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Strategies for mitigating an influenza pandemic with pre-pandemic H5N1 vaccines

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The recent worldwide spread of the swine-origin H1N1 2009 influenza outbreak has resulted in its designation as a pandemic by the World Health Organization. While it appears to result in mild symptoms, concern still exists that a more severe influenza pandemic with a high case fatality ratio might arise by reassortment or mutation of the currently circulating avian influenza (H5N1) virus. Given that recently developed candidate pre-pandemic H5N1 vaccines have shown potential for cross-strain protection, we investigated alternative vaccination strategies that exploit such vaccines using an agent-based simulation model of an actual community of approximately 30 000 people in a developed country. Assuming that a two-dose vaccination regimen would be required, we examined three vaccination strategies: pre-emptive, with vaccination applied prior to emergence of human-transmissible H5N1 influenza; reactive, where vaccination was initiated immediately after the first cases in the community were diagnosed; and a 'split' strategy where the first dose was administered pre-emptively during the pre-pandemic phase, with the second dose administered reactively. We showed that by effectively moving the delay between first and second doses into the pre-pandemic period, the split vaccination strategy achieved a substantially better attack rate reduction than the reactive strategy. Our results for an influenza strain with a reproduction number of 1.5 suggest reactive vaccination strategies that may be applicable to the current H1N1 2009 pandemic.

Keywords: pandemic influenza; H5N1 vaccines; vaccination strategies; epidemic simulation

1. INTRODUCTION

The threat of an influenza pandemic arising from the evolution of H5N1 avian influenza into a human transmissible form continues, with ongoing concern as to the occurrence of an influenza pandemic exhibiting more severe symptoms and a higher case fatality ratio than the current H1N1 2009 pandemic (Glezen 1996; Kieny *et al.* 2006; Mounier-Jack & Coker 2006). Many countries, often working with the World Health Organization (WHO), have developed pandemic plans that advocate use of social distancing and pharmaceutical interventions to minimize illness and mortality (Horvath *et al.* 2006; US Department of Health and Human Services 2006; UK Department of Health 2007). Vaccination is expected to form the major defence against a pandemic, with antiviral drug therapy and non-pharmaceutical interventions (such as school closure and home quarantining) also having a key role. While some countries have stockpiled neuraminidase inhibitor antiviral drugs, their use to control influenza pandemics

is an untested strategy. Furthermore, field data suggest that antiviral use during a pandemic may be associated with the development of clinically significant drug resistance (de Jong *et al.* 2005; Le *et al.* 2005; Lipsitch *et al.* 2007; Wu *et al.* 2009). Modelling has suggested early interventions that increase social distancing may postpone the time to peak daily incidence rates and limit the total number of cases and deaths attributed to pandemic influenza; however, great societal disruption will result from such measures (Longini *et al.* 2005; Ferguson *et al.* 2006; Germann *et al.* 2006; Glass *et al.* 2006; Wu *et al.* 2006; Milne *et al.* 2008; Kelso *et al.* 2009).

Vaccination is considered to be the most promising strategy for these reasons, but vaccines developed for seasonal influenza will offer little protection against H5N1. Promising developments of H5N1 vaccines are underway (Bresson *et al.* 2006; Lin *et al.* 2006; Treanor *et al.* 2006), with results from trials of low-dose adjuvant-enhanced, two-dose pre-pandemic vaccines demonstrating cross-strain protection (Leroux-Roels *et al.* 2007, 2008). The WHO has embarked on establishing an H5N1 vaccine stockpile and has indicated that it wishes to determine options for using such

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pre-pandemic vaccines. In a recent report, the WHO highlights the fundamental role of vaccination as the best form of protection for preventing and reducing illness and death owing to the H5N1 virus and indicates that modelling should be used to determine the effectiveness of various options for vaccination (WHO 2007).

The pandemic preparedness plans of most countries have focused on what we term reactive vaccination, initiated during a pandemic, owing to uncertainty as to the specific strain of H5N1 that may emerge in a human transmissible form. The suitability of alternative strategies, namely the split and pre-emptive strategies described below, now require consideration by public health authorities owing to the availability of candidate pre-pandemic vaccines. These developments show cross-strain and cross-clade protection to current H5N1 strains, with lasting priming effects of the first dose of at least six months and potentially much longer (Leroux-Roels *et al.* 2007; Stephenson *et al.* 2008). Together with modelling results that determine optimal vaccination regimes, such as those presented here, new vaccine developments should prompt reconsideration of how best to use vaccination, whether vaccines should be stockpiled and when they should be deployed. These include the suggestion that the first priming dose of a two-dose pre-pandemic vaccine regime should be administered in the pre-pandemic period (Osterhaus 2007; Jennings *et al.* 2008); this *split* vaccination strategy is considered in the study reported here.

Given the recent development of candidate pre-pandemic H5N1 vaccines, we then aimed to investigate different vaccination options with the intent of determining optimal mitigation strategies. We explored these strategies using a highly detailed spatio-temporal simulation model of an actual, relatively isolated community of approximately 30 000 people in a developed country. Our modelling of alternative vaccination strategies aimed to quantify the reduction in the illness attack rate achieved by different strategies. We explored various simulations to provide evidence to public health policy-makers as to how best to deploy candidate pre-pandemic vaccines.

2. MATERIAL AND METHODS

2.1. Simulation model

In previous work (Milne *et al.* 2008; Kelso *et al.* 2009), we constructed a detailed model of Albany, Western Australia, using Australian Bureau of Statistics census data, which identifies the age structure of all individuals in each *household* in the community (Australian Bureau of Statistics 2004). The households were each modelled and populated with uniquely identified individuals to match the census data, identifying individuals by age classes. The model was additionally populated with a set of schools and workplaces, referred to collectively as *contact hubs*. Western Australian government data were used to determine the location and population structure of schools, childcare facilities and employers within the Albany local government area. Software was developed to assign each child of an appropriate

age to a school or childcare centre, presuming that children attended a school as close to their home location as possible and ensuring that the known age structure of schools was maintained. Adults were assigned to workplaces similarly, using government commuter survey data. We further modelled the daily random contacts made by individuals using a community contact mechanism, biased to local interaction.

The simulation proceeded in a sequence of 12 h day/night cycles; this allows transmission in a day-time phase and a night-time phase (during which transmission occurs only in the home) to be modelled, with 12 h also being the smallest unit of time with which data related to infection development and contact locale are available. At the beginning of each cycle, the possible movement of each individual in the simulated population was determined according to the individual's current state with the new location being either a household or a workplace/school hub. The simulation algorithm then determined the interpersonal contacts of all individuals, the assumption being that all individuals in the same location were deemed to come into *potential infective contact*, with infection transmission potentially occurring between infectious and susceptible individuals. For larger hubs including schools, we assumed that individuals would come into contact with only a subset of the other members (comprising at most 10 persons). In addition, active individuals also engaged in random 'community' contacts, which was assumed to be somewhat local in nature, with contacts biased towards individuals sharing nearby home locations. The movement of individuals and the contact between them constitute a connected social network through which infection can spread (Bansal *et al.* 2006). The social network implied in our simulation is dynamic, with the contact degree of each individual changing with time (according to the day/night and weekday/weekend cycles) and in reaction to the progress of the epidemic (with individuals isolating themselves when symptomatic, or staying at home to supervise a child, for example). Full details can be found in Milne *et al.* (2008).

One infectious individual was randomly introduced into the population on day 1 and for each subsequent day, for the duration of the simulated period. Such a continuous stream of infectious individuals into the simulated population caused outbreaks to occur with 100 per cent likelihood.

Following contact between a pair of infectious and susceptible individuals (I_i, I_s), the likelihood of transmission is a function of the infectiousness of individual I_i , the age-based susceptibility of the susceptible individual I_s (which may be modified by vaccination) and the overall transmissibility of the influenza strain. A new infection state (either to remain susceptible or to become infected) was determined for the susceptible individual I_s using the transmission probability function P_{trans} as follows:

$$P_{\text{trans}}(I_i, I_s) = \beta \times \text{inf}(I_i) \times \text{susc}(I_s) \times \text{vaccine}(I_s),$$

where β is a transmission coefficient that captures the transmission potential of a particular virus strain.

This was initially chosen to give an epidemic with a final attack rate consistent with seasonal influenza and was then increased from this baseline value to achieve epidemics of higher reproduction numbers consistent with past and possible future pandemics, as described in previous work (Milne *et al.* 2008).

The infectivity parameter $\text{inf}(I_i)$ was set to 1 for symptomatic individuals and 0.5 for infectious but asymptomatic individuals, representing the reduction in infectiousness in asymptomatic individuals. The susceptibility parameter $\text{susc}(I_s)$ is directly dependent on the person's age, capturing age-varying susceptibility to transmission owing both to possible partial prior immunity and to age-related differences in contact behaviour, as described in Milne *et al.* (2008). The vaccination parameter $\text{vaccine}(I_s)$ represents the potential reduction in susceptibility owing to vaccination, representing some level of immunity. For unvaccinated individuals, or for individuals for whom the vaccine is ineffective, this parameter is 1.0, indicating no reduction in susceptibility. For individuals for whom vaccination was successful, this parameter varies over time, as described below in §3.5. Once an individual becomes infected their state determines the degree, timing and duration of infectiousness, as described in previous work (Milne *et al.* 2008).

2.2. Vaccine effectiveness

We modelled the use of a vaccine that has been manufactured prior to the start of an H5N1 pandemic and that would be administered before or during a pandemic. Trials of candidate H5N1 vaccines show that they require a two-dose regime to induce immunity (Bresson *et al.* 2006; Lin *et al.* 2006; Treanor *et al.* 2006). Vaccine effectiveness was modelled as follows: after vaccination with the first dose, each individual was randomly assumed to have had a successful or failed vaccination, with a probability according to the recipient's age. We examine vaccination with both a highly effective vaccine and one that is poorly matched; for the high-effectiveness case it is based on that of seasonal influenza, with efficacy of 70 per cent for those under the age of 65, or 60 per cent for those aged 65 years or older (Zangwill & Belshe 2004; Demicheli *et al.* 2007). Should available vaccines not be closely matched to an emergent H5N1 strain, or offer only limited cross-strain protection, we also examined a vaccine with half the seasonal effectiveness, i.e. 35 per cent (or 30% in those over 65), in line with that of mismatched seasonal influenza vaccines (Demicheli *et al.* 2007). For those where vaccination failed, the vaccine has no effect. We assume that vaccinated individuals who failed to develop immunity were no less infectious than unvaccinated individuals. It may be the case that vaccinated individuals who subsequently contract influenza experience a less severe infection, which may reduce morbidity and infectiousness. We do not model this assumption; hence our results are, if anything, somewhat conservative.

2.3. Modelling immunity

We assumed the population was immunologically naive and that complete immunity would not be achieved

without two doses of vaccine. Moreover, we assumed complete immunity would only be achieved in 70 per cent of the population after two doses of a customized vaccine (high effectiveness) and in 35 per cent after two doses of a candidate vaccine (low effectiveness), as described above. In the absence of definitive data, we made the conservative assumption that an individual would not develop any humoral immunity in the week immediately following the first vaccine dose. We further assumed that, in the proportion of the population destined to achieve full immunity, protection from infection would rise in a linear fashion from zero at one week to 30 per cent at three weeks, after the first vaccine dose.

We base the value of 30 per cent on data from two H5N1 vaccine trials that recorded the proportions of vaccinated subjects who had seroconverted (defined as having a fourfold neutralizing seroconversion rate) at 21 and 42 days after the initial dose (just before, and three weeks after the second dose, respectively). These data show that, of individuals who went on to seroconvert by day 42, between 21 and 68 per cent had seroconverted by day 21, the proportion depending on the combination of vaccine, dose size and use of adjuvant (Bresson *et al.* 2006; Leroux-Roels *et al.* 2007). We chose 30 per cent as a conservative estimate of the maximum level of partial immunity conferred after the first dose. Although vaccine trial data indicate the proportion of subjects who had 'protective' antibody titres or seroconversion at three weeks, we have used this proportion as an estimate of the final proportion of immunity at the individual level; that is, we assume that these data indicate that the first dose offers partial protection by reducing the probability of infection given an infectious challenge. In terms of cumulative probability of infection for individuals, our model is equivalent to a more direct model of the vaccine trial data (a model where there is a 30 per cent chance that each vaccinated individual jumps from zero immunity to full immunity on a uniformly distributed random day during the period of partial protection).

We assumed that full immunity developed one week after the second vaccine dose and modelled this immunity rising in a linear fashion from week 3 to week 4. This one-week time scale is based on the rapid immune response (seroconversion within 7 days) after doses of booster vaccines (Hayden *et al.* 2009). The change in the level of protection over time after vaccination is illustrated in figure 1.

Because these assumptions were critical to the model and because there is limited information to support the exact values we have used, we subjected this immunity-development time-scale assumption to a sensitivity analysis (§3.4), examining variation in the length of time for immunity to develop and variation in the level of partial protection conferred in the intermediate period. There are two distinct reasons for this sensitivity analysis. Firstly, the relationship between measured immune response and protection against infection challenge events is not precisely known; and secondly, we wish to know how our results might extend to virus strains and vaccines other than H5N1, which might have different immune response time scales, such as for H1N1 2009.

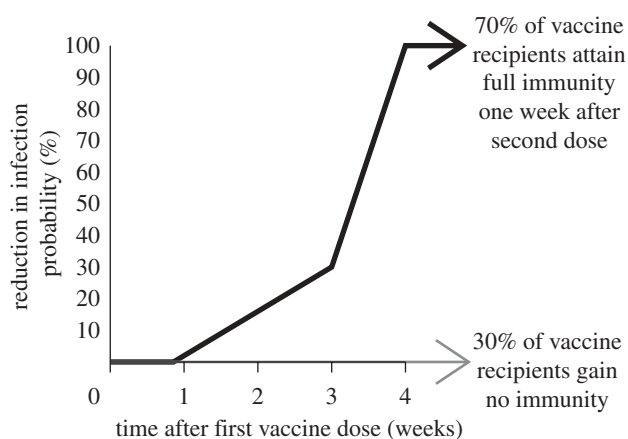


Figure 1. Model of immunity development over time following vaccination. Horizontal axis represents the time elapsed since the administration of the first vaccine dose; vertical axis shows the reduction in infection transmission probability for infectious contacts at that point in time.

Results of trials of candidate pre-pandemic vaccines indicate that the priming immune response of the first dose may be retained for periods of at least six months and possibly for as long as 7 years (Leroux-Roels *et al.* 2007; Stephenson *et al.* 2008; Hayden *et al.* 2009), with both trials indicating cross-strain protection using adjuvanted vaccines. We assumed there could be an arbitrary delay between the first and second doses, allowing for a split vaccination strategy where a single, priming dose is given prior to an epidemic, with a second, boosting dose given at the time of the epidemic. In this case, those for whom vaccination was successful developed a level of protection that remained fixed at 30 per cent until the second dose was given, whereupon they would go on to develop full immunity one week later (Hayden *et al.* 2009).

2.4. Vaccination prioritization

Both the vaccine stockpile size and the rate at which vaccination can be carried out are potentially limited, in which case a choice as to the order in which individuals are to be vaccinated must be made. In accordance with current pandemic planning (Horvath *et al.* 2006; US Department of Health and Human Services 2006; UK Department of Health 2007), we assumed that a fixed cohort of individuals would have the highest vaccination priority. In our simulation, this group was represented by the staff of the community hospital. Apart from this fixed priority group, we simulated two different prioritization strategies: a *vulnerable-first* strategy, based on the observed age-specific case fatality ratios of the 1957 influenza pandemic (Glezen 1996), the order being hospital staff first, then those aged 65 and above, those aged 0–5, those aged 45–64 and then youngest to oldest of the remainder of the population. Alternatively, we simulated a *transmitters-first* strategy where those disproportionately responsible for transmission were targeted. The prioritization order for this strategy was hospital staff first, then infants in child care together with child care staff, then school children and staff, then adult education

students and staff, then staff in businesses and then everyone else from youngest to oldest.

2.5. Vaccination strategies

We conducted simulation experiments to quantify the effect of three distinct two-dose vaccination strategies. We examined a *pre-emptive* strategy of vaccinating a certain percentage of the population in advance of an epidemic, assuming that the vaccination programme was completed at least four weeks prior to the introduction of the first infectious case into the community. We further simulated a *reactive* vaccination strategy, where the vaccination programme was initiated at the time the index infectious case arrived in the community. Finally, we simulated the *split* strategy where the priming first dose for a given percentage of the population was completed at least four weeks before the index case appeared, but the second boosting dose was administered under a programme similar to the reactive strategy, beginning at the introduction of the community index case.

We simulated these three vaccination strategies for high- and low-effectiveness vaccines, but assumed that a high-effectiveness vaccine would be unavailable for pre-emptive vaccination, giving the five vaccination strategies illustrated in figure 2. We examined different percentages of the population being vaccinated (20–100%) and with varying daily vaccination delivery rates (1–5% per day). For our simulated community of 30 000 individuals, the maximum rate corresponds to 1500 vaccinations per day. This realistic maximum could be achieved over a 20-day period by a dedicated staff of 20 working at a rate of 10 vaccinations per hour, 8 h per day. In the case that a vaccine is being distributed as it is produced (rather than being drawn from a stockpile), the reactive vaccination rate may be limited by the vaccine production rate and a 1–2% per day vaccination rate may then be the maximum possible. This may be the case with pandemic H1N1 2009 influenza when suitable vaccines become available.

These options were examined for basic reproduction numbers of 1.5 and 2.0, which are consistent with estimates derived from past pandemics (Ferguson *et al.* 2006) and are also considered for 2.5, which may be considered as a worst-case pandemic scenario. The reproduction numbers considered are also consistent with estimates for the current H1N1 2009 pandemic, namely 1.4–1.6 (Fraser *et al.* 2009) and 2.0–2.6 (Nishiura *et al.* 2009). The results for all simulated epidemics were averaged over 40 runs, each with stochastic choices made using a different random-number sequence. For all (averaged) simulations conducted, the standard deviation of final attack rates was less than 1.3 per cent of the population, as presented in table 1 in Kelso *et al.* (2009) where means and standard deviations are given for baseline unmitigated attack rates.

3. RESULTS

3.1. Comparison of strategies

In order to compare the vaccination strategies, we assumed that vaccination post epidemic initiation

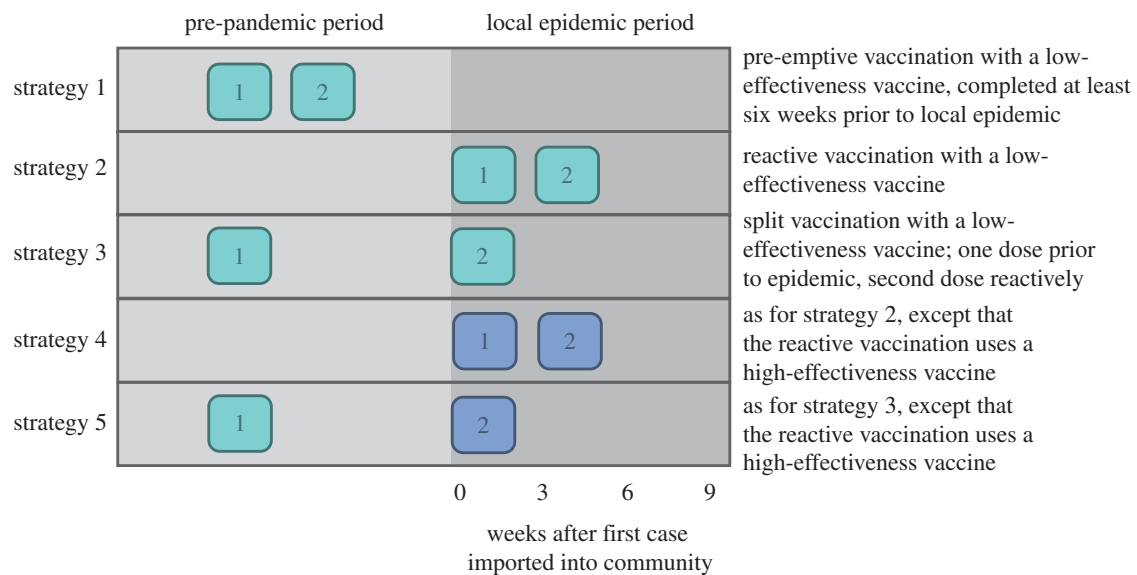


Figure 2. Schematic representation of five influenza pandemic vaccination strategies. Green, pre-pandemic vaccine; blue, pandemic vaccine dose.

Table 1. Simulated final illness attack rates and peak daily incidence rates for epidemics with unmitigated R_0 values of 1.5, 2.0 and 2.5. (Results are shown for the five vaccination strategies described in figure 2 for vaccination coverage levels of 20, 60 and 100%. Reactive and split vaccination is assumed to occur at a rate of 5% per day.)

		basic reproduction number R_0					
		1.5		2.0		2.5	
vaccination strategy	coverage	final attack rate (%)	peak daily incidence rate (per 10 000)	final attack rate (%)	peak daily incidence rate (per 10 000)	final attack rate (%)	peak daily incidence rate (per 10 000)
none		34	88	55	279	65	478
pre-emptive (low effectiveness)	20	19	31	44	167	56	342
	60	5	5	20	39	36	132
	100	3	4	11	17	25	77
reactive (low effectiveness)	20	20	35	45	186	59	390
	60	7	14	28	101	50	332
	100	6	14	24	97	48	326
split (low/low effectiveness)	20	20	35	45	178	57	354
	60	5	6	20	40	36	140
	100	3	4	12	19	26	85
reactive (high effectiveness)	20	10	13	35	118	52	313
	60	3	10	10	48	34	225
	100	2	9	8	47	30	215
split (low/high effectiveness)	20	10	13	35	105	49	249
	60	1	2	2	3	4	6
	100	1	2	1	2	1	4

took place at the maximum feasible rate of 5 per cent. A summary comparing the pre-emptive, reactive and split vaccination strategies is given in figure 3. The results of vaccinating 0, 20, 60 and 100 per cent of the population are shown in table 1, which presents both the cumulative attack rate and the peak daily incidence rate (per 10 000). It should be emphasized that these results apply under a number of specified assumptions, such as the longevity of the effect of the priming dose, and that reactive and second-dose split vaccination begins

at the same time as the first infectious cases arrive in the community.

For $R_0 = 1.5$ with an unmitigated attack rate of 34 per cent, all strategies with coverage of 60 per cent and over reduced the attack rate to below 10 per cent. With 40 per cent coverage the reactive strategy with a low-effectiveness vaccine was the only strategy to fail to reduce the attack rate below 10 per cent. With 20 per cent coverage, only the reactive and split strategies using the high-effectiveness vaccine reduced the

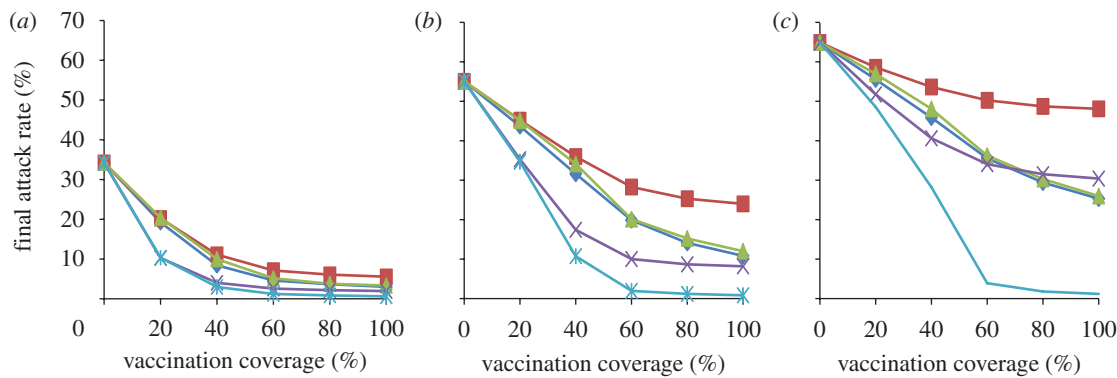


Figure 3. Final illness attack rates for five vaccination strategies, assuming vaccination coverage levels from 0 to 100%. (a) $R_0 = 1.5$, (b) $R_0 = 2.0$, and (c) $R_0 = 2.5$. Dark blue lines, pre-emptive vaccination, low-effectiveness vaccine; brown lines, reactive vaccination, low-effectiveness vaccine; purple lines, reactive vaccination, high-effectiveness vaccine; green lines, split vaccination, low-effectiveness vaccine; light blue lines, split vaccination, high-effectiveness vaccine.

attack rate below 10 per cent, where the split strategy used a low-effectiveness first dose.

For $R_0 = 2.0$ with an unmitigated attack rate of 55 per cent, only the split vaccination strategy using the high-effectiveness vaccine (for the second dose) was capable of reducing the attack rate below 10 per cent given a minimum 40 per cent coverage, reducing the attack rate to 2 per cent with 60 per cent coverage. By contrast, reactive vaccination with a high-effectiveness vaccine reduced the attack rate to 17 per cent at 60 per cent coverage. Using a low-effectiveness vaccine the best that could be achieved (at 100% coverage) was 11, 12 and 24 per cent attack rates for pre-emptive, split and reactive strategies, respectively.

For $R_0 = 2.5$ with an unmitigated attack rate of 65 per cent, only the split (high effectiveness) strategy might reduce the attack rate below 10 per cent, if coverage were above 55 per cent. The benefit of increasing coverage with both reactive strategies essentially levelled off with coverage above 60 per cent, while the split and pre-emptive (low effectiveness) strategies had a linearly improving reduction in attack rates up to 100 per cent coverage. For this high reproduction number, reactive vaccination even with 100 per cent coverage performed poorly, reducing the attack rate to 55 per cent for a low-effectiveness vaccine and to 48 per cent for a high-effectiveness vaccine. For comparison, using the split strategy with a high-effectiveness vaccine and coverage of at least 60 per cent the attack rate was reduced to less than 5 per cent and an epidemic is prevented. By contrast, reactive vaccination with a high-effectiveness vaccine reduced the attack rate to 30 per cent at 100 per cent coverage, clearly showing the timing advantage of delivering the priming first dose of the split strategy in the pre-pandemic period. Note that, for coverage above 70 per cent, the pre-emptive and split (low effectiveness) outperformed the reactive (high effectiveness) strategy.

Figure 4 depicts the time course of epidemics with R_0 values of 1.5, 2.0 and 2.5. Cumulative attack rates for baseline (unmitigated) epidemics are shown compared with the outcomes of the reactive and split vaccination strategies. It can be seen that for $R_0 = 2.0$ or

greater (figure 4*b,c*), the reactive vaccination strategy would begin producing fully immune individuals only after the epidemic is fully established and growing rapidly.

For a low-effectiveness vaccine, providing total immunity to 35 per cent of those vaccinated, the pre-emptive and split vaccination strategies had a similar effect on reducing the attack rate, and both had more impact on attack rate reduction than the reactive strategy. As the percentage of the population vaccinated increased, the difference became more marked, as it did with an increasing reproduction number. Figure 3 shows that, for $R_0 = 2.5$, with 60 per cent coverage, a 65 per cent unmitigated attack rate was reduced by the reactive strategy by only 15 per cent to a 50 per cent attack rate, but by 30 per cent to a 35 per cent attack rate for both the split and pre-emptive strategies. With the same high reproduction number, but with 100 per cent coverage, the reactive strategy reduced the attack rate to 48 per cent while the split and pre-emptive strategies reduced it to 25 per cent.

Using a high-effectiveness vaccine, providing immunity to 70 per cent of those vaccinated, the split strategy was more effective than a reactive strategy, with a substantial difference arising with higher vaccine coverage and higher reproduction numbers. For $R_0 = 2.0$, and with a coverage of 40 per cent, an unmitigated attack rate of 55 per cent was reduced to 11 per cent by the use of the split strategy compared with 17 per cent with the reactive strategy (6% difference). For $R_0 = 2.5$ and a coverage of 40 per cent, the difference between using the split strategy compared with the poorer reactive strategy was 12 per cent; with a coverage of 60 per cent or more, the difference was at least 30 per cent.

3.2. Coverage levels

The results presented in figure 3 indicate the effect various vaccination coverage percentages had on reducing attack rates for each vaccination strategy. Under some strategies and some reproduction numbers, the results suggest coverage level thresholds beyond which little further reduction in attack rates may be achieved by increased vaccination coverage. Limited vaccine

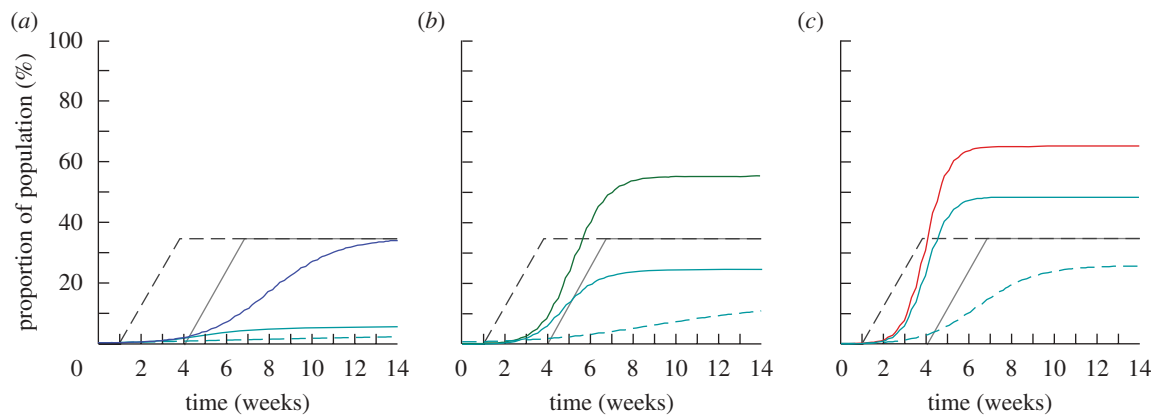


Figure 4. Cumulative attack rates for unmitigated epidemics are shown for R_0 values of 1.5 ((a) blue), 2.0 ((b) green), and 2.5 ((c) red). Assuming a vaccination programme using a low-effectiveness (35% VE) vaccine distributed at a rate of 5% per day, the number of individuals expected to be fully immune after vaccination is shown for the reactive vaccination strategy (solid grey lines) and split vaccination strategy (dashed grey lines). For the three R_0 values, the cumulative attack rates are shown for the reactive strategy (solid aqua lines) and split strategy (dashed aqua lines).

supplies may result in substantially less than 100 per cent vaccination coverage and the results give guidance as to the benefits of one strategy over another when only limited supplies are available. Not surprisingly, the higher the coverage, the larger the reduction in attack rate. For $R_0 = 1.5$, a rapid reduction was achieved as the percentage of the population vaccinated was increased up to approximately 50 per cent coverage for all strategies. Further reductions in attack rate were much less marked as the coverage rate was increased beyond 50 per cent. In contrast, with epidemics with the higher reproduction numbers, the beneficial impact of increased coverage levels varied considerably between vaccination strategies. For both the 2.0 and 2.5 reproduction numbers, the split and pre-emptive strategies using a low-effectiveness vaccine had an almost linear reduction in attack rate up to 100 per cent coverage. For both higher reproduction numbers the reactive strategy using a high-effectiveness vaccine gained little for coverage rates higher than 60 per cent. For the split strategy using the high-effectiveness vaccine, coverage beyond 50 per cent for $R_0 = 2.0$, and higher than 60 per cent for $R_0 = 2.5$, achieved little further reduction beyond the very low attack rates that occur at these threshold coverage levels.

In the latter case ($R_0 = 2.5$, split vaccination with a high-effectiveness vaccine), the vaccination coverage threshold is due to a herd immunity effect: the very low final attack rate is evidence that the mitigated R_0 is close to 1.0. On the other hand, the lack of further reduction of attack rate in the corresponding reactive vaccination case is not a herd immunity effect: it occurs because the progress of the epidemic overtakes the vaccination programme, meaning that the last 40 per cent of the vaccine is distributed too late. The fact that the reactive vaccination strategy is limited by vaccination rate (while the split strategy is not) is evidenced in figure 5, which indicates that increasing the vaccination rate above 5 per cent per day would improve reactive vaccination (figure 5*b*(iii)), but will not further improve split vaccination (figure 5*a*(iii)).

3.3. Daily vaccination rates

Figure 5 presents the result of simulation experiments that examine the impact of varying daily vaccination rates ranging from 1 per cent of the population per day to a maximum of 5 per cent per day, assuming 100 per cent coverage of the population. The reactive and split strategies were compared for three reproduction numbers for both high- and low-effectiveness vaccines and for both the vulnerable- and transmitters-first prioritization methods. Figure 5 again demonstrates that the split vaccination strategy performed better than the reactive strategy and, additionally, that the transmitters-first priority better reduced the attack rate than the vulnerable-first priority.

There was a key daily vaccination threshold when using the split strategy (figure 5*a*), where vaccinating beyond these given threshold numbers had little further effect on reducing the attack rate. For $R_0 = 1.5$ and the low-effectiveness vaccine, a threshold of 2 per cent existed, but with the high-effectiveness vaccine, the threshold was 1 per cent for both priority regimes. With $R_0 = 2.0$, key thresholds were 3 per cent for the low-effectiveness vaccine and 2 per cent for the high-effectiveness vaccine using the vulnerable-first priority, but in both cases the thresholds were lower (approx. 2% and 1%, respectively) if the transmitters-first strategy was used. When $R_0 = 2.5$ and using the split strategy, a 2 per cent per day threshold was key when using a high-effectiveness vaccine and a transmitters-first delivery prioritization strategy. This threshold changed to 3 per cent for the vulnerable-first priority and to 3 per cent for both priority methods when using the low-effectiveness vaccine. Under all daily vaccination rates ranging from 1 to 5 per cent, the split vaccination always performed substantially better than a reactive strategy. While a key threshold existed for the split strategy, the benefits with increasing daily vaccination rates using the reactive strategy up to and including 5 per cent per day appeared linear for reproduction numbers 2.0 and 2.5 (figure 5*b*).

These results illustrate the timing advantages of the split strategy (and indeed the transmitters priority over

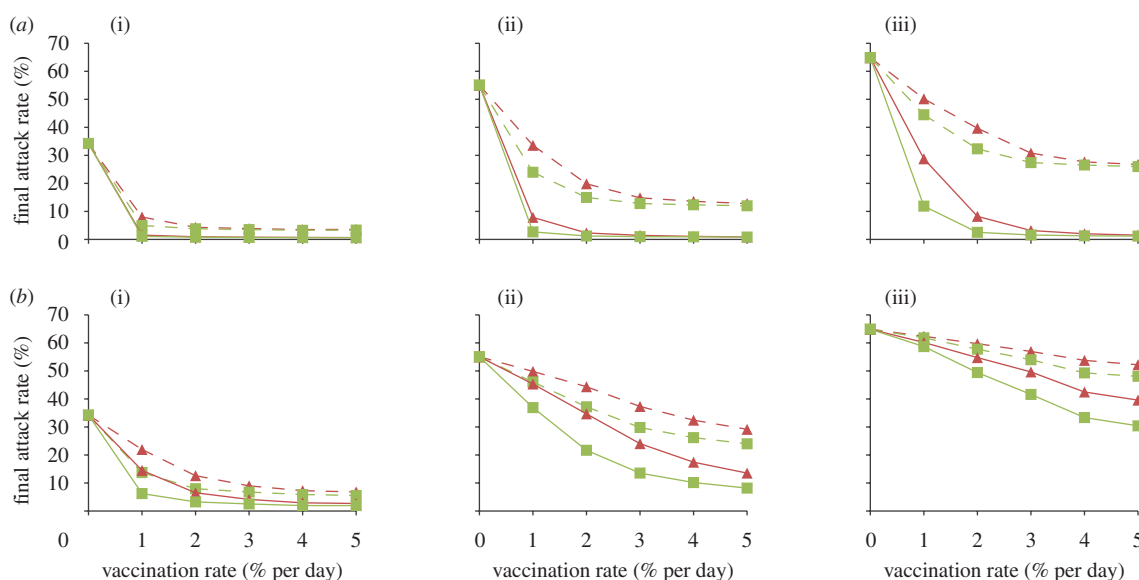


Figure 5. Relationship between final attack rate and daily vaccination rate for (a) split vaccination and (b) reactive vaccination, assuming 100% vaccination coverage. (a,b)(i) $R_0 = 1.5$; (a,b)(ii) $R_0 = 2.0$; (a,b)(iii) $R_0 = 2.5$. Dashed brown lines, vulnerable first, low effectiveness; dashed green lines, vulnerable first, high effectiveness; solid brown lines, transmitters first, low effectiveness; solid green lines, transmitters first, high effectiveness.

the vulnerable priority) when compared with the reactive strategy where no obvious delivery rate thresholds exist (figure 5*b*). The reduction in attack rate for the reactive strategy was linear with respect to increases in the delivery rate and for all rates and reproduction numbers considered resulted in significantly higher attack rates. These results signify the logistical benefits of the split strategy over the reactive one when considering the feasibility of vaccinating given percentages of the population on a daily basis, and again give credence to the split strategy being superior to the reactive one.

3.4. Sensitivity analyses

Owing to uncertainty as to some of the key assumptions made, and following the approach of Ferguson *et al.* (2005, 2006) and Germann *et al.* (2006), we tested the sensitivity of our results to alternative parameter settings related to serial interval, age-specific attack rate and immunity-development time scales. These particular parameters were selected as those which most strongly influenced the outcome of the vaccination interventions modelled in our study, and those which previous simulation experiments by the authors (Milne *et al.* 2008, electronic supplementary material, text S2) indicate would have the most impact on the results.

3.5. Immunity development

Our simple model of immunity development after successful vaccination, illustrated in figure 1, is based on observations that individuals do not achieve a full immune response prior to receipt of a second dose (Leroux-Roels *et al.* 2007), but that immunity acquisition is rapid after the second dose (Hayden *et al.* 2009). The degree of immunity present in the intermediate period between vaccine doses is uncertain, both because immune response observations from vaccine trials

(Bresson *et al.* 2006; Lin *et al.* 2006; Treanor *et al.* 2006; Leroux-Roels *et al.* 2007) are sampled at 21-day (or 28-day) intervals and because the precise relationship between measured immune response and protection against infectious challenge is not known. In order to gauge the sensitivity of our results to these unknowns, we systematically varied three key parameters:

- (i) The length of time between vaccine doses. Our baseline assumption was three weeks, matching that of the H5N1 vaccine trials. We examined longer time periods between doses, namely from three to six weeks.
- (ii) The time to develop full immunity after the second dose. Our baseline assumption was that full immunity was conferred one week after the second dose. We examined alternative delays of 3, 14 and 21 days to reach full immunity.
- (iii) The level of 'partial protection' against infection achieved before the second dose. Our baseline assumption was that after one dose individuals who would achieve full immunity after the second dose were 30 per cent less likely to become infected if they contacted an infected individual. We examined alternative 15 and 50 per cent reductions in infection probability.

Of these, the most influential was the time between vaccine doses (figure 6). As might be expected, the effect of greater vaccine dose spacing on the reactive vaccination strategy is similar to a reduced rate of vaccination, with vaccination become decreasingly effective with the increasing vaccine dose spacing. The effect is most pronounced at $R_0 = 2.0$, where increasing the vaccine dose spacing from three to four, five or six weeks increases the final attack rate from 8 to 17, 28 or 37 per cent, respectively (assuming vaccination with a

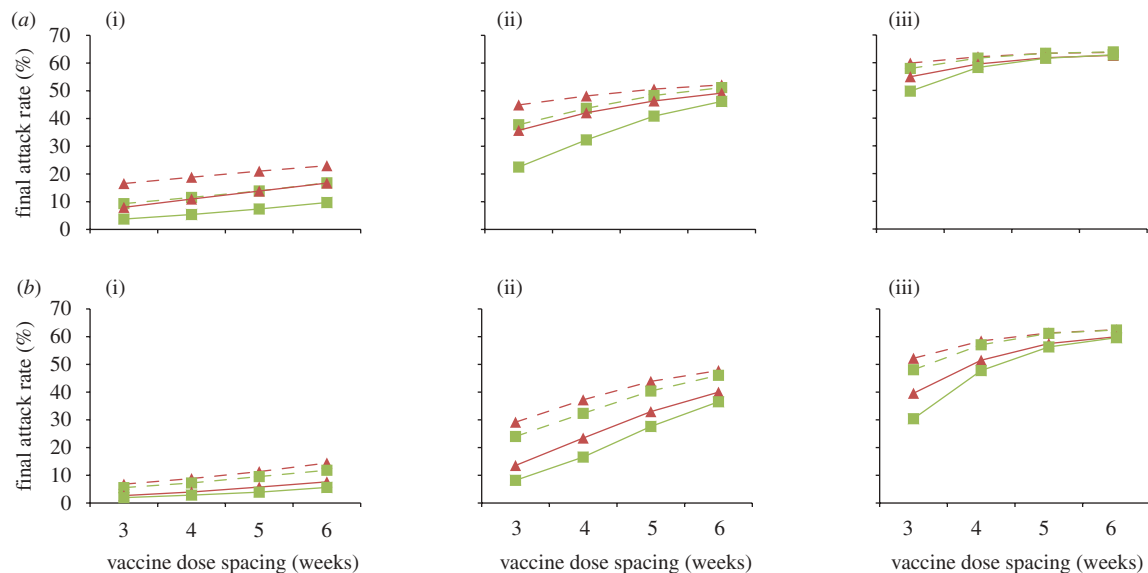


Figure 6. Relationship between final attack rate and spacing between vaccine doses for (a) 60% vaccination coverage at 2% per day and (b) 100% vaccine coverage at 5% per day. (a,b)(i) $R_0 = 1.5$; (a,b)(ii) $R_0 = 2.0$; (a,b)(iii) $R_0 = 2.5$. Dashed brown lines, vulnerable first, low effectiveness; dashed green lines, transmitters first, low effectiveness; solid brown lines, vulnerable first, high effectiveness; solid green lines, transmitters first, high effectiveness.

high-effectiveness vaccine at a rate of 5% per day and 100% vaccine coverage). Note that varying the time between vaccine doses is relevant only to the reactive strategy since the split strategy assumes that the first vaccine dose is delivered in the pre-pandemic period; this is prior to simulation initiation, which occurs on pandemic emergence in the modelled community.

The reactive vaccination strategy showed some sensitivity to the delay in reaching full immunity (after the administration of the second dose), with the effect being more marked at higher R_0 values. For example, at $R_0 = 2.5$, increasing the delay to full immunity from 7 to 21 days after the second dose increased the final attack rate from 30 to 41 per cent. The split vaccination strategy was relatively insensitive to the period required to reach full immunity: the greatest change was observed with $R_0 = 2.5$ with a high-effectiveness vaccine; increasing the full immunity delay from 7 days to 21 days increased the final attack rate from 8 to 12 per cent.

The level of partial protection provided by vaccines in the intermediate period between vaccination doses was most significant in the case of reactive vaccination at $R_0 = 2.0$, with vaccination at 5 per cent per day, a high-effectiveness vaccine and 100 per cent vaccine coverage. In this case, a 15 per cent level of partial protection gave a final attack rate of 40 per cent (compared with 30% for our baseline assumption of 30% partial protection). In all other cases, the lower 15 per cent level of partial protection resulted in an attack rate no more than 5 per cent higher than the baseline assumption, in most cases being less than 2 per cent. In all cases, a vaccine with a higher level of partial protection (50% rather than 30%) did not result in any significant improvement in effectiveness.

3.6. Influenza natural history assumptions

Our simulations indicate that timing factors in immunity development and deployment of vaccines can

significantly affect the outcome of a vaccination programme. We therefore examined the sensitivity of each vaccination strategy to alternate assumptions about the time scale of the progression of infection in individuals. Slower or more rapid progression of infection in individuals gives rise to longer or shorter serial intervals, which in turn influences the timing of the overall epidemic. Our baseline assumption used in the main results was that individuals became infectious (at a reduced level) 24 h after infection, and exhibited symptoms (and became fully infectious) 24 h later. We examined shorter and longer time scales, with 12 or 36 h from infection to initial infectiousness, respectively, with symptoms developing 24 h later in both cases. In all cases, we modelled the total duration of infection as 6 days. For each of these time scales, we adjusted the basic infection probability parameter β to give unmitigated epidemics with our representative R_0 values of 1.5, 2.0 and 2.5. We performed this step because altering the individual infection time scale parameters while keeping all other parameters fixed results in epidemics with different R_0 values and final attack rates; our goal, however, was to compare vaccination strategies for epidemics with the same R_0 but different underlying characteristics. The characteristics of these alternative baseline epidemics are given in table 2.

We found that the reactive vaccination strategy is very sensitive to the individual infection time scale. In the case of 100 per cent coverage and a vaccination rate of 5 per cent per day, decreasing or increasing the serial interval by 0.7 days (17 h) resulted in an approximate doubling or halving of the final attack rate, as shown in figure 7. In contrast, the split vaccination strategy was relatively robust to the individual infection time scale, the greatest sensitivity occurring at higher R_0 values and slower vaccination rates: at $R_0 = 2.5$ in the case of 60 per cent vaccination coverage and

Table 2. Characteristics of baseline (unmitigated) epidemics with three different time scales for the progression of infection in individuals: short (12 h to infectiousness, 36 h to symptom onset), medium (24 h to infectiousness, 48 h to symptom onset), and long (36 h to infectiousness, 60 h to symptom onset). For each infection time scale, the serial interval, day of greatest daily incidence rate and final attack rate are given; results are repeated for R_0 values of 1.5, 2.0 and 2.5.

	infection time scale	serial interval (days)	day of peak incidence rate	final attack rate (%)
$R_0 = 1.5$	short	2.3	47	33.7
	medium	3.0	58	34.2
	long	3.7	71	31.6
$R_0 = 2.0$	short	2.2	29	55.2
	medium	2.9	38	55.1
	long	3.6	48	53.7
$R_0 = 2.5$	short	2.1	22	65.0
	medium	2.7	29	64.9
	long	3.5	37	64.0

vaccination at 2 per cent per day, the short, medium and long individual infection time scales gave final attack rates of 9.6, 6.8 and 4.8 per cent, respectively.

Our baseline model assumed an influenza epidemic in which children have a higher attack rate than adults. This pattern is typical for seasonal influenza and was seen in the 1957 pandemic (Glezen 1996). We found that a vaccination strategy that prioritized children (the transmitters-first strategy described previously) was more effective in reducing the final attack rate than one that prioritized according to influenza case fatality risk, assuming the age-specific case fatality rate of the 1957 pandemic (Glezen 1996). Given that a new pandemic influenza strain may exhibit a different age-specific attack rate profile, we examined a scenario where there was an even attack rate among age groups, such as occurred with the 1968 pandemic (Davis *et al.* 1970). We therefore examined the effectiveness of each vaccination strategy (and prioritization strategy) in this even attack rate scenario.

We found that our results are largely insensitive to the age-specific attack rate profile. Each of the basic vaccination strategies (pre-, reactive or split vaccination) was affected in the same way by changing the attack rate profile. The effectiveness of the transmitters-first and vulnerable-first prioritization strategies was differentially affected by the change in attack rate profile. In most cases the vulnerable-first strategy was slightly more effective, with final attack rates being 1–2% lower. Conversely, the transmitters-first prioritization was less effective with final attack rates being mostly 1–2% higher, although larger differences were observed (up to 7%) at R_0 values of 2.5 in cases of partial vaccine coverage.

The magnitude of these changes was, however, not sufficient to change the optimal strategy for attack rate reduction: in all cases, prioritization of school children remained optimal even when attack rates across age groups were equal.

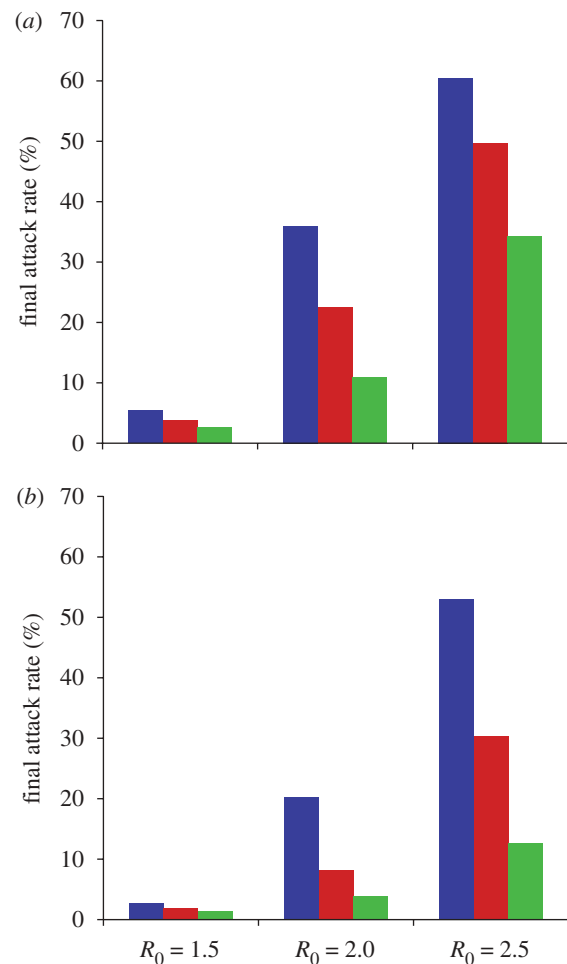


Figure 7. Final attack rates for the reactive vaccination strategy applied to epidemics with three different individual infection time scales—short (blue), medium (red) and long (green)—as described in the text. Results are shown for (a) 60% vaccination coverage at 2% per day and (b) 100% vaccine coverage at 5% per day.

4. DISCUSSION

We have examined vaccination scenarios that may be adopted if a readily transmissible human-to-human strain of influenza H5N1 emerges, a quite different situation from the current influenza H1N1 2009 pandemic where only the reactive strategy is appropriate. Our results have shown that the pre-emptive and split vaccination strategies produced the greatest reduction in the illness attack rate, with the reactive strategy giving the least mitigating effect. In all simulation experiments performed, the split and pre-emptive strategies performed equally well using vaccines with the same effectiveness. This highlights the ability of the split strategy to create a sufficient pool of immune individuals rapidly enough to significantly reduce the epidemic growth rate, even though vaccination with the second dose is not initiated until infectious cases arrive in the community. Our results suggest that we gain nothing by delivering both doses of a pre-pandemic vaccine pre-emptively during the pre-pandemic period, compared with only vaccinating with the first priming dose in this period and following this up with a reactive

second boosting dose after epidemic emergence, as suggested by Jennings *et al.* (2008) and Osterhaus (2007). Moreover, the split strategy may be preferred to the pre-emptive strategy for two reasons: one, it requires only a single dose to be administered to prime the population prior to pandemic emergence, halving the initial cost in comparison with pre-emptive vaccination; and two, it allows for the candidate second boosting dose to be continuously updated to better match currently circulating H5N1 strains, to be produced ready for distribution when human-transmissible H5N1 emerges.

In our study we have examined the three vaccination strategies using both high- and low-effectiveness vaccines, corresponding to both well and poorly matched vaccines. We thus cover the situation where an effective vaccine *is* available at the time the pandemic strain enters the community. This is a feasible scenario given studies which suggest that some existing pre-pandemic H5N1 vaccines may be good matches given evidence of cross-clade protection (Leroux-Roels *et al.* 2007).

The alternative is a scenario where a high-effectiveness vaccine is unavailable, either owing to the failure to develop a well-matched vaccine or the deliberate use of a smaller antigen dose as part of a dose-sparing regime (Riley *et al.* 2007), which results in a less effective vaccine. In this situation where only a less effective vaccine is available, our results indicate that a sufficiently large quantity of vaccine can be effective if it can be deployed in a timely fashion. This result can be seen in a marked fashion when we examine the highest reproduction number considered ($R_0 = 2.5$); here the pre-emptive and split strategies with the low-effectiveness vaccine outperformed reactive vaccination with the high-effectiveness vaccine for vaccine coverage levels greater than 60 per cent. With 100 per cent coverage, the difference is most apparent, with the split and pre-emptive strategies (both low effectiveness) reducing the attack rate to 26 per cent, while the reactive (high effectiveness) strategy reduces it to 30 per cent. This suggests that waiting until a pandemic emerges before developing and deploying a customized, pandemic vaccine may be a poorer strategy than using larger quantities of a lower effectiveness, candidate vaccine under a split strategy.

The results presented indicate the advantages of using the pre-emptive and split vaccination strategies over the reactive strategy under the three reproduction numbers considered, with the advantages becoming more marked for higher R_0 numbers. Reproduction number (together with serial interval) characterizes the rate of growth in the number of infectious cases, which is a time-dependent property. The difference in the mitigating effect of the pre-emptive and split strategies over the reactive strategy is also related to time. With pre-emptive vaccination, all individuals who will become immune owing to vaccination (rather than owing to developing immunity through becoming infected and recovering) are in this immune state *prior* to the introduction of the index cases into the community at the start of the epidemic, meaning that some level of herd immunity exists at epidemic onset. In contrast, as the best-case reactive strategy is initiated

at the same time as the index case appears in the community, this strategy takes a minimum of four weeks for full immunity to occur in the first individuals vaccinated. The difference in the rate of growth of an epidemic owing to the higher transmissibility of a particular virus strain, as characterized by a higher reproduction number, determines how effective reactive vaccination may be.

When comparing the split and reactive strategies, the higher the reproduction number R_0 , the less effective reactive vaccination becomes. This arises owing to the higher epidemic growth rate with the higher R_0 where the number of infected individuals increases faster than the ability of the maximum vaccination rate considered (5%) to deliver a sufficient pool of immune individuals at any point of time. In effect, epidemic development ‘outruns’ the creation of immune individuals via vaccination. In contrast, and for all reproduction numbers considered, the split strategy creates immune individuals faster than the unmitigated epidemic growth rate.

4.1. Comparison with related work

Several previous studies have modelled reactive vaccination as an intervention in an influenza pandemic (Bansal *et al.* 2006; Ferguson *et al.* 2006; Germann *et al.* 2006; Mylius *et al.* 2008). All studies that modelled the timing of the start of the vaccination programme and/or vaccination rate found these to be important factors in the success of the intervention. Each of these studies also modelled two alternative strategies for prioritization of a limited vaccine supply, similar to our transmitters-first and vulnerable-first strategies. The results from each study form a consistent pattern, and our results reconfirm this pattern (our simulations included age-specific case fatality results that have not been presented here). The transmitters-first strategy is always better at reducing the final attack rate. Where age-specific case fatality is modelled, transmitters-first is also the better strategy at reducing the overall case fatality ratio, unless the vaccination programme is initiated too late (Bansal *et al.* 2006; Mylius *et al.* 2008) or R_0 is too high (Bansal *et al.* 2006), in which case the vulnerable-first strategy is optimal. In addition, we found that the vulnerable-first strategy might be optimal if vaccination took place at an insufficient rate or if coverage was too low.

Two simulation studies are methodologically similar to our study (being individual-based, micro-simulation models), but model at a whole-of-country scale, making it difficult to directly compare vaccination initiation timing and vaccination rates with our study (Ferguson *et al.* 2006; Germann *et al.* 2006). Both these studies found that, for reactive vaccination, 90 per cent coverage at low vaccination rates (0.5% and 1% of the population per day, respectively) could be effective in reducing the attack rate. This appears to be at odds with our findings that reactive vaccination needs to take place at rates *greater* than 1 per cent per day to be effective, and this only for a reproduction number no higher than 1.5. However, in these previous whole-of-country studies, vaccination begins on (or

before) the arrival of the pandemic *somewhere* in the country; the arrival of the pandemic virus in a typical 30 000 member community in the countries considered in these studies will be delayed by at least 20–30 days from the start of the national vaccination programme (depending on R_0). This may allow a sufficient cohort to be vaccinated even given the low vaccination rate and to have developed immunity prior to the outbreak of the local epidemic, effectively resulting in partial pre-emptive vaccination. Germann *et al.* found that a strategy of halving vaccine dosage (by giving only the first of a two-dose regimen) but doubling coverage and vaccination rate to be superior to a full two-dose regimen (Germann *et al.* 2006) with the assumption that a half (single) dose would result in half the effectiveness of full vaccination. A detailed modelling study by Riley *et al.* (2007) using data on the immunological responses for a range of doses of candidate pre-pandemic vaccines (Bresson *et al.* 2006; Lin *et al.* 2006; Treanor *et al.* 2006) has examined the question of dose-sparing in situations where the amount of vaccine available is limited, such as will be the case with the current H1N1 2009 virus. They have determined that wider coverage with lower doses is a better strategy than lesser coverage with a higher dose, with respect to the overall population benefit of reduction in attack rate. We have not examined this issue in the study reported here, other than to give results for ‘full’ and ‘half’ effectiveness vaccines at a range of coverage levels. Ferguson and colleagues have assumed a single-dose vaccine with high effectiveness (70% reduction in susceptibility), noting that ‘if two doses were required one month apart to achieve the same level of protection, then vaccination needs to start a month earlier still for the same impact’ (Ferguson *et al.* 2006)—our results confirm this assumption.

We have constructed a highly detailed model of a real community to be as realistic as possible using all data that were available to us. When data were unavailable, we have made realistic assumptions based on that available in the literature. We have then used this model to conduct a thorough examination of the mitigating impact that may be achieved under a range of vaccination strategies, including the effect of different rate-of-delivery and coverage levels. We have looked at vaccination in isolation to allow us to determine which strategies are optimal and to give clear guidance to public health authorities. While it has only approximately 30 000 individuals, the Albany model has many of the characteristics of a much larger conurbation, such as the existence of a central business district, commuting patterns from a rural hinterland into the main centre, movement of workers and children from suburbs to workplaces and schools and the presence of a hospital.

In practice, vaccination will be used in conjunction with social distancing measures and with the use of antiviral drugs for treatment and prophylaxis, and this will be the subject of a future modelling study. While we have built as accurate a model as possible, uncertainties exist regarding estimates of inter-person contact which may result in transmission, particularly the contact that occurs within the home, school or workplace. Furthermore, it is unclear what level of

self-imposed social distancing may occur during a pandemic. Future studies will be necessary to better understand changing patterns of contact and to determine how they might affect the benefit accruing to various interventions. In this study, such issues should have little effect on our results as we are comparing the relative reduction in attack rates under the range of vaccination interventions, with all other parameter settings in the model remaining constant.

4.2. Relevance to H1N1 2009 influenza

Only a reactive vaccination strategy is available to public health authorities for the current H1N1 2009 pandemic. The effectiveness of this strategy is inherently limited by the ability of vaccine manufacturers to produce supplies at a sufficient rate to arrest the growth dynamics of infection in the community. Our results may suggest appropriate strategies to be adopted in the current H1N1 2009 setting, specifically results relating to reactive vaccination timing. Here, the results that assume a reproduction number of 1.5 are relevant, given early estimations of a basic reproduction number in the range 1.4–1.6 (Fraser *et al.* 2009). Furthermore, it is likely that a two-dose vaccination strategy will also need to be adopted owing to the novel nature of the current influenza strain. Our results indicate that dynamic vaccination of 60 per cent of the population at a rate of 2 per cent of the population per day with a well-matched (high-effectiveness) vaccine would reduce the final attack rate from 34 to 4 or 8 per cent if the vaccine is not well matched.

Our reactive vaccination results will not be applicable to communities where the current H1N1 pandemic achieves sustained internal transmission before vaccination begins. In particular, our results which indicate that the transmitters-first vaccination prioritization is more effective in reducing the attack rate compared with a vulnerable-first strategy are not applicable, as these results depend on reactive vaccination being initiated concurrently with epidemic emergence. This cannot now occur as this prioritization strategy relies on vaccinating those most likely to spread the virus (owing to high contact patterns, i.e. children) at a rate that exceeds the infection rate. In the current situation, where the vaccination programme will be initiated *during* the pandemic rather than at pandemic outset, Bansal *et al.* (2006) and Mylius *et al.* (2008) indicate that the vulnerable-first strategy may be optimal for minimizing case fatality.

Given that a suitable vaccine will arrive either during or after the Southern Hemisphere winter, a reactive strategy is the only one available to countries in that region. In contrast, depending on the arrival time of suitable vaccines, it is possible that either a pre-emptive or split strategy may be initially suitable in the Northern Hemisphere in anticipation of a second, larger pandemic wave later this year.

5. CONCLUSIONS

There are important policy implications that arise following this study. If it is thought likely that the H5N1 virus

will cause a pandemic, then our results suggest a strategy of starting to vaccinate now using currently available, candidate pre-pandemic vaccines to administer a priming dose. Given the limited shelf-life of current candidate vaccines (less than 1 year), rather than building up large stockpiles that would be necessary under any feasible vaccination strategy, the split strategy may suggest a store-in-person policy (Jennings *et al.* 2008). Such a store-in-person, split vaccination policy has a number of significant advantages. These include the logistical benefits of developing and using suitable vaccine production, distribution and administration of resources before pandemic emergence, allowing for a potentially large cohort of primed individuals prior to a pandemic. Such a cohort may have some reduction in susceptibility owing to priming, but perhaps more significantly they may be rapidly brought to full immunity post-pandemic initiation via a single boosting dose. That the maximum benefit may be achieved by a split vaccination strategy has recently been postulated by Jennings *et al.* (2008); in this study, we use a simulation model to demonstrate that this is indeed the case.

Our results indicate that a split strategy is to be preferred over a reactive strategy, where this is feasible. Indeed we have shown that it can be better to use a split strategy with a low-effectiveness vaccine rather than wait until emergence before producing and administering a strain specific vaccine. This highlights that reactive vaccination is a poor strategy as it is left until pandemic emergence before it is initiated, and requires administration of two doses to confer full immunity.

The results offer up evidence which is of benefit to policy-makers in determining vaccination policy, particularly in the optimal use of pre-pandemic vaccines. Results suggest which strategies, daily vaccination rates and vaccination levels are required to achieve optimal protection during a pandemic. They indicate the minimum resources needed to make the split strategy highly effective and to allow the reactive strategy to offer at least some effect. They indicate minimum vaccination coverage levels required, again giving indication as to the scale of doses required by an individual country for a given strategy to be effective. The results also indicate coverage level and vaccination rate thresholds beyond which little further gain may be achieved. While the results vary depending on reproduction number, for the highest examined (namely $R_0 = 2.5$), it is optimal to use a split strategy with a minimum 2 per cent daily vaccination rate for the boosting dose and with a minimum of 60 per cent of the population being vaccinated.

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