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Quantifying the Effect of Non-Pharmaceutical Interventions during an Influenza Pandemic

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Summary

Background

Non-pharmaceutical interventions are embedded within the pandemic influenza preparedness plans of most countries and appear in current WHO recommendations. However, the potential impact of social distancing measures, such as school closure, reducing workplace numbers, reducing social and community contacts and increasing home isolation, is not well understood. These interventions have the potential to 1) reduce the overall and peak illness attack rates and the consequential excess mortality attributed to the pandemic, and 2) to delay the peak daily attack rate, allowing time to distribute and administer antiviral drugs and, possibly, suitable vaccines.

Methods and Findings

Given the key role of individual-to-individual contact in the time-course of an outbreak we constructed a micro-simulation model of a real population centre of 30,000. We used census and additional government data to capture the daily contact patterns found within and between households, school and workplace hubs and in the wider community. Using this model we then examined the mitigating effect of non-pharmaceutical social distancing interventions with specific emphasis on quantifying the effect which these alternative interventions have on the time-course of an outbreak. Simulation experiments were used to examine each intervention in isolation and in combination, under various initiation times, with triggers determined by time since a defined community case load or by the case load itself. These options were examined for reproduction numbers ranging from 1.5, consistent with some estimates from previous pandemics, up to 3.5, which may be a worst-case scenario.

For plausible parameter settings, with an R_0 of 1.5, pre-emptive school closure may reduce the final attack rate by 72% (from 31% to 8.5%); applying school closure following a 2% diagnosed case threshold being reached reduces the final attack rate by 40% (to 18%). We find that for higher R_0's a combination of intervention measure can be effective when single measures fail. For an R_0 of 3.5 a combined intervention including school closure, reduced community contact, case isolation and 50% workplace absenteeism may reduce the final attack rate by 84% (from 73% to 12%) when applied pre-emptively; reducing the attack rate by 68% (to 23%) using a 0.1% diagnosed case threshold; and reducing the attack rate by 34% (to 48%) for a 2% case threshold. These results for an R_0 of 3.5 highlight the criticality of intervention timing, showing that even a one week delay has a significant impact on the overall attack rate.

Conclusions

We have shown a strong relationship between the early, continuous and combined application of non-pharmaceutical interventions and a reduction in the cumulative illness attack rate and the daily peak attack rate and a delay in the occurrence of this peak. These results hold for all R_0's considered though they are more effective for lower R_0's. In addition we show the time-criticality of application of interventions under various trigger thresholds. Our results are supported by archival and statistical evidence from 43 US cities and conform closely to the effect seen, with respect to the strength, timing and duration of similar interventions in reducing excess deaths attributed to the 1918-19 pandemic. The results give guidance as to which combination of non-pharmaceutical interventions may be most effective in mitigating an influenza pandemic and they highlight the deleterious effect of delaying their implementation.

Introduction

Concern exists that the avian H5N1 influenza virus may become readily transmissible between humans, leading to a pandemic with significant mortality[1]. Epidemiological models have been used to analyse the beneficial effects of alternative containment measures [2-8] and to capture pandemic influenza spread at the whole of country [2-6] or whole world level [7]. In preparation for a pandemic, many countries have stockpiled drugs, including antiviral medication, and equipment which may be in high demand and not readily available at the time. Preparation for the pandemic also includes the development of vaccines targeting specific strains, with vaccines against influenza A H5N1 currently being trialled. However, even with rapid vaccine development, it may be six or more months from outbreak initiation before a safe and effective vaccine is available. Antiviral treatment and prophylaxis will therefore be the earliest pharmaceutical intervention used.

A number of countries [9-11] have adopted influenza pandemic plans which feature the treatment of a significant proportion of the population with neuraminidase inhibitor (NI) antiviral drugs, however their use to control influenza pandemics is an untested strategy. Furthermore, while the World Health Organisation is establishing regional antiviral stockpiles, it is likely that many countries will not have timely access to this stockpile. Field data [12,13] and theoretical modelling also suggests that antiviral use during a pandemic may be associated with the development of clinically significant drug resistance [14]; the use of antiviral medication against H5N1 is based on the success of these drugs against H3 and H1 in trials, but there are no trial data for H5. Given these constraints on antiviral use and efficacy,

together with the time delay for a safe and effective vaccine, the role of non-pharmaceutical interventions becomes more important. Modelling [15] has suggested early interventions that increase social distancing may postpone the time to peak attack rates and limit the total number of cases and deaths attributed to pandemic influenza. This theoretical work has recently been supported by an archival study of excess deaths attributed to the 1918-19 pandemic in 43 US cities [16] and by the work of [17].

Given the likely success of social distancing and the historical evidence for decreased attributable deaths following early and layered interventions, we aimed to further investigate different options for social distancing, based on the timing of, and the triggers for, the introduction of these interventions, sequentially and parallel. We explored these options using a highly detailed spatio-temporal model of an actual, relatively isolated community of ~ 30,000 people in a developed country. We examined social distancing measure that included school (and child care) closure, reduced workplace attendance, reduced social and community contact and increased home isolation of cases. These measures, which were adopted in past pandemics, may still provide the best strategy for controlling a future pandemic. Our re-examination of these potentially unpopular social distancing measures using a simulation model has the aim of providing a detailed quantification of the potential effect of non-pharmaceutical interventions on the growth-rate of an influenza pandemic. We believe that our modelled population provides us with is a large enough experimental test-bed within which to capture the daily mobility of individuals as found in developed nation urban settings, as they move from home to workplaces and schools on a daily cycle, revelling the impact of non-pharmaceutical interventions in a clearly quantifiable manner. Furthermore, the population is small enough to permit the practical acquisition of actual, detailed population demographic and mobility data giving rise to a model with a high level of realism.

Using this model of contact between individuals and a stochastic model of person-to-person influenza transmission, we simulated the progress of pandemic influenza after introduction into the community, without mandated interventions. We then conducted simulation experiments to quantify the effect of the above interventions, each in isolation and in combination, under various initiation times, with triggers determined by time since a defined community case load or by the case load itself. These options were examined for reproductive numbers ranging from 1.5, consistent with some estimates from previous pandemics, up to 3.5, which may be a worst-case scenario.

We have shown a strong relationship between the early, continuous and combined application of non-pharmaceutical interventions and a reduction in the cumulative illness attack rate, the daily peak attack rate and delaying the occurrence of this peak. These results hold for all R_0's considered though they are more effective for lower R_0's. We show the time-criticality of application of interventions under various trigger thresholds. Our results are supported by the archival and statistical evidence [16] from 43 US cities and conform closely to the effect seen, with respect to the strength, timing and duration of similar interventions in reducing excess deaths attributed to the 1918-19 pandemic.

Methods

The Model

We have constructed a geographic and demographic model of Albany, Western Australia using a patch-based spatial structure [18-20], utilising Australian Bureau of Statistics Census Collection Districts [21] as the finest level of spatial detail where each collection district consists of approximately 200 physically adjacent *households*. Each patch was populated with a number of households according to the census data; the constituent households each being uniquely populated with individuals to match the corresponding collection district data, identifying individuals by age classes.

The model has been additionally populated with a set of schools and workplaces, referred to collectively as *contact hubs*. Government data is used to obtain a comprehensive list of schools, childcare facilities, adult education institutions and employers, including the patch in which they are located and their nominal daytime population. Each child has been assigned to a school or childcare centre, presuming that children attend a school as close to their home location as possible, and ensuring that known age structure of schools is maintained. Adult students and workers were assigned adult education institutions and workplaces respectively with this assignment being made with reference to commuter survey data for Albany. Households and hubs together form vertices of a *mobility graph*, whose edges connect households with hubs that share common individuals, as pictured in Figure 1. This approach captures workplaces and schools where high levels of contact and hence transmission may occur. In addition to household and hub contact, we modelled the daily random or untraceable contacts made by individuals by a *community contact* mechanism. This contact was assumed to be somewhat local in nature, with contacts between individuals from nearby patches (or the same patch) being relatively more likely to occur then those between individuals whose home locations are far apart. In any daytime cycle when an individual is not housebound through illness, he or she randomly pairs with several other such individuals, and potentially infectious contact was deemed to have occurred. This community contact occurs at a given rate which ensures that the household:hub:community locale of infection ratios align with data obtained from previous studies of seasonal outbreaks [22].

Model Construction

A mobility network graph is constructed by an *allocation algorithm*, realised in software. This algorithm allocates individuals to school or workplace hubs according to the demographic data for each residential patch, workplace and school/childcare or further education location. Hence school age children are allocated to primary or secondary schools according to age, giving a higher allocation probability to the closest school by distance from the patch centroid. The allocator therefore uniquely matches the individuals in each patch to the appropriate contact hub. The development of such a "high-fidelity" individual-based model of Albany, Western Australia requires not only that the size and age structure of households, workplaces and schools be correctly generated to match exactly with the unique household demographic data provided by the census datasets, but also that the assignment of individuals to schools and workplaces result in the correct movement of commuting individuals between households and daytime locations (as reported in the available commuter survey data). While the modelled schools and workplaces will not be identical to the real Albany with respect to which actual individuals are assigned to which hubs, this demographic and mobility model statistically matches the available data as exactly as is possible.

The allocation of individuals to households and contact hubs creates a network data structure, which is used by the simulation algorithm, explicitly moving individuals from home to contact hub during the day phase of the simulation cycle. Individuals are then moved back to

their appropriate household for the evening phase. This mechanism thus permits the direct modelling of population movement to schools and workplaces and allows for the explicit modelling of influenza transmission within the home, within schools and childcare centres and within the workplace.

The Simulation Algorithm

Using this model, we conducted stochastic, individual-based spatial *simulations* of epidemic spread, assuming that one new infection is introduced into the simulated population for the duration of the simulation, ensuring that an epidemic ensues with every one of the (stochastic) simulations run. The simulation proceeds in a sequence of 12-hour day/night cycles. During each cycle the location of each individual is computed: either *home* or *hub*, taking into account the cycle type (i.e. day/night, weekend/weekday), the individual's infection status (whether they are susceptible, infected and/or symptomatic or immune), whether an adult needs to stay at home to look after a child, and any social distancing interventions which may be in effect. During any cycle, individuals in the same location (household or hub) were deemed to come into *potential infective contact* and infection transmission may thus occur between infected and susceptible individuals. During each cycle, both the movements and interpersonal contacts of all individuals in the simulated population are determined, and the state of each individual is updated accordingly. Note that for larger hubs including schools, it is unlikely that an individual will come into close contact with every other member of the hub during a cycle. These larger hubs were divided into fixed mixing groups, with a maximum size of 10 individuals per group. In schools these mixing groups consist of same-aged children where possible; in workplaces they were randomly assigned.

When an infectious and susceptible individual come into contact during a cycle, the probability that the infection is transmitted was calculated based on the symptomatic state of the infectious individual (asymptomatic individuals are 50% as infectious as those who are symptomatic), the age of the susceptible individual, and a basic virus transmissibility parameter. The probability of transmission of infection for multiple contacts during a cycle is assumed to be independent; multiple successful transmissions are the same as a single successful transmission. Age-based susceptibility factors were derived by calibrating to seasonal influenza infection data from a study in Tecumseh, Michigan in 1977-1978 [22], which is thought to have relative age attack rates similar to the 1957 influenza pandemic [23].

For each contact event, an infection state (either to remain susceptible or become infected) is randomly chosen for the susceptible person based on the transmission probability. Once an individual becomes infected, the state of the infected individual proceeds according to an *infection model*, which determines the degree, timing and duration of infectiousness and (independently) the development of symptoms.

Modelling Mobility and Contact

The movement of individuals and the contact between them is governed by a contact network, as pictured in Figure 1. For each simulation cycle, individuals in the same immediate contact group come into (potentially infective) contact, which can occur within a household, school, workplace or the community, as discussed above. The overlapping memberships of households and other contact groups thus form a connective social network through which infection can spread.

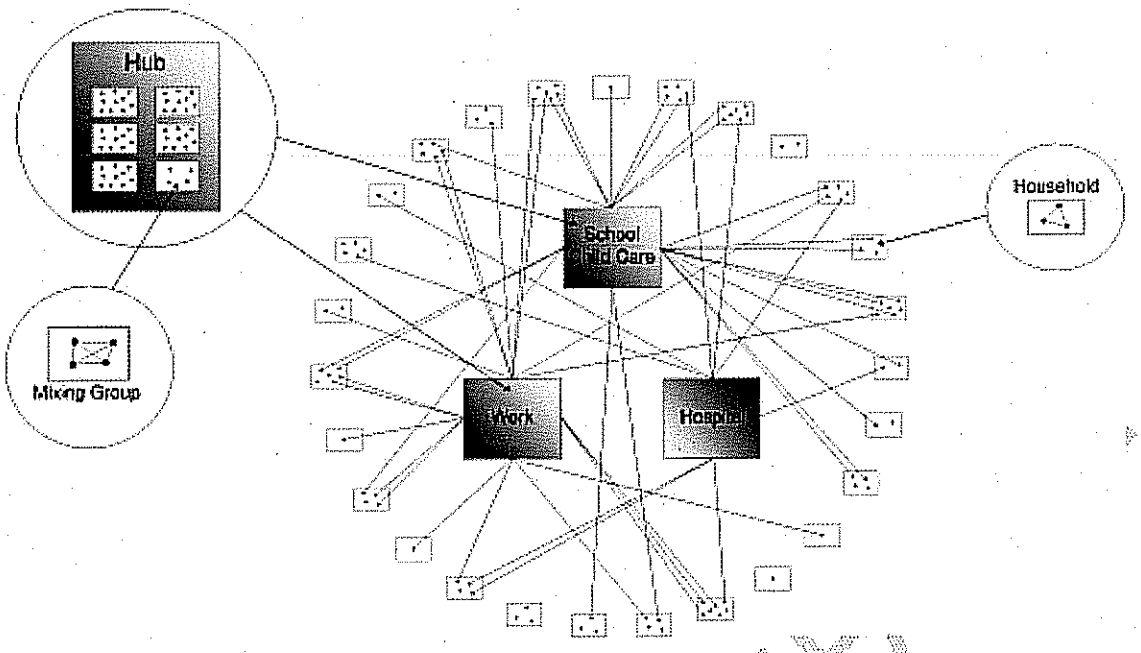


Figure 1 : Household and hub contact network.

Influenza is introduced into the Albany population area on day 0 and randomly allocated to a household in the model. One infectious individual is also introduced for each subsequent day for the duration of the simulated period, the individual being randomly determined. This continuous stream of infectious individuals (modelling the import of infected individuals from outside the simulated population) allows outbreaks to occur with 100% likelihood. If only single introductions occur, in many low R_0 simulation runs the outbreak rapidly dies out due both to the random allocation of the infectious case and the stochastic nature of the transmission parameters and community contact.

Transmission may occur within households and these also form sub-populations whose structure is also determined by the allocation algorithm to exactly match the census dataset. Each individual is therefore assigned to one household, where each household contains the appropriate number of individuals of the appropriate ages to match the census data for that uniquely identified household. Individuals becoming infected within a contact hub during the day-time phase move back to the household in the evening, and after an incubation period these individuals may then infect other household members.

Infection also occurs within the wider community; this *community contact* is in addition to any commuting movement that the individual may perform during the cycle. During the day time phase, every active individual makes a notional return trip to one or more residential patches, the destinations being determined by population density and distance from home residential patches (this can include a "trip" to the person's home patch). For each of these community contact trips, the individual is randomly paired with another individual who also is making a trip to the same patch, and a potentially infective contact occurs.

Modelling Transmission

Where an infected individual comes into contact with a susceptible individual, the probability of the infection being transmitted is calculated according to the *transmission function* see Eqn 1. Given contact has occurred between an infectious person and a susceptible person, via

the above contact model, the likelihood of transmission is a function of the infectiousness of the infected individual, the age-based susceptibility of the susceptible individual and the overall virulence or transmissibility of the influenza strain. If a susceptible person is exposed to multiple infectious persons during a simulation cycle, it is assumed that the probability of transmission from each one is independent of the others. Only one successful transmission is required for a susceptible person to become infected. Successful transmissions beyond the first have no further affect.

A new infection state (either to remain susceptible or become infected) is randomly chosen for the susceptible person based on the transmission probability. Specifically, the probability of transmission is the function:

$$P_{trans}(I_i, I_s) = \beta_v \times trans(I_i) \times susc(I_s) \qquad \text{Eqn 1}$$

where P_{trans} is the overall probability of transmission (a function of the state of the infectious and susceptible individuals), where β_v is the nominal infectiousness of the virus strain, $trans(I_i)$ is the transmissibility of the infected person I_i, and $susc(I_s)$ is the susceptibility of the susceptible person I_s. All of these parameters are real numbers on the domain [0,1]. The transmissibility of an infected person is governed by the infection model, where $trans(I_i)$ is 1 for symptomatic persons, and 0.5 for asymptomatic persons. The susceptibility $susc(I_s)$ is a function directly dependent on the susceptible persons age. As the simulator employs seven age groups, there can be up to seven different relative susceptibilities.

To achieve a realistic age specific infection rate, age-specific susceptibility parameters and a general transmissibility parameter β_v were calibrated against the serologic infection rates reported for H3N2 in 1977-1978 in Tecumseh, Michigan, Figure 5 of [22]. This particular study reported on rates in the seasonal influenza outbreak in the winter of 1977-1978. The higher illness attack rates in the younger age groups may suggest that adults were partially protected by earlier exposure to inter-pandemic influenza, or that younger individuals may have closer contact with others and hence increase their effective susceptibility. The Tecumseh study of seasonal influenza determined an age-specific illness attack rate somewhat similar to the age profile for the 1957 influenza pandemic [23]. This calibration gives us the age-specific susceptibility values which are used across all scenarios. The resultant parameter settings (assuming $\beta_v = 0.07$) are given in Table 1. This procedure gives a transmissibility model for seasonal influenza: in order to model transmissibility of a novel pandemic influenza strain β_v is increased (see the Baseline Determination section below).

Table 1 : Calibrated age-based susceptibility factors.

$age(I_s)$	$susc(I_s)$
0-5	0.8272
6-12	0.6248
13-17	0.8800
18-24	0.7900
25-44	0.5609
45-64	0.4187
65+	0.7900

Modelling Infection

Once an individual becomes infected, the state of the infected individual proceeds according to an *infection mechanisml* which determines the degree, timing and duration of infectiousness and the development of symptoms. We assume that infected individuals pass through a latent incubation period of 1 day followed by an infectious period set at 5 days. We have also assumed a constant infectivity for the infectious period, which is a simplification of a normal-type infectivity distribution found in studies of viral shedding [24].

Infection is taken to last 6 days: 1 day latent, 1 day asymptomatic and infectious, 4 days infectious (either symptomatic or asymptomatic). Once an individual has become infected, they are assumed to be immune to re-infection for the duration of the simulation. We assume also that influenza symptoms develop one day into the infectious period, with 20% of infections being asymptomatic among children and 32% being asymptomatic among adults. These percentages were derived by summing the age-specific antibody titres determined in Table 5 of [25], giving aggregate totals for those under age 20, and adults over age 20. Symptomatic individuals will withdraw into the home with the following probabilities; adults 50% and children 90%, which is in keeping with the work of [4,26].

Hospital Model

The 120-bed Regional Hospital is explicitly included in our simulation model due to its role as the largest contact hub in Albany. Hospital admissions may occur from two sources; each symptomatic influenza case which occurs is deemed to have a 1% chance of resulting in hospitalisation. In addition, we assume that there is a "normal" flow of patients into and out of the hospital, modelled by a per-person, per-day probability of hospitalisation and discharge for the non-hospitalised and hospitalised population respectively. These parameters are adjusted so that the average hospital occupancy and length of patient stay matches actual hospital data obtained.

Contact within the hospital is deemed to take two forms. Firstly, we treat the hospital as a regular employment hub; this models mixing between hospital staff. In addition, the hospital is divided into "patient mixing groups" (which we call "rooms"), each containing a fixed number of beds (8). Each admitted patient is assigned to a room with a vacant bed; in addition, each rooms is associated with two hospital staff members (staff members can be associated with more than one room if there are less than twice as many staff as rooms). During every simulation phase (day and night), contact occurs between all pairs of patients in the same room, and between the staff associated with a room and each patient in the room.

Baseline Determination

We have assumed a scenario where pandemic influenza has broken out in another part of the world eg. South-east Asia and that our modelled population is aware of its likely arrival. To achieve this we derived an effective baseline which assumes some level of spontaneous social distancing, whereby people significantly moderate their contact behaviour in response to public health announcements and news reports of the morbidity and mortality of a prior outbreak in another country. This pandemic behaviour contrasts with that which occurs with seasonal influenza where overall mobility and contact patterns of asymptomatic individuals, and even some who are ill and symptomatic, remain unaltered.

The baseline parameters were chosen to give rise to an epidemic with the following characteristics:

43% of infections occurring in households, 28% in schools and workplaces, and 29% from community contact. Based on seasonal influenza data [22] it has been estimated that 33% - 37% of transmission occurs in the household [3]. Given that public knowledge of a current pandemic will induce behavioural changes, namely spontaneous social distancing, we believe that it is reasonable to assume a lower level of community, school and workplace contact and thus a relatively higher proportion of household transmission. Without reliable data on the relative proportions of hub and community transmission, we assume that they contribute equally to out-of-household transmission.

The infectiousness parameter β_v was then increased to achieve epidemics with target R_0 values of 1.5, 2.0, 2.5 and 3.5 ; the β_v values corresponding to each target R_0 are shown in Table 2. Note that a listing of model parameter values may be found in the Appendix.

Table 2 : β_v values for R_0 scenarios.

β_v	R_0	Scenario
0.070	1.3	Original seasonal influenza calibration
0.083	1.5	Pandemic low R_0
0.116	2.0	Pandemic high R_0
0.152	2.5	Pandemic very high R_0
0.238	3.5	Pandemic extreme R_0

The reproductive number R_0 is not calculated analytically, but is instead experimentally determined by considering 10,000 separate random single index cases. This reproductive number is thus not R_0, but rather a related quantity R_{rand}. The difference between R_0 and R_{rand} as discussed by Ferguson in [3]; as it has little effect on our results we will refer to this form of reproduction number as R_0 in what follows.

Studies indicate that the influenza pandemics of the twentieth century have an R_0 between 1.3 and 1.7 [23] Note that these R_0 values have been estimated from historical data where various intervention measures are known to have been active; in contrast, our baseline scenarios assume no mandated intervention measures with the only control being the spontaneous social distancing measures mentioned above. We therefore set transmissibility parameters to derive epidemics with a range of R_0's of 1.5, 2, 2.5 and 3.5. The higher R_0's of 2.5 and 3.5 give hypothetical "worst case" epidemics which would occur with no explicit interventions. While past influenza epidemics of this magnitude have not been observed, our results show that plausible intervention measures can reduce these epidemics to effective R_0 values in the 1.3 to 1.7 range. The characteristics of baseline outbreaks under each of the four R_0 scenarios is given in Table 3.

Table 3 : Simulated outcome of baseline (no-intervention) epidemic for four R_0 values

	$R_0 = 1.5$		$R_0 = 2.0$		$R_0 = 2.5$		$R_0 = 3.5$	
	mean	95% CI	Mean	95% CI	mean	95% CI	mean	95% CI
Final infection rate (%)	40.7	±0.5	67.3	±0.2	79.9	±0.1	91.4	±0.1
Final attack rate (%)	34.1	±0.4	55.3	±0.2	65.0	±0.1	73.4	±0.1
Peak ill population (%)	5.3	±0.17	17.2	±0.17	28.4	±0.17	46.9	±0.16
Peak daily attack rate	262	±8.9	840	±10.6	1401	±17.1	2498	±30.2
Peak attack day	55	±2.3	36	±1.0	27	±0.7	19	±0.4
Serial interval	2.98	±0.005	2.87	±0.004	2.74	±0.003	2.45	±0.003

For an epidemic with a basic reproduction number R_0 of 1.5, our effective baseline yields an infection rate of 50% with a symptomatic (illness) attack rate of 35%, which is consistent with the influenza pandemics in 1957 and 1968 [23]. This attack rate assumes that no public health mandated interventions have occurred and it is this which we take as the baseline for examining the efficacy of non-pharmaceutical intervention.

Modelling Interventions

We simulate four different non-pharmaceutical intervention measures. These are as follows:

School closure. We assume that upon closure of a school, students and teachers spend weekday daytime cycles at home rather than at the school hub. This means that no contact takes place at that school hub, but that these individuals will contact any other individuals present in their household during the day cycle. We assume that no *additional* community contact occurs (community contact is deemed to occur in all daytime cycles for active individuals, regardless of whether they were present at a hub or home). We also assume that if school closure would result in a child or young child being present in a household alone, one adult from the household is also kept at home (and thus does not make hub contacts). We assume school closure applies to childcare facilities, all schools, and all adult educational institutions.

Increased case isolation. Our baseline assumption is that upon becoming symptomatic, there is a 50% chance that an adult, and 90% chance that a child, will withdraw to their household (become inactive) for the duration of their infection (infectivity and symptoms are deemed to cease at the same time). When the increased case isolation measure is in effect, this increases to 90% for adults and 100% for children. We assume that withdrawn individuals make only household contacts while withdrawn.

Workplace absenteeism. When this measure is in effect, each person attending a (non-school) workplace hub has a 50% chance each day of staying home instead of attending the hub (the choice is made independently each day and applies only to that day). Individuals staying at

home make no hub contacts but do contact all other individuals also at home during the day cycle.

Background contact reduction. When this measure is in effect, it is assumed that individuals participating in community contact during a cycle make only 50% the baseline number of effective contacts.

Results

In this report we present five main series of simulations:

1. Baseline (no intervention) simulations, showing the final attack rate, and the time at which certain case count thresholds are reached.

2. For each of the four intervention measures, simulations showing the effect of delaying the introduction of intervention.

3. For each of the four intervention measures, simulations showing the effect of maintaining interventions for different durations.

4. For each of the four intervention measures, simulations showing the effect of different levels of compliance to intervention measures.

5. Simulations showing the effectiveness of various combined intervention measures.

All simulation series have been conducted with epidemics have R_0 values of 1.5 and 2.5. Results for all simulated epidemics are averages of 40 runs, each with stochastic choices made with a different random-number sequence. We present cumulative attack rate plots for each intervention series; corresponding daily attack rate plots can be found in the Appendix.

Baseline Epidemics and Trigger Thresholds

Table 3 gives significant statistics of the baseline (no intervention) simulated epidemics with basic reproductive numbers of 1.5, 2.0, 2.5 and 3.5.

In our simulations that examine the introduction timing of intervention measures, we assume that intervention measures are triggered by a certain case count threshold being reached. For this purpose we assume a *ascertainment efficiency* of 50%: in order for a case to be counted towards an intervention trigger threshold, it is assumed that the following sequence of events must occur:

1. The individual becomes infected.
2. The individual experiences symptomatic infection.
3. They present to a health care professional who is participating in a monitoring scheme.
4. The infection is correctly diagnosed as pandemic influenza.
5. The case is correctly reported to the monitoring scheme.

The 50% ascertainment efficiency is the conditional probability that 5) occurs, given that both 1) and 2) have occurred.

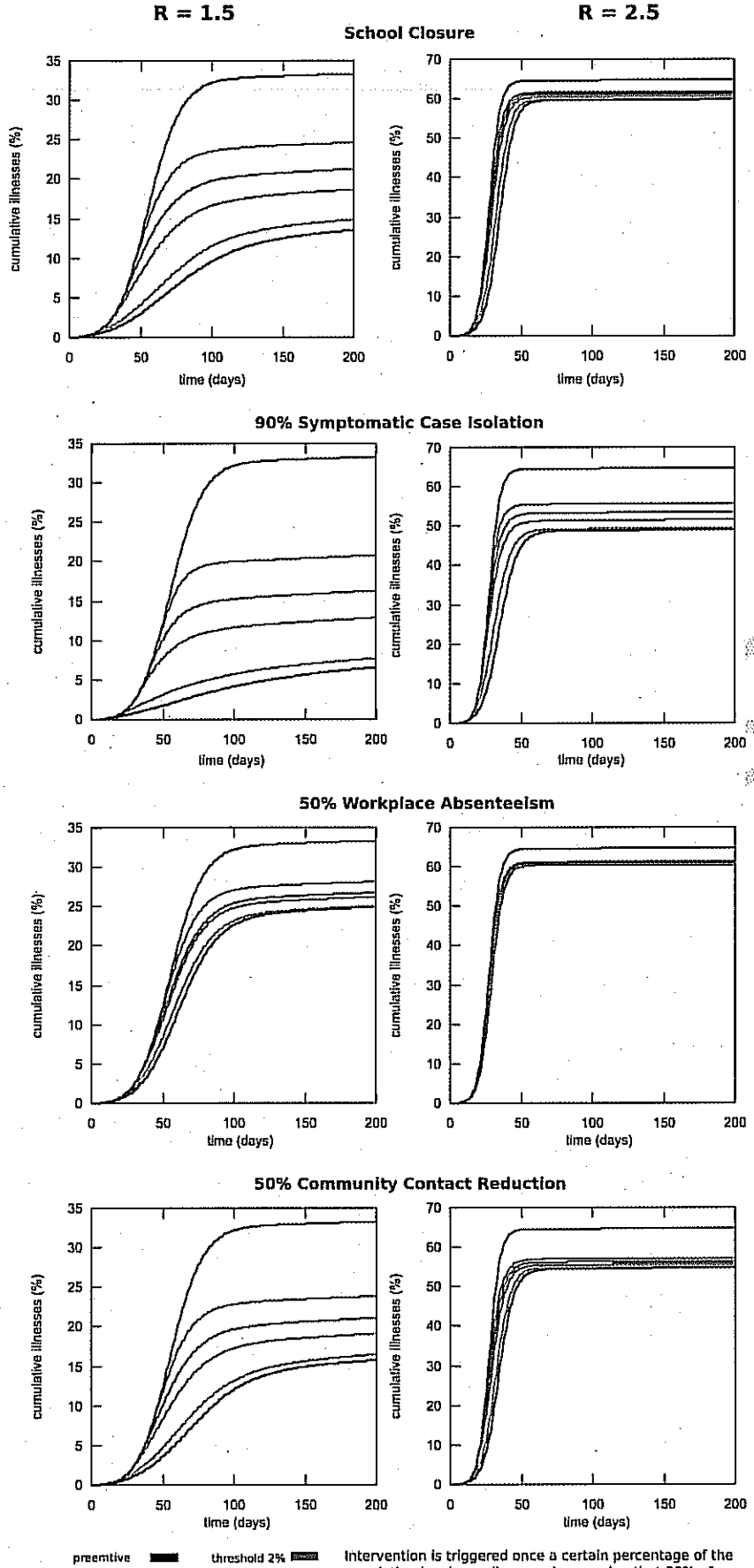
Table 4 : Baseline Case Thresholds and Trigger Timings

			R_0			
			1.5	2.0	2.5	3.5
Threshold %	Cases Diagnosed	Actual	Days Before Threshold Reached			
0.05 %	15	30	9	7	6	5
0.1 %	30	60	13	9	8	6
0.5 %	150	300	24	16	13	10
1.0 %	300	600	30	19	15	11
2.0 %	600	1200	37	23	18	13
4.0 %	1200	2400	46	27	21	15
8.0%	2400	4800	58	32	24	17
	Duration		171	101	86	58
	Final AR %		31 %	53 %	63 %	72 %

Table 4 shows the range of trigger thresholds considered and the corresponding delays in intervention measure implementation if these thresholds are used as the triggers. These timing delays are generated as averages over 40 different randomly seeded simulation runs.

In the following, we present figures capturing the cumulative attack rates determined by simulation for the range of simulation scenarios discussed above.

Figure 2 : Timing of Intervention Implementation



Intervention Timing

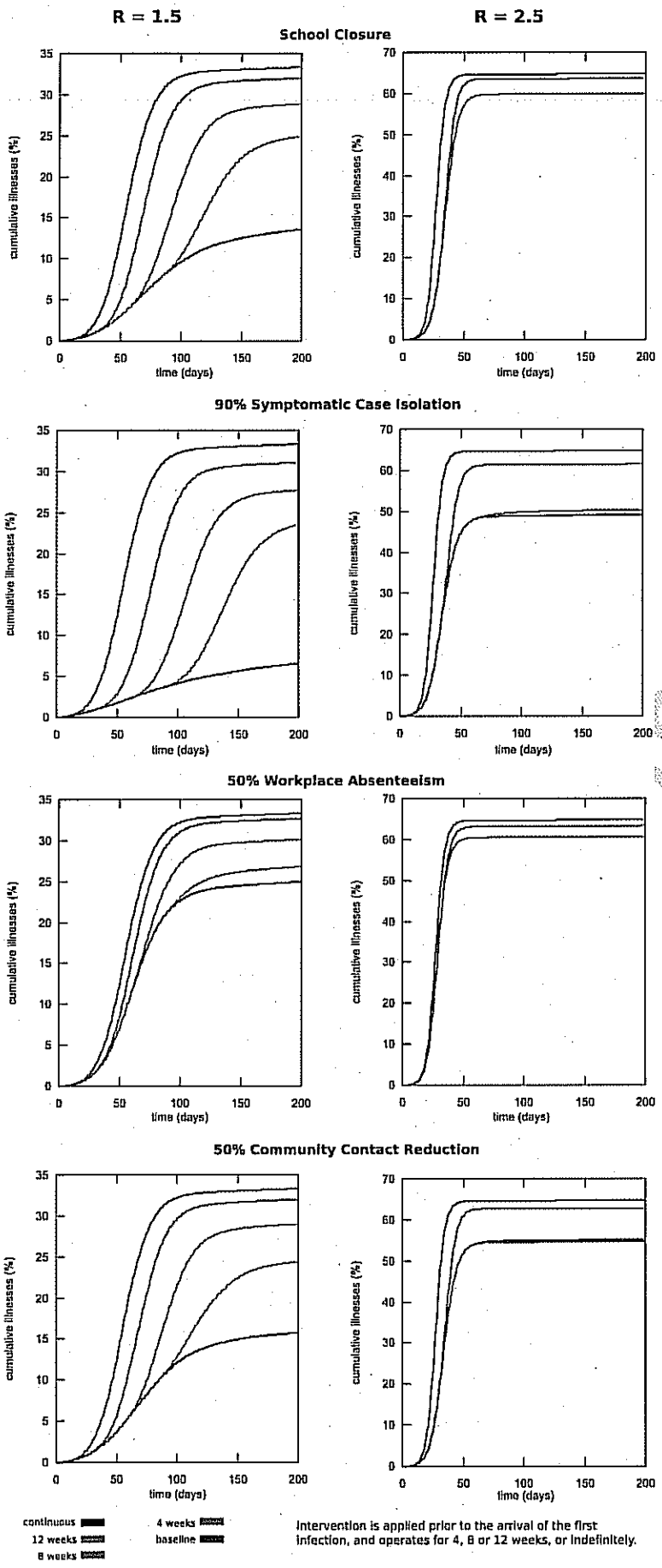
Figure 2 shows the effect of the four intervention measures when introduced at a number of different notified community case count thresholds, ranging from 0.1 % to 4 % (20 to 1200 notified cases).

For epidemics with R_0 of 1.5, all measures are effective if introduced without delay, with 90% case isolation having the greatest effect (a potential reduction in final attack rate from 34% to 7%).

In all cases, the 0.1% community case threshold (ie introduction after 30 ascertained cases) achieves essentially the same effect as the optimal pre-emptive introduction strategy. Waiting for higher thresholds to be reached results in less effective intervention; waiting for the 4% case threshold (1200 ascertained cases) results in approximately half the potential reduction in final attack rate being lost..

For epidemics with R_0 of 2.5, none of the simulated measures are highly effective in reducing the final attack rate, even when applied pre-emptively. Early introduction of intervention measures can however make significant reductions in the *peak daily* attack rate. If applied at or before the 0.1% threshold, school closure, case isolation, workplace absenteeism and community contact reduction reduce the peak daily attack rate from approximately 1250 to 900, 600, 1100 and 800, respectively. Figures showing daily attack rates are presented in the Appendix.

Figure 3 : Duration of Interventions



Intervention Duration

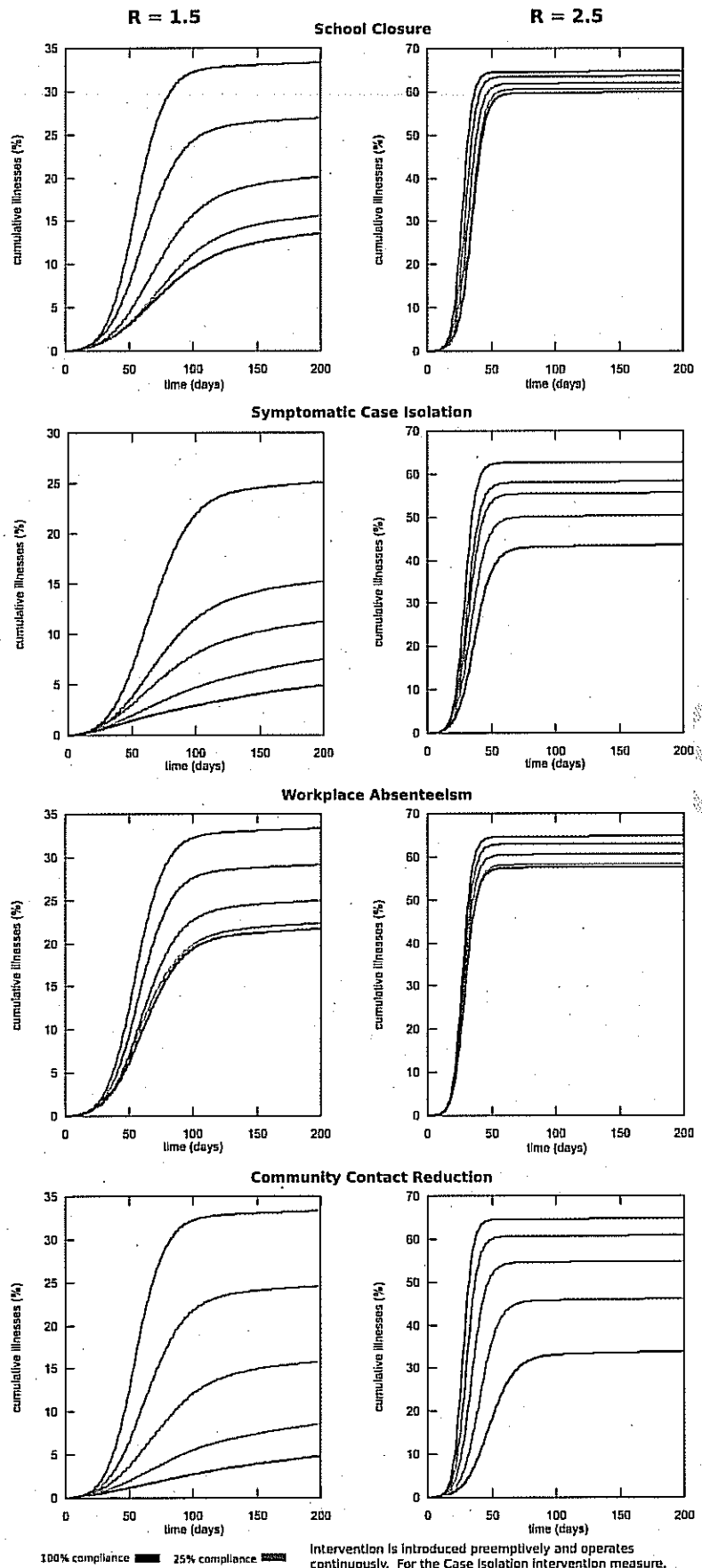
Figure 3 shows the effect of the four intervention measures when maintained for 4, 8 or 12 weeks.

For epidemics with R_0 of 1.5, all measures are effective if introduced without delay and maintained longer than 12 weeks. Where intervention measures terminated at 12 weeks, only about half the potential final attack rate reduction is achieved (except in the case of 50% workplace absenteeism: in this case a 12 week intervention achieves most of the potential effect, this is however only a reduction from 33% to 26%).

The daily attack rate plots (presented in the Appendix) show that for the school closure, case isolation and community contact reduction measures, the relaxation of measures at 12 weeks occurs after a peak in the epidemic, but while there is still a large susceptible population, resulting in a second epidemic wave.

For epidemics with R_0 of 2.5, none of the simulated measures are highly effective in reducing final attack rate regardless of the duration for which they are applied. The main period of the epidemic occurs between weeks 1 and 7; what effect the interventions *do* have occurs before this time and there appears to be no benefit in extending interventions beyond 8 weeks in these situations. As noted in the previous section, the interventions do significantly reduce the peak daily attack rates, provided that they are maintained for at least 8 weeks duration.

Figure 4 : Levels of Compliance to Interventions



Intervention is introduced preemptively and operates continuously. For the Case Isolation intervention measure, the 5 compliance levels represent household isolation of 100%, 87.5%, 75%, 67.5% and 50% (baseline) symptomatic cases.

Compliance to Intervention Measures

Figure 4 shows the effect of the four intervention measures, assuming different levels of compliance.

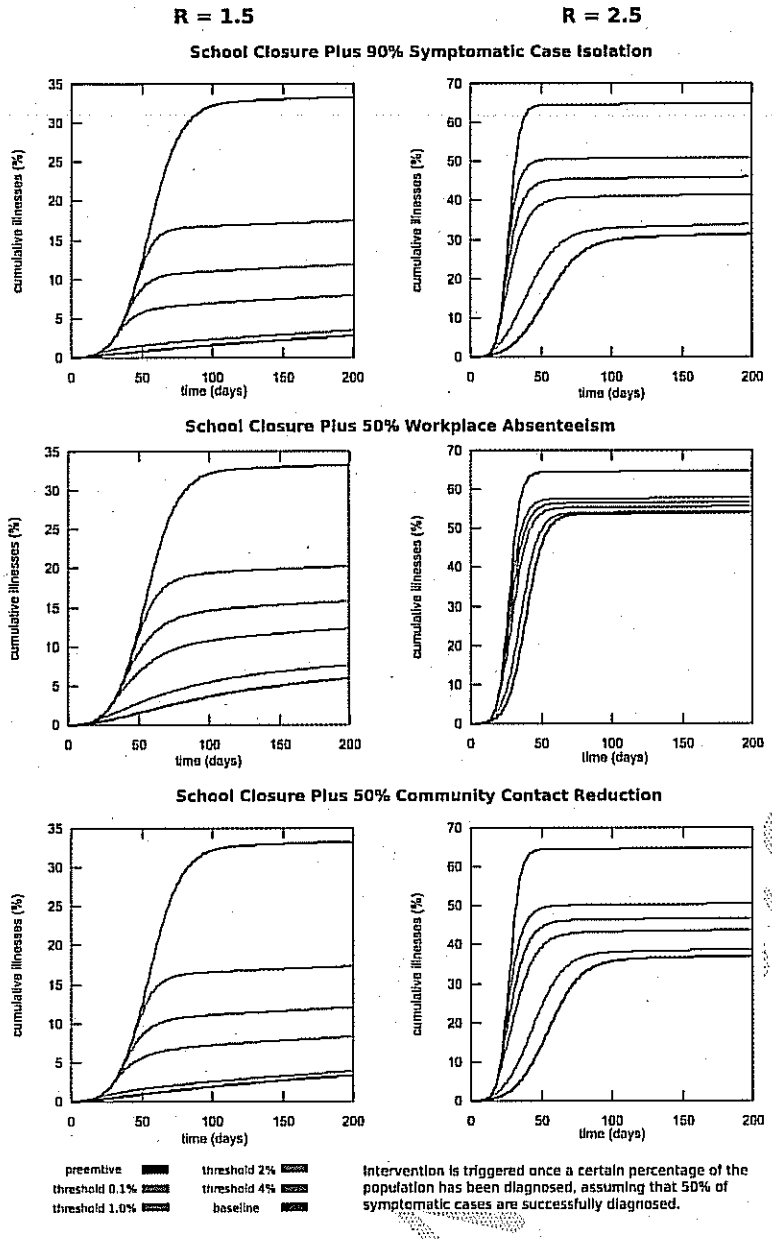
The definition of "level of compliance" is particular to each intervention measure:

- For school closure compliance levels of less than 100%, it is assumed that schools remain open, but each day the probability that each student attends is equal to the compliance level. When at school, pupils make contact with other member of their usual mixing group that are also present. We simulate compliance levels from 0 to 100%.
- Our baseline assumption is that 50% (90% for children) of symptomatic individuals withdraw to their household for the period of their infection; this increases to 90% (100% for children). We simulate adult compliance levels (withdrawal probabilities) from 50% to 100%.
- Our workplace absenteeism measure assumes that for each working day, each working individual attends their workplace with a certain probability. We simulate compliance levels from 0 to 100%.
- Our community contact reduction measure assumes that while the measure is in effect, the number of effective contacts made by individuals is reduced by a certain proportion. We simulate contact reductions from 0% (no intervention) to 100% (the unrealistic case of a total cessation of contact outside of household, schools and workplaces).

The results are unsurprising, with higher compliance levels giving greater reductions in final attack rate and peak daily attack rates.

One point worth noting is that for the case

Figure 5 : School Closure Combination Interventions



isolation measure, it appears that at $R_0 = 1.5$ even modest improvements in compliance can make a significant difference; increasing household isolation from 50% to 67.5% reduces the final attack rate from 25% to 15%.

Combinations of Intervention

In common with other simulation studies (eg [3], [6], [15]), we find that no single social distancing measure is effective at controlling epidemics with an $R_0 \geq 2.5$.

Figure 5 shows the effect of combining school closure with each of the other measures. At $R_0 = 1.5$, all succeed in keeping the final attack rate under 8% if applied at the 0.1% case count threshold and continued indefinitely. At $R_0 = 2.5$, the school closure plus case isolation and school closure plus community contact reduction measures can reduce the final attack rate to 30% and 35% respectively, while the school closure plus workplace absenteeism combination is less effective. At $R_0 = 2.5$, all the combination measures at least halve the peak daily attack rate if implemented at the 0.1% threshold.

Figure 6 : Combination of All Interventions

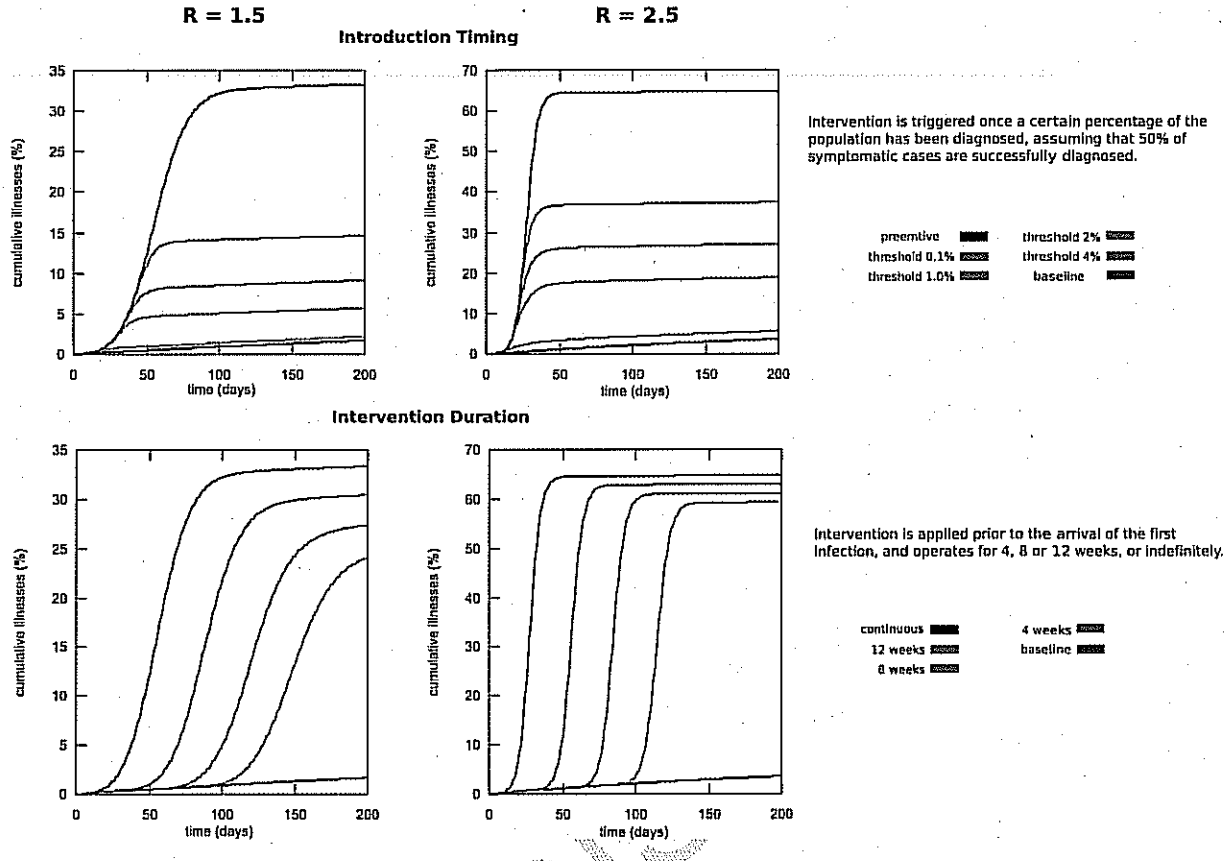


Figure 6 shows the effect of applying all the modelled intervention measures simultaneously. The resulting combined measure is highly effective even with an R_0 of 2.5, keeping the final attack rate under 5%, provided that the measures are applied promptly and continuously. Waiting for the 1% or higher trigger thresholds results in a significant loss in effectiveness. Similarly, as soon as the interventions are relaxed, the epidemic resumes its unmitigated course.

Discussion

We have shown a strong relationship between the early, continuous and combined application of non-pharmaceutical interventions and a reduction in the cumulative illness attack rate, the daily peak attack rate and delaying the occurrence of this peak. These results hols for all reproduction numbers considered but are more effective for the lower numbers. We show the time-criticality of application of interventions under various trigger thresholds. Our results are supported by the archival and statistical evidence [16] from 43 US cities and conform closely to the effect seen, with respect to the strength, timing and duration of similar interventions in reducing excess deaths attributed to the 1918-19 pandemic. This latter result gives support to our modelling approach and hence to the results which we have generated

Our results also align with the few epidemiology observations of the impact of school closure on influenza epidemics. During the 1920 influenza outbreak on Kelley's Island, Ohio [27], households containing a school child were infected several days earlier than the rest of the community. Furthermore, school closure was associated with a decline in population incidence of the disease. More recently in Israel [6], a 30% reduction in paediatric

presentations to health practitioners was observed during a two week teachers' strike which occurred in the middle of the influenza season, compared to the periods before and after.

Many of the mitigation measures which will be used to reduce the scale of a future influenza pandemic require significant time delays before they may be initiated. Policy makers may hesitate to introduce draconian legislation to close workplaces and shut down transport links; individuals may be slow to moderate their behaviour and follow rigorous self-imposed social distancing; time is required to manufacture vaccines; delays will occur before vaccines and antiviral drugs are distributed and administered. We have shown that early school closure may have a significant effect on slowing the rate of spread of an influenza pandemic in an urban setting which has mobility patterns as found in the industrialised world. This delay in the rate of growth of an influenza outbreak is significant as it gains time to invoke further mitigation measures; we find that the impact of further social distancing measures is markedly enhanced when superimposed on a timely school closure intervention.

We have shown that pre-emptive school closure, that is closure prior to an outbreak within a spatially discrete population, is highly effective in slowing the early spread of an epidemic in that community. Timely school closure can be readily mandated by government authorities and may be viewed as a preferred initial line of defence. Even for influenza strains with a high probability of transmission, possibly due to low immunity and hence high susceptibility, giving R_0's of 2.5 and 3.5, we have shown that the slowing of the rate of spread of an epidemic achieved via early school closure increases the efficacy of the additional non-pharmaceutical intervention measures.

The use of a highly detailed model of an extant combined urban and country community permits the effects of mitigation strategies to be revealed. For example, we can clearly see the effect of timely interventions at the early stages of an epidemic. The availability of detailed data and its use in creating the model clearly indicates how non-pharmaceutical interventions such as school closure, partial workplace closure and individually adopted social distancing may be used to reduce the cumulative number of individuals becoming ill (the symptomatic attack rate) and delay the peak in the daily attack rate.

Our simulation model contains several parameters that are difficult to estimate. We have conducted a series of simulations to determine the sensitivity of each of our considered intervention measures to key model parameters. There are several cases in which alternative model parameters result in a significantly less effective intervention measure: school closure is less effective if school contact group sizes are assumed to be smaller or if random community contact is larger; the increased case isolation measure is less effective if 40% or more of cases are asymptomatic; the workplace absenteeism measure is less effective for larger school contact group sizes or smaller workplace group sizes; and reduction in community contact is less effective if we assume larger school contact group sizes.[1] Further details can be found in the Appendix.

In this paper, the quantity referred to as "R_0" differs from the proper definition of R_0. Instead of referring to the average number of infections that would be caused by a *typical infected individual* in a totally susceptible population, it refers to the average number of infections that would be caused by a *random member of the population*, if they were to become infected in a

[1] We comment here only on alternative assumptions that lead to intervention measures being 70% (or less) as effective compared to our standard baseline parameters.

totally susceptible population. In [3] this quantity is referred to as R_{rand}. In as far as our results are interpreted by "observable" quantities such as final attack rates[2], daily attack rates and case count thresholds, the precise definition of R_0 is relatively unimportant; it is simply a parameter representing the potential severity of the epidemic. In order to compare our results with other studies, or historical estimates, or estimates made in the early stages of a new pandemic, the relationship between R_{rand} and R_0 in our simulation needs to be determined. Intuitively, for low R_0 values R_{rand} should underestimate R_0. For a stochastic, individual-based spatial influenza simulation of the US and UK, analysis in [3] estimated that for $R_0 < 2.0$, $R_0 \sim R_{rand} + 0.2$).

It should be noted that these results are applicable to industrialised populations and are probably not applicable to developing countries having lower population mobility, and higher population densities. In such countries we may find much higher daily contact rates and hence reduced opportunities for limiting contact and achieving isolation in the household.

In conducting the simulations for this report, we find that we have far from exhausted the range of scenarios which could be simulated with the current simulation model and software. With modest additions to the software and underlying model, a wide range of further intervention policies and phenomena lie within the reach of our simulation methodology. Several such extensions follow naturally from the results presented in this report, as follows:

- Combinations of non-pharmaceutical intervention measures seem to be able to control even highly virulent epidemics. A fuller study of the possible combinations and likely compliance levels may reveal particularly effective (or ineffective) combinations.
- It should be relatively straightforward to provide approximate measures of "social" or "economic" costs of epidemics and proposed intervention measures; for example, counts of school and work days lost.
- Assuming a fixed mortality rate allows the current final attack rate results to approximate the expected mortality rates under various scenarios. A more detailed model, including age-specific mortality rates, or mortality rates that vary according to pressure on medical services, could provide a more sophisticated analysis of expected mortality.
- The interaction of introduction timings and duration could be further investigated; for example, scenarios which create or avoid epidemics consisting of multiple waves.
- The interaction between planned anti-viral and vaccination interventions, and non-pharmaceutical interventions.

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[2] Note that by attack rate we mean illness attack rate.

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Appendix

Sensitivity Analyses

We examined the sensitivity of our simulation results to 8 key model parameters. We examined two alternative settings for each parameter, one significantly greater and the other significantly smaller than the value used for the standard baseline (standard baseline values are listed below in the Baseline Simulation Model Parameters section), giving sixteen additional sensitivity analysis scenarios (SAS). Table SI1 describes each SAS.

Table SI 1 : Sensitivity Analysis Scenarios

Parameter	Description	Values (low, standard, high)
Behavioural Scenarios		
Background Contact	Number of individuals randomly contacted in community per day by active individuals.	(2,4,8)
Class Size	Size of contact group in school hubs.	(5,10,20)
Workgroup Size	Maximum size of contact groups in workplace hubs.	(5,10,20)
Illness Withdrawal	Probability that an adult individual will withdraw to household upon experiencing symptomatic infection. Children always withdraw with probability 0.9, or 1.0 if case isolation is in effect.	(0.25,0.5,0.75)
Biological Scenarios		
Infective Duration	Number of days during which infected individuals are infectious	(3,5,8)
Asymptomatic Infectiousness	Relative infectiousness of asymptomatic infected individuals.	(0.25,0.5,0.75)
Asymptomatic Proportion	Probability that an infected individual experiences asymptomatic infection.	(0.1,0.3,0.4)
Symptom Latency	Delay in appearance of symptoms from infection (all infected cases become infectious after 24 hours).	(36 hrs, 48 hrs, 60 hrs)

For each SAS, the following procedure was adopted:

1. A set of age-specific susceptibility parameter values were found so that the age-specific attack rates match, as closely as possible, that of the seasonal influenza profile recorded by the Tecumseh 1978-1979 study.
2. Each of these scenarios was simulated. While the overall infection rate and age-specific infection rates are very similar (see above-Joel???), the epidemics do differ in other characteristics, such as R_0, the location of infections and the resulting serial interval. Some characteristics of these baseline SAS are given in table SI2.
3. For each of the baseline SAS scenarios described in Table SI1: β_v or β_{virus} parameter value (See Eqn 1) was determined to ensure that the resulting epidemic had an R_0 value of 1.5 .
4. For each of the SAS R_0 = 1.5 scenarios, the four different intervention measures examined in the main article were simulated, and the results compared to the baseline no intervention R_0 = 1.5 scenario. It is assumed that the intervention measures are applied pre-emptively from the beginning of the simulation. Table SI3 shows the sensitivity of each intervention measure to each SAS. For each intervention measure and each SAS, the percentage reduction in final attack rate is given. Where the SAS leads to a final attack rate reduction differing by greater than 30% from the reduction given by the standard baseline, the proportional difference is also given (in red where

the SAS results in a less effective intervention, and in green for a more effective intervention).

Table SI2 : Sensitivity Analysis Scenario Baseline Epidemic Characteristics

		R_0	Serial Interval	% Home Infections	% Hub Infections	% Community Infections
Standard baseline		1.29	5.98	46	30	24
Background Contact	**2**	1.34	5.91	50	34	16
	8	1.27	6.00	39	25	35
Class Size	**5**	1.37	6.04	49	22	28
	20	1.19	5.84	40	40	20
Workgroup Size	**5**	1.27	5.99	48	24	27
	20	1.27	5.93	42	36	21
Illness Withdrawal	**0.25**	1.29	6.07	43	31	26
	0.75	1.30	5.81	49	28	22
Infective Duration	**3**	1.27	5.09	45	30	24
	8	1.38	9.45	47	28	24
Asymptomatic Infectiousness	**0.25**	1.32	6.39	49	27	23
	0.75	1.27	5.67	43	31	25
Asymptomatic Proportion	**0.1**	1.26	6.03	45	30	24
	0.4	1.20	6.12	39	35	26
Symptom Latency	**36**	1.39	5.93	48	27	24
	60	1.26	5.98	43	32	25

Table SI 3 : Intervention Measures Sensitivity (at $R_0 = 1.5$)

		School Closure	90% Case Isolation	50% Workplace Absenteeism	50% Community Contact Reduction
		Final Attack Rate Reduction %			
Standard baseline		75	92	25	60
Background	**2**	94	92	34 (+0.36)	48
Contact	**8**	36 (-0.50)	94	19	75
Class Size	**5**	44 (-0.40)	95	37 (+0.47)	86 (+0.44)
	20	91	72	15 (-0.41)	30 (-0.49)
Workgroup	**5**	74	89	12 (-0.52)	62
Size	**20**	66	92	38 (+0.50)	49
Illness	**0.25**	66	97	30	66
Withdrawal	**0.75**	84	72	19	53
Infectious	**3**	73	83	23	55
Duration	**8**	81	97	33 (+0.33)	78
Asymptomatic	**0.25**	78	97	26	70
Infectiousness	**0.75**	66	73	23	52
Asymptomatic	**0.1**	74	91	24	56
Proportion	**0.4**	67	45 (-0.51)	19	43
Symptom	**36**	79	98	41 (+0.62)	84 (+0.41)
Latency	**60**	75	70	21	52

Additional Results

Figure 7 : Comparison of School Closure Trigger Conditions

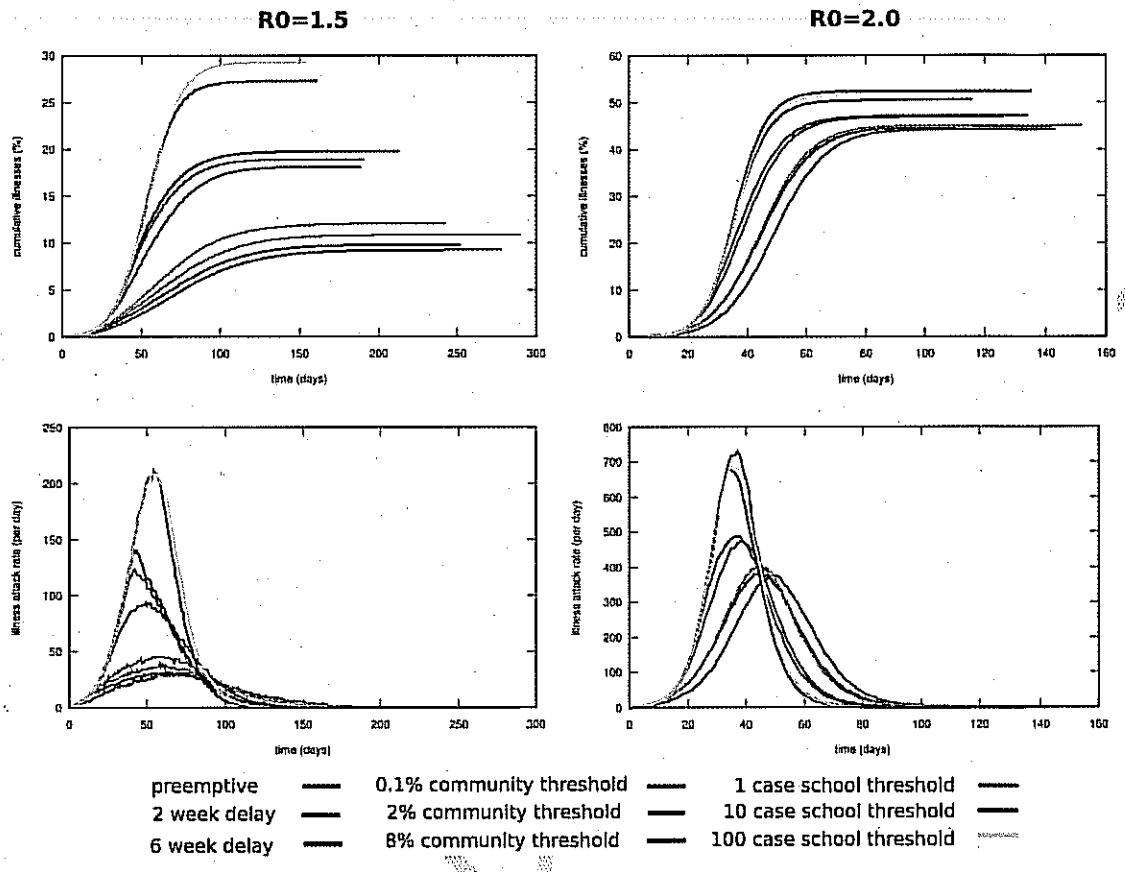
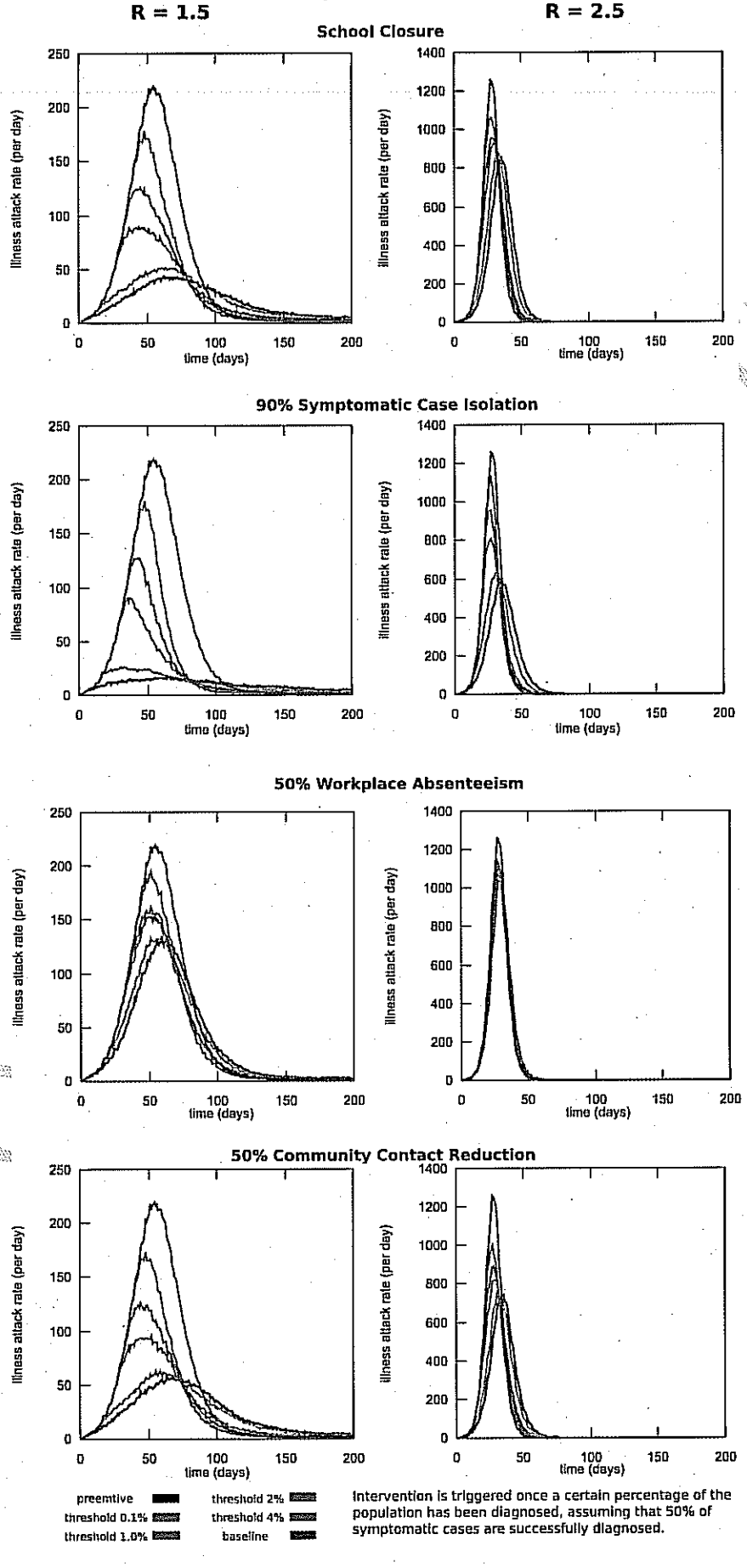


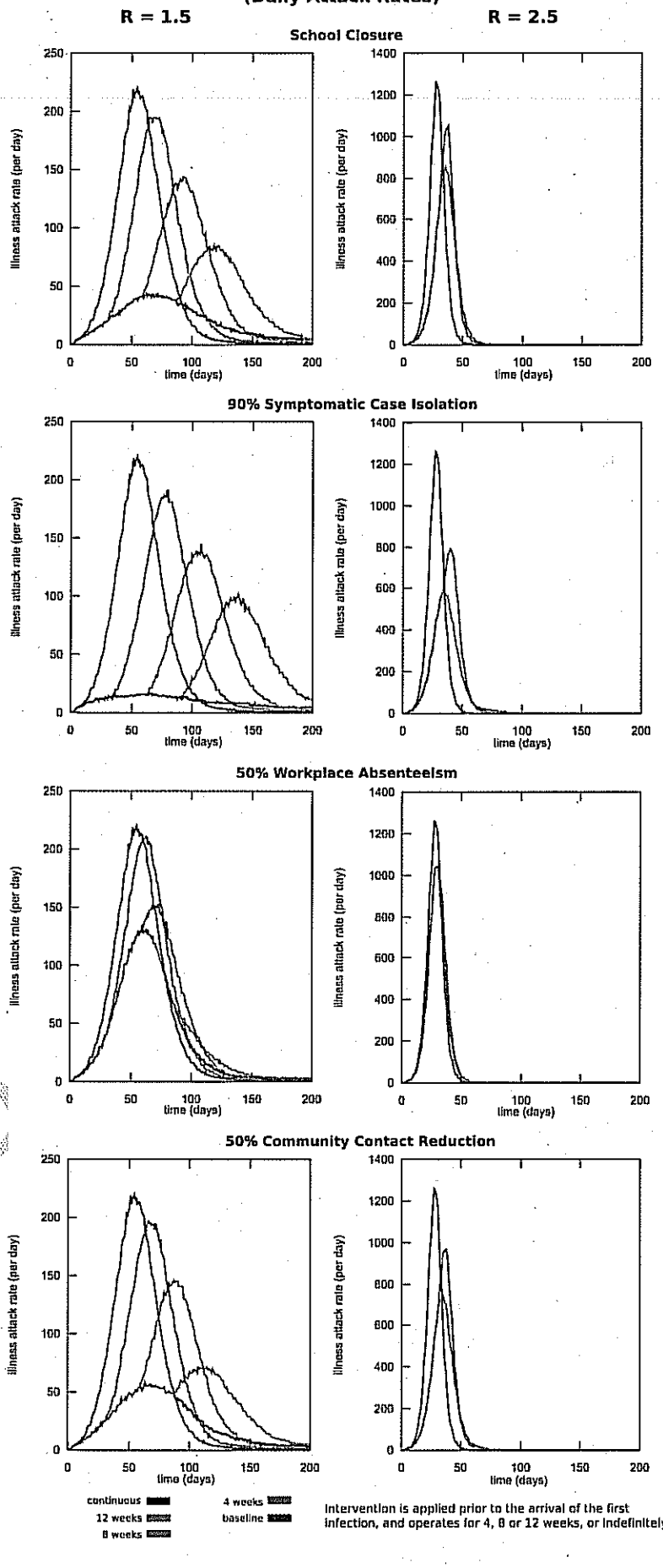
Figure 7 compares the two school closure policies and relates them to a theoretical policy of closing schools after a delay (of 0, 2 or 6 weeks) from the first case entering the diagnosed population. For an R_0 of 1.5, waiting for 0.1 % (30) diagnosed community cases or waiting for 1 case in each school is roughly equivalent to closing schools 2 weeks after the beginning of the epidemic, resulting in a final attack rate of approximately 11%. Waiting for 2% (600) community cases or 10 cases in each school is approximately equivalent to closing schools 6 weeks after the beginning of the epidemic, resulting in a final attack rate of approximately 19%. Waiting for 8% (2400) community cases, or 100 cases in each school, results in a final attack rate of approximately 28%.

Figure 2 : Timing of Intervention Implementation (Daily Attack Rate)



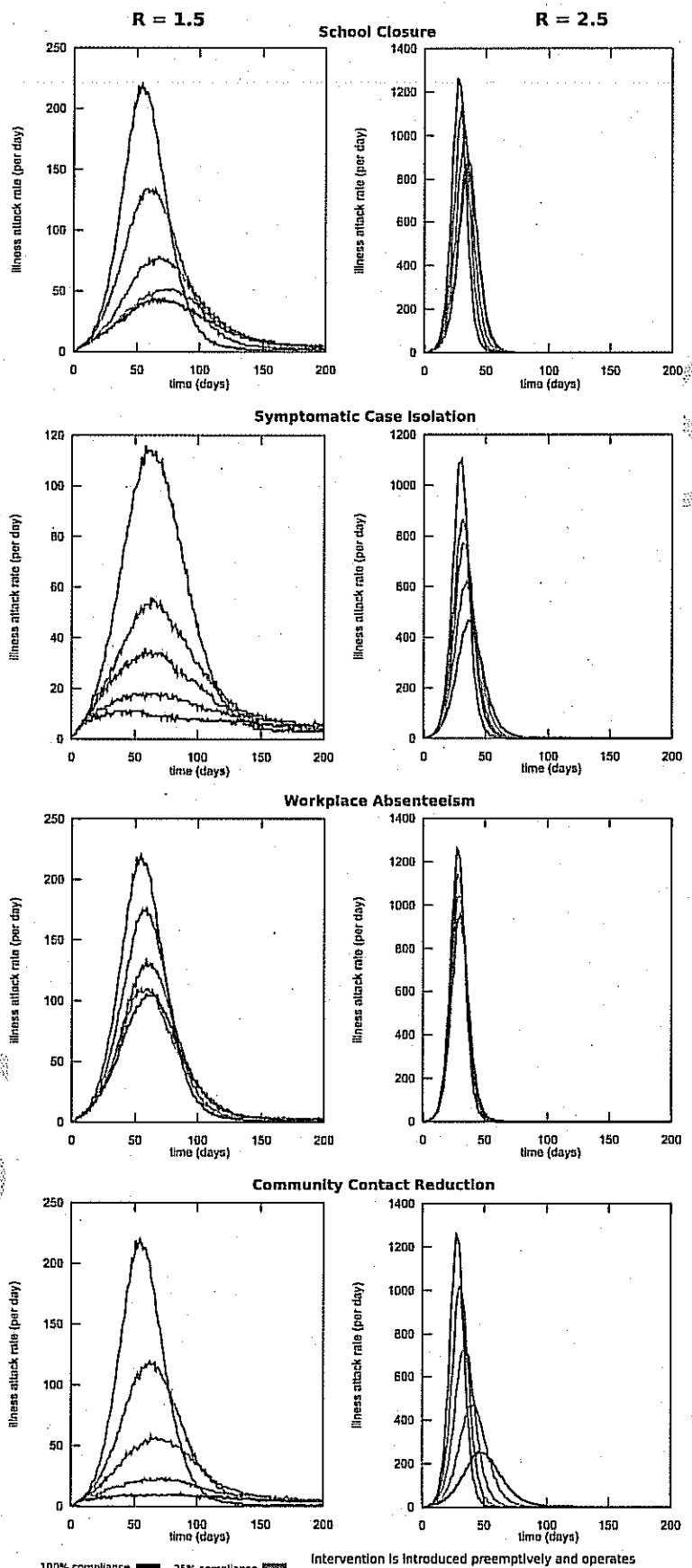
Intervention is triggered once a certain percentage of the population has been diagnosed, assuming that 50% of symptomatic cases are successfully diagnosed.

Figure 3 : Duration of Interventions (Daily Attack Rates)



Intervention is applied prior to the arrival of the first infection, and operates for 4, 8 or 12 weeks, or indefinitely.

Figure 4 : Levels of Compliance to Interventions (Daily Attack Rates)



Intervention is introduced preemptively and operates continuously. For the Case Isolation intervention measure, the 5 compliance levels represent household isolation of 100%, 87.5%, 75%, 67.5% and 50% (baseline) symptomatic cases.

Figure 5 : School Closure Combination Interventions (Daily Attack Rates)

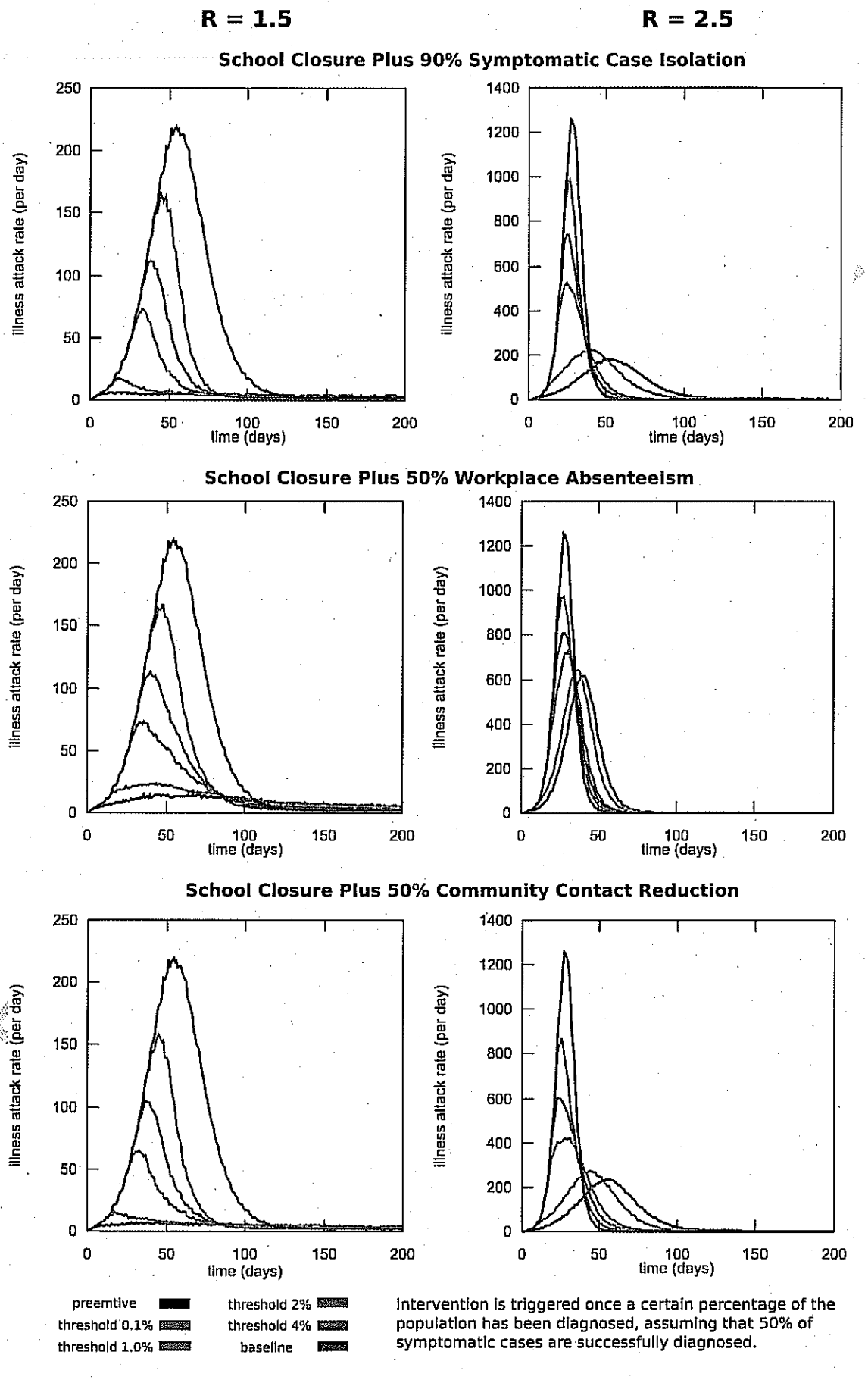
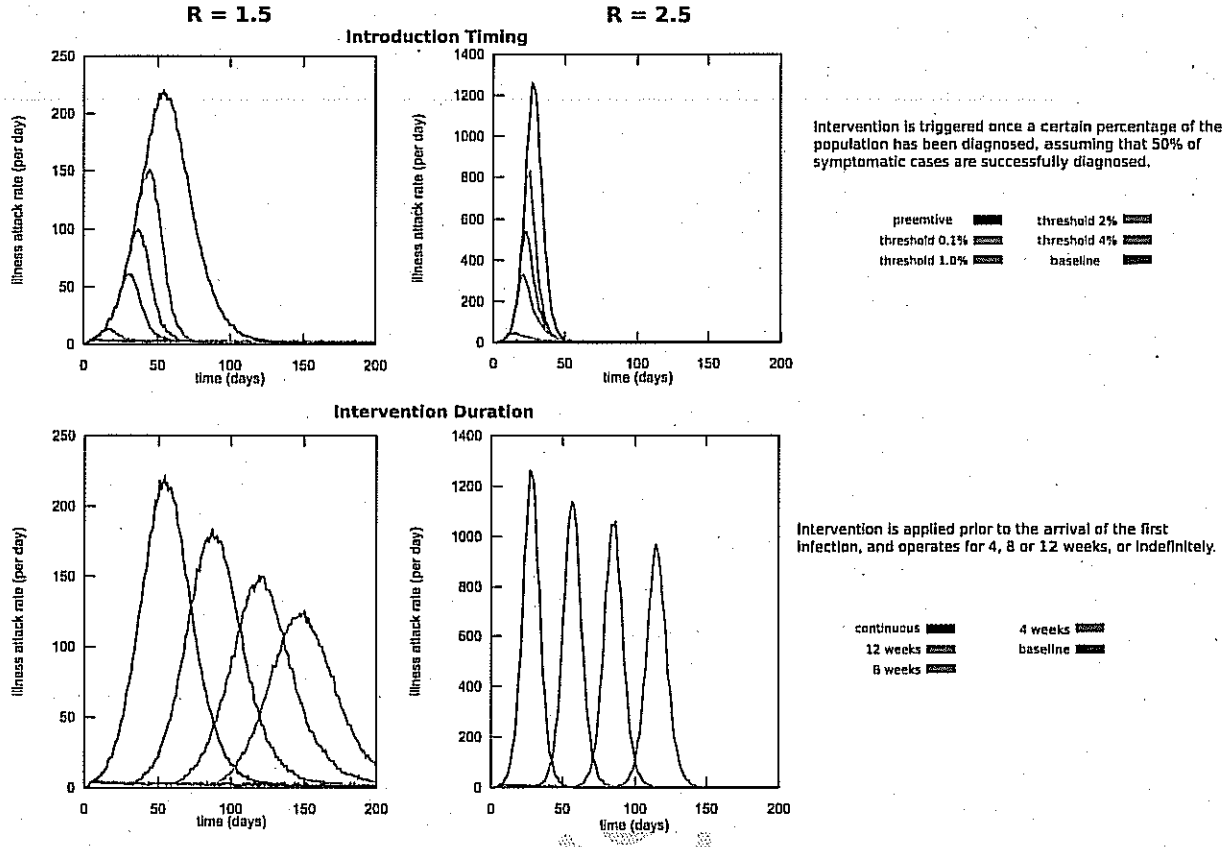


Figure 6 : Combination of All Interventions (Daily Attack Rates)



Baseline Simulation Model Parameters

Transmission and Infection Characteristics

<table>
<tr><th>parameter</th><th>meaning</th><th>value(s)</th></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>β_v</td><td>Fundamental transmission probability</td><td><table><tr><th>R_0</th><th>β_v</th></tr><tr><td>1.3</td><td>0.07</td></tr><tr><td>1.5</td><td>0.083</td></tr><tr><td>2.0</td><td>0.116</td></tr><tr><td>2.5</td><td>0.152</td></tr><tr><td>3.5</td><td>0.238</td></tr></table></td></tr>
<tr><td>$susc(I_s)$</td><td>Age-based susceptibility factor, a function of the potential infectee's (susceptible individual I_s) age.</td><td><table><tr><th>$AGE(I_s)$</th><th>$susc(I_s)$</th></tr><tr><td>0-5</td><td>0.8272</td></tr><tr><td>6-12</td><td>0.6248</td></tr><tr><td>13-17</td><td>0.88</td></tr><tr><td>18-24</td><td>0.79</td></tr><tr><td>25-44</td><td>0.5609</td></tr><tr><td>45-64</td><td>0.4187</td></tr><tr><td>65+</td><td>0.79</td></tr></table></td></tr>
<tr><td>$trans(I_i)$</td><td>Reduction in transmission probability for asymptomatic infectors.</td><td>1.0, if I_i is symptomatic;
0.5, if I_i asymptomatic</td></tr>
<tr><td>Pr(asymptomatic)</td><td>Probability that an individual experiences an asymptomatic infection.</td><td>0.2, for ages 0-18;
0.32, otherwise</td></tr>
<tr><td>Transmissibility Delay</td><td>Period of time between infection and the point at which an infected individual becomes infectious.</td><td>24 hours</td></tr>
<tr><td>Symptom Latency</td><td>Period of time between infection and onset of symptoms.</td><td>48 hours</td></tr>
<tr><td>Infection Duration</td><td>Period of time from infection to end of symptoms and infectiousness.</td><td>6 days</td></tr>
</table>

Contact and Behavioural Parameters

parameter	meaning	value(s)
Pr(withdrawal)	Probability that a symptomatic infected individual will withdraw to household upon appearance of symptoms.	0.9 for ages 6-17; 0.5 otherwise.
withdrawalPeriod	Period of time, from appearance of symptoms, that a withdrawing individual with remain at home	4 days
BCC	Background Contact Count. Number of effective community contacts made per day (for each individual participating in community contact).	4.0
maxClassSize	Maximum size of mixing groups in schools, childcare centre and adult education institutions	10
maxWorkgroupSize	Maximum size of workplace mixing groups.	10
seedRate	Average number of new infections imported into simulation per day.	1.0
seedDuration	Number of days at beginning of simulation in which infections are seeded.	365