangements. In the case of a 50% attack rate, this threshold is crossed if AVs are not used for community care, but that with 50% of cases treated, the number of hospitalised cases peaks below 10,000 (see Table 6.1), while prophylaxis of 40% of case contacts halts the epidemic entirely, so that hospitalisations are comparatively negligible.

In the case of a 70% attack rate, none of these intervention strategies can prevent the number of hospitalisations from rising above 10,000. However, the peak number is reduced in the treatment only strategy, while prophylaxis can delay the time at which this threshold is crossed by several months. Details on the period of time over which hospitalisations exceed 10,000 cases, the peak number of cases requiring hospitalisation and the time of this peak are presented in Table 6.2, along with an estimate of the number of patients requiring an alternative to hospitalisation over the course of the epidemic. The latter figure is calculated by assuming that 10,000 is the maximum number of currently hospitalised influenza patients that the health care system can accommodate, and then counting any excess patients over this number.

Hosp. Length	Attack Rate	Intervention	Period of $>10^4$ cases (weeks)	Peak cases	Peak time (weeks)	Extra patients that need to be accommodated
7 days	50%	None	24.8-33.5	19,370	28.9	52,000
		50% Treated	Never	8,123	39.6	0
		40% given Prophylaxis	Never	Negligible	8.3	0
	70%	None	13.2-21.5	46,570	17	162,000
		50% Treated	17.1-26.2	29,520	57.2	126,000
		40% given Prophylaxis	31.8-40	43,930	35.5	162,000
		50% Treated & 40% given Prophylaxis	53.4-61.8	42,570	57.2	152,000

Table 6.2 Period in which more than 10,000 cases are in need of hospitalisation, timing of the peak number of such cases, the peak number of cases and an estimation of the number of additional patients over this period of time that will be in need of hospital treatment.

6.4. Conclusions

Transmission by health care workers

A substantial proportion of infections will be due to HCWs if they are not protected by PPE and AVs. The proportion infected by HCWs is reduced substantially by the use of PPE and prophylactic use of AVs for HCWs.

Number of courses of antiviral drugs needed

If AVs are only used dynamically to prophylax health care workers and not for interventions in the community, then our models suggest that the stockpile will last over the course of the first wave of an epidemic. However, this will not alter the course of the epidemic.

If AVs are also used to prevent community transmission through the use of prophylaxis of contacts of new infectious cases, the stockpile will run out before the peak of the epidemic if elimination is unsuccessful. However, the peak of the epidemic can be delayed through this strategy for several months, which may facilitate wide-spread distribution of a vaccine before the peak of the epidemic.

Hospitalisations

The number of cases requiring hospitalisation rises above 10,000 for a significant period of time for an epidemic with a high attack rate. The peak number of cases requiring hospitalisation can be reduced through treatment of infectious cases, and delayed through prophylaxis of case contacts.

6.5. Discussion

i. Limitations

The models used here take a very simplified view of the health care workforce, without reference to its geographic distribution.
The calculations of the number of beds do not take into account the differing severity of the disease in hospitalised patients, and the requirements for different levels of hospital care.
The calculations in this section consider only interventions based on the use of anti-viral drugs.

ii. Further work needed

The healthcare workforce has a much larger percentage of female than male workers and in view of family commitments, this may imply that the workforce may suffer from more absences in a pandemic due to the need to care for children, particularly if there is a high attack rate amongst children. The effect of this issue in the broader framework of work attendance during a pandemic, and the issue of compliance with taking of antiviral drugs will be explored as part of the NHMRC funded project which is currently under way.

Alternatives to hospitalisation have been considered here in an indirect way by estimating the number of extra beds that will need to be found over the course of a pandemic. However, the timing and form of these alternatives will have some impact on the number of antiviral courses required for HCWs, and these two issues may need to be considered in more detail.

The time-specific demand for prophylactic AVs to maintain the health care services should be addressed in more detail, and with reference to the State/Territory services and the demand from other essential service providers.

7 DISCUSSION

We conclude with some comments on the main results, covering reasons for these results and their sensitivity to underlying assumptions. We also point out issues that have not yet been addressed adequately.

7.1. Border control

In the event that transmission gathers momentum in the source region, our calculations indicate that border screening is likely to delay an Australian epidemic only by several days (rather than several weeks or a few months), unless the number of travelers from the source region entering Australia is reduced to virtually zero or quarantining of travelers arriving from the source region is virtually 100% effective. Our calculations assume that we can achieve the same R in Australia as is achieved in the source region with assistance from the international community. The main drivers of the results on the likely delay are

i. the proportion of recently infected travelers who are pre-symptomatic, and
ii. the exponential growth of infections in the source region (that typically occurs in epidemics).

The results on the likely delay are quite robust to plausible alternative assumptions, unless we can achieve and sustain $R<1$ in Australia. In the latter event a local epidemic would fade out, repeatedly when there are multiple importations. The exponential growth of infections in the source region (when $R>1$) means that after a while the mean number of recently-infected individuals who arrive during the pre-symptomatic stage of their infection increases rapidly and any feasible level of border control is unlikely keep all infected individuals out for long.

Border control is only useful for preventing disease entry, and provides very little further benefit once an epidemic has gathered widespread momentum within Australia. Once there is widespread transmission within Australia, its exponential growth will contribute far more cases than will transmission chains from new importations.

7.2. Limiting transmission

Some interventions implemented in isolation were found to have a modest effect on reducing transmission, by which we mean (roughly) that they cause a substantial reduction in the number of eventual cases and a lower epidemic curve when R is 1.5 but have little effect when $R=2.5$ or larger. They can still play a substantial role in the overall control if other interventions, such as personal infection control and distancing, are able to bring the effective reproduction number close to 1.

Isolating individuals as soon as possible after diagnosis was found to have a modest effect on reducing transmission, particularly under the assumption of a peaked infectiousness function. This result is sensitive to the assumption that the potential for infecting others prior to becoming symptomatic is substantial. Evidence suggests that this is likely for currently circulating strains of the influenza virus, but it may not be the case for a newly emerged influenza virus. Ferguson *et al.* (2005) and Longini *et al.* (2005) assume that infectiousness begins after becoming symptomatic. The factor by which isolating cases reduces R is sensitive to the shape of the infectiousness function (flat or peaked), but it is not sensitive to the magnitude of R_0. The reason why isolating cases has a modest effect stems from the fact that, in practice, an influenza case is likely to present after a considerable part of their potential to infect others has passed.

Personal infection control and distancing measures such as wearing a P2 mask, frequently washing hands and avoiding unnecessary close contacts, have considerable potential to reduce transmission. Not only can they reduce the eventual attack rate, but they also lower the epidemic curve substantially

and delay the peak of the epidemic. As a consequence, the epidemic is less disruptive under this control measure. However, this intervention relies on the co-operation of individuals. Community members are likely to comply with requests to practice personal infection control and distancing if severe illness or death is seen to be likely for the emerged pandemic influenza, but compliance is likely to be low if individuals think that the health risk from pandemic influenza is similar to that from currently circulating influenza. Personal infection control and distancing can be very effective because the transmission rate is reduced by both susceptible and infected individuals seeking to avoid infectious contacts.

Closing schools was found to have a modest effect on reducing transmission. This conclusion goes against the expectation of some experts, because children are thought to be infectious longer and their behaviour and hygiene suggests they play a major role in the transmission. However, this perception of children's higher susceptibility and infectivity does not seem to translate to transmission at school being a major driver of community transmission. The modest effect of closing schools is found for choices of parameters values that are consistent with available data on influenza attack rates of children relative to adults from past pandemics, even when we allow for plausible rates of unobserved asymptomatic infections. We should note, however, that closing schools does assist in reducing the attack rate in school children, and so this measure may play a role in helping to protect school children – particularly if they were unwilling to adopt personal infection control measures.

The effect of closing non-essential workplaces depends on the number of individuals that modify their behaviour. Per individual, the effect is less than that of closing schools, because adults spread less infection than children, but there are many more adults than school children, so the overall effect may be greater. If all children stay home from school and a large proportion of adults stay home from work, there is the potential to eliminate disease spread for low values of the reproduction number.

The conclusion that restricting travel within Australia provides limited scope for delaying the spread of infection from one capital to another when $R>1$ is, like the results on border control, quite robust. Once the incidence of infection starts its exponential growth in one capital, travel from there has to virtually stop completely to prevent geographic spread of the infection. However, there does seem scope for remote areas to be able to delay importation of the infection into their area by carefully monitored travel restrictions into their area.

To reduce transmission substantially, quarantining households has to be timely. Then household members who may be infected are prevented from circulating in the community prior to onset of symptoms. In other words, quarantining prevents some infected individuals from circulating in the community earlier than is possible by isolating them once they become a diagnosed case. The cost is that some individuals will be quarantined unnecessarily. Compliance may be a problem, but can potentially be boosted by offering quarantined household members AVs to protect them from infections/severe illness. Timely quarantining of affected households that are large is particularly effective.

Timely use of AVs for prophylaxis of individuals likely to be, or to have been, exposed to an infected person reduces transmission in a similar way to personal infection control and distancing. That is, there is a reduced chance of being infected and, when infected, there is a reduced potential to infect others. Therefore, just like personal distancing, timely use of AVs for prophylaxis has the potential to reduce transmission substantially and hence delay the peak of the epidemic. However, in contrast to personal distancing, targeted use of AVs for prophylaxis has some practical difficulties. These include:

i. Many courses of AVs will be dispensed unnecessarily.
ii. It takes time to identify, reach and dispense AVs to potentially exposed community members.

Timely dispensing of AVs for prophylaxis is therefore difficult to achieve in practice. Dispensing AVs for prophylaxis to an individual who is already infected reduces transmission only by lowering that person's infectivity, from the time when AVs are administered.

Our assessment of the reduction in transmission resulting from using AVs for targeted prophylaxis is reliant on estimates of effectiveness made from studies on circulating influenza. The effectiveness against a newly emerged influenza virus may be different.

Combining the interventions

The above comments often relate to interventions used singly, which enables us to compare their effects relative to each other. In practice interventions will be used in combination. A useful way to judge how effective the interventions are in combination is to estimate their effect on the reproduction number and, in particular, seeing if the combination can bring the effective reproduction number below 1. The question of whether $R<1$ can be achieved depends critically on the value of R_0. One must therefore face the possibility that the newly emerged pandemic influenza is very infectious, quite different from circulating influenza and that antecedent immunity is minimal. In other words, the baseline R_0 may be higher than we have assumed. For a crude calculation, let us suppose that 'isolating diagnosed cases' and 'personal infection control and distancing' are able to reduce R by a factor of 0.8 and 0.5, respectively. Further, suppose that 'household quarantining' and 'use of AVs for prophylaxis' are each able to reduce R by a further factor of 0.5. The factor of 0.5 for these two interventions is more speculative since these interventions are not independent of 'isolating diagnosed cases' and they depend on how quickly households are quarantined and targeted AVs are dispensed. Achieving these fractional reductions for the four interventions simultaneously in the field would be challenging. Combining these interventions gives an effective reproduction number of $0.8\times0.5\times0.5\times0.5\times R_0 = 0.1R_0$. Setting this to 1 suggests that we can obtain an effective R below 1 even if R_0 is as large as about 10. If this could be achieved the infection can be eliminated with probability 1 if that combination of interventions is sustained until fade-out occurs.

7.3. The importance of rapid responses

Our calculations indicate that for every intervention the benefit is greatest, and often considerable, when it is introduced as early as possible. Indeed, upon identification of the first Australian case, we should respond as quickly as possible with every feasible intervention, in the affected Australian location. A big response at the very beginning maximises the chance of achieving elimination of a new outbreak, especially so because the available resources can be focused on relatively few cases and their contacts. A big effort at the start is also a good way to delay the peak of the local epidemic if elimination can not be sustained.

If border control is introduced this should also occur early, because its value once the local epidemic has gathered momentum is minimal. In particular, if mass quarantine (or partial home quarantine) of arriving passengers is contemplated, then this should occur at the beginning. It serves little point once the local epidemic has gathered momentum with little prospect of elimination.

Rapid response means that the period for which we need to keep R below 1, to eliminate an outbreak, is shorter. A shorter period of intervention also means that the drain on the AV stockpile is less.

7.4. Using the AV stockpile

Non-targeted use of AVs for prophylaxis reduces transmission minimally, and is therefore wasteful. However, there is a compelling case for using AVs liberally (but targeted) at the very beginning. The initial response should include treating every case reached within 48 hours of onset of symptoms with AVs and using AVs liberally for timely prophylaxis of any individual who was potentially exposed to an infectious individual, or is likely to be so exposed. This is justified by the fact that the liberal use of AVs for treatment and targeted prophylaxis at the start

i. provides treatment to all early cases and allows us to assess AV effectiveness for treatment,

ii. improves the chance of achieving early elimination, because targeted prophylactic use of AV drugs can reduce transmission substantially, if the targeted dispensing of drugs is timely,
iii. helps to delay the peak of the local epidemic, should early elimination fail,
iv. will not make a large dent in the AV stockpile, if reviewed after a nominated number of cases or affected households, and
v. provides the opportunity to estimate the effectiveness of AVs to reduce transmission and severity of illness for the newly emerged pandemic influenza.

The last of these is crucial for making objective decisions about the strategic use of the remaining stockpile.

7.5. What data should be collected during the early stages of a pandemic?

The results in this report rely on parameter values that are estimated from data on past pandemic influenza or using data from studies of currently circulating strains of influenza. Characteristics, such as the reproduction number, the mean duration of the incubation period and the effectiveness of AVs, may be quite different for a newly emerged strain of influenza. Some of our results are sensitive to these parameter values. For example the total effort required to eliminate the infection would be much greater, and more difficult to achieve, if R_0 is much larger than the values used in our calculations. It is therefore necessary to estimate these parameters afresh using data from the early stages of a local epidemic. Estimates of the effectiveness of AVs for treatment and prophylaxis are particularly crucial because of the limited supply of these drugs.

Collecting data during the early stages of a local epidemic requires careful planning because the response teams will be extremely busy trying to contain the outbreak. Data collection must be made simple, kept to a minimum and seen to be vital. The aims are to estimate parameters needed for strategic planning, to assess the effectiveness of interventions against the new virus and to determine if the initial liberal use of AVs for treatment and targeted prophylaxis is sustainable.

A full analysis of data requirements is yet to be undertaken. However, with the goal of

i. estimating central transmission characteristics of the newly emerged pandemic influenza,
ii. estimating effectiveness measures for antiviral drugs,
iii. assessing the effectiveness of some interventions, and
iv. determining how sustainable the initial use of AVs is,

collecting data on the first 500 affected households seems an excellent target. Households seem the ideal unit for data collection, as such data are required to estimate the effectiveness of household quarantining and the effectiveness of AVs to reduce infectivity. The number of courses of AVs used for treatment, targeted prophylaxis of plausible contacts and prophylaxis of health care and other essential workers should also be monitored over this time. Models can then be used to project the course of the epidemic and the corresponding use of AVs, and provide an objective basis for decisions about the management of the AV stockpile.

7.6. What would happen if R_0 is much larger?

We can not know with any certainty what the value of R_0 will be. The illustrative calculations in this report have generally used values in the range 1.5–3.5. Let us take a more pessimistic scenario and see what might happen in the event that everyone is highly susceptible and R_0 large. Suppose that R_0 for the newly emerged pandemic influenza is 10, say, and the latent, incubation and infectious periods are similar to those of currently circulating influenza strains. What would happen?

The first point to make is that for this scenario the attempt by WHO to eliminate the newly emerged pandemic influenza in the source region is highly likely to fail. The epidemic will grow at an amazing rate in the source region and the infection is likely to be imported into Australia within a fortnight.

Consider the growth of such an epidemic in terms of generations, where a generation occurs about 3 days after the previous generation (because of the short latent and infectious periods). A crude calculation for the first few generations, which ignores the depletion of susceptible individuals, is as follows:

Generation	1	2	3	4	5	6	7
Approx day	0	3	6	9	12	15	18
Cases	1	10	100	1000	10,000	100,000	1,000,000

In the absence of interventions an epidemic like this would infect virtually everyone in the location within a month. This is also evident from Figure 2.2, where the depletion of susceptibles is allowed for. The same is true for any infectious disease with such a large basic reproduction number. For example, in some populations measles is thought to have a value of R_0 near 15. A similarly dramatic epidemic would happen if measles were initiated in a *fully susceptible population*, with two differences. First, incidences in successive generations would rise even more rapidly. Second, generations would be more separated in calendar time, because the latent and infectious periods are longer for measles. The generation interval for measles is about 14 days.

The results about the *relative* effectiveness of interventions in this report have application to the R_0 = 10 scenario, provided the progression characteristics of the infection in an infected individual are similar to those we have assumed in the report. For example, with the peaked infectiousness function, isolating diagnosed individuals 1–2 days post symptoms could reduce the total infectivity of an infective by a modest 20%. By itself this will reduce R by a factor of 0.8 to 8. This has a minimal effect on the course of the epidemic. Personal infection control and avoiding exposure continues to have more potential to reduce R. For example, with $\lambda_S = \lambda_I = 0.7$ personal distancing would reduce R by a factor $\lambda_S \times \lambda_I = 0.49$ to about 5. In absolute terms, this will not alter the course of the epidemic a great deal either, see Figure 2.2, but in terms of contributing towards bringing R down to 1 personal distancing clearly has more potential than isolating diagnosed cases. Similarly the results for other interventions continue to apply in terms of the factor by which they reduce R. However, it is only when R is brought down to the range 1 to 3, by a combination of interventions, that we see an appreciable effect on the dynamics of the epidemic, i.e. the eventual attack rate and a flatter, delayed epidemic. The closer R is to 1, the bigger the effect.

A major consequence of the observation that interventions do not alter the dynamics of an epidemic a great deal until they, in combination, bring R close to 1 is that the use of antiviral drugs for prophylaxis of traced contacts is justified only if such use brings R close to, or below, 1. Current calculations suggest that the use of antiviral drugs for prophylaxis of traced contacts is not a good strategy for using the stockpile if $R_0 \geq 4$.

7.7. **Future work**

There are some important issues that can be addressed more comprehensively than the timeline has permitted. These include:

1. A more comprehensive analysis of the best way to utilize the AV stockpile. Specifically, one crucial issue is to seek guidance on the choice of alternative strategies for the use of AVs in the event that AV resistance develops.
2. An assessment of how well the health care sector can cope, by modeling the dynamics of infection among health care workers, allowing infected health care workers to be infected, have time away from work to recover and then return to work.
3. Incorporating the capacity of jurisdictions to respond into the calculations.

Some of these are under current investigation.

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REFERENCES

1. Addy CL, Longini IM, Haber M (1991). A generalized stochastic model for the analysis of infectious disease final size data. *Biometrics* **47**, 961-974.
2. Anderson RM, May RM (1991). *Infectious Diseases in Humans: Dynamics and Control*. Oxford University Press.
3. Athreya KB, Ney PE (1972). *Branching Processes*. New York-Heidelberg: Springer-Verlag.
4. Australian Bureau of Transport and Regional Economics. Australian Domestic Airline Activity. Aviation Statistics Domestic Monthly 106 October 2005 Available from: http://www.btre.gov.au/statistics/aviation/domestic.aspx
5. Bailey NTJ (1975). *The Mathematical Theory of Infectious Diseases and its Application*. London: Griffin.
6. Becker NG, Glass K, Li Z, Aldis G (2005). Controlling emerging infectious diseases like SARS. *Mathematical Biosciences* **193**, 205-221.
7. Becker NG, Glass K (2005). The impact of imported infection. (In press, as a peer-reviewed chapter in a book.)
8. Crosby AW Jr (1976). *Epidemic and Peace, 1918*. Connecticut: Greenwood Press.
9. Davis LE, Caldwell GG, Lynch RE, Bailey RE, Chin TD (1970). Hong Kong influenza: the epidemiologic features of a high school family study analyzed and compared with a similar study during the 1957 Asian influenza epidemic *American Journal of Epidemiology* **92**, 240-247.
10. Day T, Park A, Madras N, Gumel A, Jianhong W (2006). When is quarantine a useful control strategy for emerging infectious diseases? *American Journal of Epidemiology* **163**, 479-485.
11. Edmunds, WJ, O'Callaghan, CJ, Nokes, DJ (1997). Who mixes with Whom? A Method to Determine the Contact Patterns of Adults That May Lead to the Spread of Airborne Infections. *Proceedings: Biological Sciences* **264**, 949-957.
12. Elveback LR, Fox JP, Ackerman E, Langworthy A, Boyd M, Gatewood L (1976). An Influenza simulation model for immunization studies. *American Journal of Epidemiology* **103**, 152-165.
13. Ferguson NM, Cummings DAT, Cauchemez S, Fraser C, Riley S, Meeyai A, Iamsirithaworn S, Burke DS (2005). Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature* **437**, 209-214.
14. Fraser C, Riley S, Anderson RM, Ferguson NM (2004). Factors that make an infectious disease outbreak controllable. *Proceedings of the National Academy of Science* **101**, 6146–6151.
15. Fox JP, Hall CE, Cooney MK, Foy HM (1982). Influenza virus infections in Seattle families, 1975-1979. I. Study design, methods and the occurrence of infections by time and age. *American Journal of Epidemiology* **116**, 212-227.
16. Gamage B, Moore D, Copes R, Yassi A, Bryce E (2005). Protecting health care workers from SARS and other respiratory pathogens: a review of the infection control literature. *American Journal of Infection Control* **33**, 114-121.
17. Gani R, Hughes H, Fleming D, Griffin T, Medlock J, Leach S (2005). Potential impact of antiviral drug use during influenza pandemic. *Emerging Infectious Diseases* **11**, 1355-1362.
18. Glass K, Becker NG (2005). Evaluation of measures to reduce international spread of SARS. *Epidemiology and Infection* (in press).
19. Green LE, Medley GF (2002). Mathematical modelling of the foot and mouth disease epidemic of 2001: Strengths and weaknesses. *Research in Veterinary Science* **73**, 201-205.

20. Hayden FG, Fritz R, Lobo MC, Alvord W, Strober W, Straus SE (1998). Local and systemic cytokine responses during experimental human influenza A virus infection. Relation to symptom formation and host defense. *Journal of Clinical Investigation.* **101**, 643-649.

21. Hayden FG, Treanor JJ, Fritz RS, Lobo M, Betts RF, Miller M, Kinnersley N, Mills RG, Ward P, Straus SE (1999). Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza. *Journal of the American Medical Association* **282**, 1240-1246.

22. Hayden RG, Atmar RL, Schilling M, Johnson C, Poretz D, Paar D, Huson L, Ward P, Mills RG (1999) Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *New England Journal of Medicine* **341**, 1335-1343.

23. Hayden FG, Treanor JJ, Betts RF, Lobo M, Esinhart JD, Hussey EK (1996) Safety and efficacy of the neuraminidase inhibitor GG167 in experimental human influenza. *Journal of the American Medical Association* **275**, 295-299.

24. Jordan WS Jr, Denny FW Jr, Badger GF, Curtiss C, Dingle JH, Oseasohn R, *et al.* (1958). A study of illness in a group of Cleveland families, XVII. The occurrence of Asian influenza. *American Journal of Hygiene* **68**, 190-212.

25. King GE, Markowitz LE, Patriarca PA, Dales LG (1991). The clinical efficacy of measles-vaccine during the 1990 measles epidemic. *Pediatric Infectious Disease Journal* **10**, 883-888.

26. Loeb M, McGeer A, Henry B, Ofner M, Rose D, Hlywka T, Levie J, McQueen J, Smith S, Moss L, Smith A, Green K, Walter SD (2004). SARS among critical care nurses, Toronto. *Emerging Infectious Diseases* **10**, 251-255.

27. Longini IM, Halloran ME, Nizam A, Yang Y (2004). Containing pandemic influenza with antiviral agents. *American Journal of Epidemiology* **159**, 623-633.

28. Longini IM, Koopman J (1982). Household and community transmission parameters from final distributions of infections in households. *Biometrics* **38**, 115-126.

29. Longini IM, Nizam A, Xu S, Ungchusak K, Hanshaoworakul W, Cummings DAT, Halloran ME (2005). Containing pandemic influenza at the source. *Science* **309,** 1083-1087.

30. Mantle J, Tyrrell DA (1973). An epidemic of influenza on Tristan da Cunha. *Journal of Hygiene* (*London*) **71**, 89-95.

31. McCracken K, Curson P (2003). Flu downunder: a demographic and geographical analysis of the 1919 epidemic in Sydney, Australia. Pages 110–131 in *The Spanish Influenza Pandemic of 1918–19.* Phillips H and Killingray D (Eds). Routledge, London, 357p.

32. Meltzer MI, Cox NJ, Fukuda K. (1999). Modeling the economic impact of pandemic influenza in the United States: Implications for setting priorities for intervention. *Emerging Infectious Diseases.* **5**,659-671.

33. Mills CE, Robins JM, Lipsitch M (2004). Transmissibility of 1918 pandemic influenza. *Nature* **432**, 904-906.

34. Monto AS, Koopman JS, Longini IM (1985). Tecumseh study of illness:XIII, Influenza infection and disease, 1976-1981. *American Journal of Epidemiology* **121**, 811-822.

35. Nguyen-Van-Tam JS, Hampson AW (2003). The epidemiology and clinical impact of pandemic influenza. *Vaccine* **21**, 1762-1768.

36. O'Neill PD, Balding DJ, Becker NG, Eerola M, Mollison D (2000). Analyses of infectious disease data from household outbreaks by Markov chain Monte Carlo methods. *Applied Statistics* **49**, 517-542.

37. Ramsay M, Gay N, Miller E, Rush M, White J, Morgan-Capner P (1994). The epidemiology of measles in England and Wales: rationale for the 1994 national vaccination campaign. *Commun Dis Rep* **4**, R141-6.

38. Riley S, Fraser C, Donnelly CA, Ghani AC, Abu-Raddad LJ, Hedley AJ, Leung GM, Ho L-M, Lam T-H, Thach TQ *et al*. Transmission dynamics of the etiological agent of SARS in Hong Kong: Impact of Public Health Interventions, *Science* **300**, 1961-1966.
39. Roberts MG, Tobias MI (2000). Predicting and preventing measles epidemics in New Zealand: Application of a mathematical model. *Epidemiology and Infection* **124**, 279-287.
40. Samaan G, Patel M, Spencer J, Roberts L (2004). Border screening for SARS in Australia : what has been learnt? *Medical Journal of Australia* **180**, 220–223.
41. Spicer CC, Lawrence CJ (1984). Epidemic influenza in Greater London. *Journal of Hygiene* (*London*) **93**, 105-112.
42. Tourism Victoria. Domestic Visitation to Regions of Victoria year ending September 1999-2005 . 2005 Available from: http://www.tourism.vic.gov.au/images/assets/All_PDFs/research/dec05/domestic-visitation-to-regions-of-victoria-year-ending-sept%201999-2005.pdf
43. Tourism New South Wales. Travel to Sydney Year ended September 2005. Available from: http://corporate.tourism.nsw.gov.au/corporatelive/downloads/research/sydney%20sep%202005.pdf
44. Treanor JJ, Hayden FG, Vrooman PS, Barbarash R, Bettis R, Riff D, Singh S, Kinnersley N,Ward P, Mills RG (2000). Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza. *Journal of the American Medical Association* **283**, 1016-1024.
45. Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K (2003). Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. *Health Technology Assessment* **7**, 1-170.
46. Welliver R, Monto AS, Carewicz O, Schatteman E, Hassman M, Hedrick J, Jackson HC, Huson L, Ward P,Oxford JS (2001). Effectiveness of oseltamivir in preventing influenza in household contacts. *Journal of the American Medical Association* **285**, 748-856.
47. WHO Writing Group (2006). Nonpharmaceutical interventions for pandemic influenza, international measures. *Emerging Infectious Diseases* **12**, 81–87
48. WHO Writing Group (2006). Nonpharmaceutical interventions for pandemic influenza, national and community measures. *Emerging Infectious Diseases* **12**, 88-94.
49. Wilder-Smith A, Goh KT, Paton NI. (2004) Experience of severe acute respiratory syndrome in Singapore: importation of cases, and defense strategies at the airport. *Journal of Travel Medicine* **10**, 259–262.
50. Yen M-Y, Lin YE, Su I-J, Huang F-Y, Huang F-Y, Ho M-S, Chang S-C, Tan K-H, Chen K-T, Chang H, Liu Y-C, Loh C-H, Wang L-S, Lee C-H (2006). Using an integrated infection control strategy during outbreak control to minimize nosocomial infection of severe acute respiratory syndrome among healthcare workers. *Journal of Hospital Infection*, **62**, 195-199.

APPENDIX A – GLOSSARY OF TERMS

Antiviral drugs (AVs). Australia has a large stockpile of oseltamivir. Accordingly, in this report antiviral drugs refers mainly to oseltamivir and the effectiveness parameters used in calculations relate this drug.

Attack rate. The proportion of individuals infected. Unless specified otherwise it means the attack rate achieved by the end of the epidemic.

Baseline attack rate. The eventual attack rate achieved when there are no interventions.

Containment refers to the use of interventions to limit transmission, particularly during the early stages of the spread, with the aim of reducing the number of cases before a vaccine becomes available.

Delay distribution. The report expresses the effect of border control measures in terms of the delay from the time when the emergence of a pandemic strain of influenza has been declared, by WHO, until an Australian outbreak gathers momentum. This delay is random and, for brevity, its probability distribution is referred to as the delay distribution.

Deterministic model. These models ignore the chance element in transmission, so that each run of the model produces exactly the same outcome once you fix the parameter values.

Elimination refers to achieving complete fade-out of the infection from the local region.

Epidemic curve. Unless indicated otherwise, the epidemic curve refers to the graph, over calendar time, of the number of individuals who are infected but not yet removed (recovered or dead).

Eradication refers to achieving global fade-out of the infection.

Exponential growth occurs when a value increases by a multiplicative factor per unit of time. In contrast, linear growth occurs when a value increases by a constant per unit of time. For example, the series 1, 2, 4, 8, 16, 32, … is growing exponentially, whereas the series 1, 3, 5, 7, 9, 11, … is growing linearly.

Generation. Cases can be classified into generations, where the primary case(s) might make up Generation 1. All susceptible individuals who have an infectious contact with a case from Generation 1 become cases of Generation 2. Similarly for Generations 3, 4, etc. Working with generations is convenient when interest is in the reproduction number and the probability of an outbreak gathering momentum, but is less informative about the calendar-time dynamics of disease spread.

Incubation period. The time from infection until onset of symptoms.

Infectious contact. This is a contact made by an infectious individual that would lead to infection of the contacted person if the latter has no immunity and is not protected by other interventions, such as wearing a P2 mask.

Infectiousness function. The quantity that indicates how infectious an individual is as a function of the time since being infected.

Infectious period. The post infection period during which contact with the infected individual may lead to infection. The chance that infection occurs depends on the value of the infectiousness function at that time.

Latent period. The period from the time an individual is infected until the infectious period starts.

Pandemic influenza refers to a pandemic of a newly emerged strain of human influenza, as distinct from a global spread of *avian* influenza and world-wide spread of currently circulating human influenza strains.

Parameter. Any model constant that is unknown and needs to be estimated from data. Examples of parameters are R_0, the basic reproduction number, and θ, the probability that an individual avoids being infected by a specific infected household member during the course of the latter's infectious period.

Quarantine. Partial home quarantine is considered for arrivals from at-risk regions. We assume they are required to remain at home for two days, by which time they would be symptomatic if infected. Household members of such arrivals are free to mix with the wider community though, and are not quarantined until the arrival becomes symptomatic, at which point the entire household is isolated. We also consider quarantine of a household following the diagnosis of a household member. Household quarantine is continued until the household outbreak is over, but we permit partial compliance.

Reproduction number (R). When individuals are homogeneous and mix uniformly, the reproduction number is the mean number of infections generated during the infectious period of a single infective.

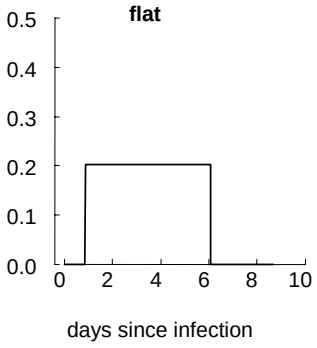
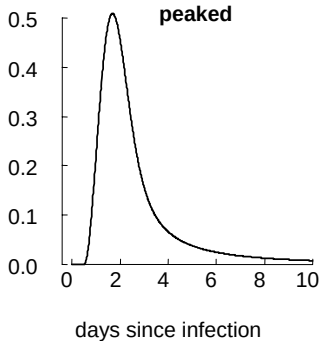
> **Basic reproduction number (R_0).** This is the reproduction number when there is no immunity, nor any deliberate intervention in disease transmission, i.e. when an infective meets only fully susceptible individuals.
>
> For influenza it may be that previous exposure to currently circulating strains, or vaccinations to protect against them, provides some immunity against a newly emerged strain. In this report the basic reproduction number is taken to be the R corresponding to a community in which there has been no exposure to the *emerged* strain, nor any immunisation by a vaccine developed for the *emerged* strain.
>
> **Effective reproduction number.** This is the reproduction number when interventions are in place, or a fraction of individuals are no longer susceptible.

Screening sensitivity is defined as the probability that border screening identifies an infected arriving passenger who is symptomatic.

Stochastic model. These models incorporate a chance element in transmission, so that each run of the model is likely to differ from the previous run even when the same parameter values are used

APPENDIX B – DEFAULT PARAMETER VALUES

A discussion of each choice of parameter values follows this table.

Description	Symbol	Default value	Plausible range	Special case(s)	
Basic reproduction number	R_0				
Low		1.5			
Medium		2.5			
High		3.5			
Influenza attack rate for calibrating α	**AR**			**1968**	**1957**
Adults		0.34	[0.2, 0.5]	0.37	0.23
School children		0.45	[0.35, 0.55]	0.42	0.46
Household escape parameter	θ				
R_0 = 1.5		0.82		0.84	0.84
R_0 = 2.5		0.74		0.76	0.76
R_0 = 3.5		0.69		0.71	0.71
Fraction of between-household mixing at work/school	f_S	0.6	[0.45, 0.75]		
Increased mixing between children at school	α	1.25		1.15	1.15
Between-household transmission rate	μ				
R_0 = 1.5		1.05		0.91	0.91
R_0 = 2.5		1.62		1.46	1.46
R_0 = 3.5		2.04		1.84	1.84
Prior immunity in adults	η_A	0		0	0.35
Prior immunity in children	η_C	0		0	0
Incubation period	D_A	2	[1.8, 2.2]		
Infectiousness function					
					
Number of travelers from an infected region into Australia on day *t*	k_t	200	[10, 400]		
Probability of detecting a symptomatic traveler at the border on departure	s_D	0.5	[0, 1]		
Probability of detecting a symptomatic traveler at the border on arrival	s_A	0.5	[0,1]		

Description	Symbol	Default value	Plausible range	Special case(s)
Relative infectivity while taking Oseltamivir e_i = *1: fully infectious,* e_i = *0: not infectious*	e_i	0.275	[0.15, 0.4]	
Relative infectivity while taking Oseltamivir as treatment e_t = 1: *fully infectious,* e_t = 0: *not infectious,*	e_t	0.7	[0.25,1.0]	
Relative susceptibility while taking Oseltamivir e_s = *1: fully susceptible,* e_s = *0: fully protected*	e_s	0.25	[0.1, 0.4]	
Relative susceptibility due to PPE e_p = *1: fully susceptible,* e_p = *0: fully protected*	e_p	0.23	[0.1, 0.8]	
Mean number of close contacts made by an infective individual	κ	18.3	[15,25]	
Probability that a general case infects their GP at presentation.	p	0.005	[0.001, 0.01]	
Fraction of their infectivity that an individual spends in the community before being isolated. (For a flat infectiousness function it is the fraction of the infectious period spent in the community before being isolated. In general it is the fraction of the area under the infectiousness function up to the time of isolation.)	f	0.8	[0.6, 1]	
Mean number of general public individuals infected by a case when there is no control.	m	see R_0		
Fraction of population that is school-aged	π_C	0.18		
Fraction of the population that are GPs	π_D	0.001		
Fraction of the population acting as influenza-dedicated health-workers	π_H	0.01		
Remaining individuals	π_A	0.809		

DISCUSSION OF DATA SOURCES

R_0 – basic reproduction number

[Longini *et al*. (2005): range for R_0 from **1.1** to **2.4**]
[Gani *et al*. (2005): range for R_0 from **1.28** to **2.0**]
[Ferguson *et al*. (2005: R_0 = **1.8**, range from **1.0** to **2.0**]
If we calibrate R_0 to influenza attack rates in western countries from past pandemics, we get values between 1.1 and 1.7, even assuming up to 20% prior immunity. However, these attack rates arise under conditions in which many controls were already in place. We consider three scenarios for R_0 – low (1.5), medium (2.5) and high (3.5).

Attack rate in adults and schoolchildren

Data from the 1957 and 1968-69 pandemics show different age-specific influenza attack rates [Davis *et al*. (1970)]. In 1957, there was a high attack rate in 10-20 year olds, while the attack rate in adults was much lower. In this pandemic, 85% of household outbreaks were initiated by a 5-19 year old. In 1968-69, the attack rate was fairly uniform across age groups, and between 50% and 55% of household outbreaks were initiated by a 5-19 year old.

θ – probability that an individual avoids being infected by a specific household member

O'Neill *et al*. (2000) estimate θ **= 0.84** with 99% credible bounds (read from figure) of **[0.78, 0.89].** The data used for these estimates come from a Tecumseh study over influenza epidemic seasons. Infection was serologically confirmed, so should include asymptomatic cases. The overall influenza attack rate in this data is fairly low, so different values of θ should be used for the higher values of R_0. Influenza attack rates in 1957 in Cleveland (47% of individuals and 90% of households infected) also suggest that θ should be relatively high.
Clearly θ should vary according to the assumed reproduction number, so three values are given.

f_s – proportion of between-household mixing that occurs during work/school hours

α – increased rate of mixing between children at school

μ – baseline mean number of cases an infective infects in the community

Adults: Assuming adults are awake for 16 hours/day (=112 hours/week), and have a working week of 40 hours. Assume they spend 3-7 hrs per day at home during the week, and 4-13 hrs per day at weekends, giving a total of 23-61 hrs/week. This would put f_s in the range 0.45-0.78.
School children: Assuming children are awake for 14 hours/day (=98/week), and have a school week of 32.5 hours. Assume they spend 4-6 hrs per day at home during the week, and 5-11hrs per day at weekends, giving a total of 30-52 hrs/week. This would put f_s in the range 0.48-0.71.
The adult/school children values are sufficiently similar that it seems reasonable that one value should be used for both. We adopt a default value of 0.6 with a plausible interval of [0.45,0.75].
Once f_s has been fixed, θ, μ and α are calculated to be consistent with R_0 and the attack rates.
Note that this is calibrated to the $SEIR_H$ model, which takes account of within-household mixing.. In the SEIR model, f_s and α should be adjusted as follows: f_s =0.35, α = 1.8, μ = 1.4, 2.33, 3.26 (R_0 = 1.5,2.5,3.5)

η_A, η_C – prior immunity in adults and children

In some situations, individuals may have some immunity to a pandemic strain arising from recent exposure to influenza. Our default scenario assumes that there is no prior immunity, but we also consider the case where relatively high immunity in adults leads to an age-specific influenza attack rate such as that seen in the 1957 pandemic [Davis *et al*. (1970)]. This is similar to assumptions used by Elveback *et al*. (1976).

D_A – days from infection until symptom onset (incubation period)

[Gani *et al*. (2005): D_A **= 4.5** days (2 days latent plus 2.5 days infectious and asymptomatic)]
[Longini *et al*. (2004): D_A **= 1.9** days]
[Ferguson *et al*. (2005): D_A **= 1.48** days, σ =0.47]
We assume the default value for D_A to be 48 hours.

Infectivity

[Gani *et al*. (2005): latent period of **2** days, infectious period of 4 days]
[Longini *et al*. (2004): latent period of **1.9** days, infectious period of 4.1 days]
[Ferguson *et al*. (2005): assumes infectivity function]
The flat infectivity function assumes a latent period of 1 day, and an infectious period of 5 days. The peaked infectivity function is taken from [Ferguson *et al*. (2005)].

e_i – relative infectivity when taking Oseltamivir
e_t – relative infectivity when taking Oseltamivir as treatment

[e_i = 1: no effect of antivirals on infectivity, e_i = 0.5: infectivity while on antivirals reduced by half, e_i = 0: not infectious at all when on antivirals]
[Hayden *et al*. (1999): e_i **= 0.29**, based on area under curve of viral titre]
[Treanor *et al*. (2000): e_i **= 1.0** - ie no effect on infectivity]
[Hayden *et al*. (1996): e_i **= 0.13** if 26 or 32 hrs after innoculation
e_i **= 0.25** if 50 hrs after innoculation]
[Longini *et al*. (2005): e_i **= 0.38**, Longini *et al*. (2004): e_i **= 0.2**]
We adopt the value e_i **= 0.275**.
In some models we also allow for antivirals to be less effective at reducing infectivity if they are taken after onset of symptoms. In these models, we adopt e_t **= 0.7**.

e_s – relative susceptibility while taking Oseltamivir

[e_s = 1: fully susceptible when on antivirals, e_s = 0.5: susceptibility while on antivirals reduced by half, e_s = 0: completely protected when on antivirals]
[Hayden *et al*. (1999): e_s **= 0.57**, based on prob. infection,
e_s **= 0.0**, based on prob. of shedding Note small n.]
[Hayden *et al*. (1996): e_s **= 0.18**, based on prob. infection.
e_s **= 0.04**, based on prob. shedding.]
[Longini *et al*. (2005) and Longini *et al*. (2004): e_s **= 0.7**]
[Hayden *et al*. (1999): e_s **= 0.50**, based on lab confirmed infection]
[Welliver *et al*. (2001): e_s **= 0.11**, lab. confirmed, post-exposure prophylaxis within 48 hours of symptom onset of a household member (index case not given antivirals)]
[Cochrane review of all Neuraminidase Inhibitors: e_s **= 0.26** (naturally occurring), e_s **= 0.4** (lab. confirmed)]
We adopt the value e_s **= 0.25**.

e_p – reduction in susceptibility due to personal protective equipment

[Loeb *et al*. (2004): e_p**=0.22**]
[Yen *et al*. (2006): e_p**=0.23**]
Both of these trials have P-values of around 0.02-0.03, which suggests that the 95% confidence intervals are wide. We assume e_p **= 0.23**.

κ - the mean number of close contacts made by an infective individual

[Edmunds *et al*. (1997): κ**= 18.3**]

***p* – probability that a general case infects a GP at presentation.**

Data suggest that health care professionals are more likely than general individuals to be infected during the influenza season [Gamage *et al.* (2005)]. If we assume that every infected individual consults a GP, there will be 300-400 consultations per 1000 individuals over the course of the pandemic. Australia has around 1-1.2 GPs per 1000 individuals, so this suggests that each GP will have an average of 250-400 consultations from individuals infected with pandemic flu.

We calculate that:

if $p = 0.001$ GPs have a 22-33% chance of being infected by a patient

if $p = 0.01$, GPs have a 92-98% chance of being infected by a patient

However, the assumption that every infected individual consults their GP is probably unrealistic. The UK pandemic plan assumes there will be 50 consultations per 1000 individuals over the course of the pandemic (based on data from 1969). Under this assumption, each GP will have 42-50 consultations from infected individuals, and

$p = 0.001$ GPs have a 4-5% chance of being infected by a patient

$p = 0.01$ GPs have a 34-39% chance of being infected by a patient

Note that in each case this is not the attack rate for GPs, since they will also have a force of infection acting on them from their household and the general community – this just gives us the extra infection attributable to their role as a GP.

We adopt the value $p = 0.05$ as the default value of this parameter.

***f* – fraction of the infectivity an individual spends in the community before being isolated**

(for the flat infectiousness function f is the fraction of the infectious period spent in the community)

During the SARS outbreak, the shortest time from onset of symptoms to isolation that was achieved was around 2 days in Singapore. For influenza, isolation two days after onset of symptoms would correspond to $f = 0.6$. We adopt a default value of $f = 0.8$, and consider the range [0.6,1.0].

***m* – mean number of general cases infected by a general case if no isolation**

This parameter is used in the model with GPs and HCWs but without children as a separate class. As p is small, we can assume that this is equal to R_0.

π_C, π_D, π_H and π_A – fraction of the population in different classes.

π_C is calculated from census data, π_D from the AIHW medical labour force survey (which estimates around 20,000 GPs for Australia). Total essential/emergency services personnel constitute around 5% of the population, but any one individual should not be on prophylaxis for more than six weeks. If we assume that 10-20% are on prophylaxis at any one time, and the remainder are not any more likely to be exposed than a general individual, then 100,000-200,000 essential service personnel would be on prophylaxis at any time, using up 1,000-2,000 courses per day.

In particular, we assume that π_H is some fraction of the HCW population that is on prophylaxis, and that is at high risk of encountering the virus (say because they are treating patients in a hospital). Total health worker numbers (including GPs etc) are around 750,000 – that is between 4% and 5% of the population. We assume that around 20-25% of these are on prophylaxis, giving $\pi_H = 0.1$.