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Modelling the effect of seasonal influenza vaccination on the risk of pandemic influenza infection

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Abstract

Background: Recent studies have suggested that vaccination with seasonal influenza vaccine resulted in an apparent higher risk of infection with pandemic influenza H1N1 2009. A simple mathematical model incorporating strain competition and a hypothesised temporary strain-transcending immunity is constructed to investigate this observation. The model assumes that seasonal vaccine has no effect on the risk of infection with pandemic influenza.

Results: Results of the model over a range of reproduction numbers and effective vaccination coverage confirm this apparent increased risk in the Northern, but not the Southern, hemisphere. This is due to unvaccinated individuals being more likely to be infected with seasonal influenza (if it is circulating) and developing hypothesised temporary immunity to the pandemic strain. Because vaccinated individuals are less likely to have been infected with seasonal influenza, they are less likely to have developed the hypothesised temporary immunity and are therefore more likely to be infected with pandemic influenza. If the reproduction number for pandemic influenza is increased, as it is for children, an increase in the apparent risk of seasonal vaccination is observed. The maximum apparent risk effect is found when seasonal vaccination coverage is in the range 20-40%.

Conclusions: Only when pandemic influenza is recently preceded by seasonal influenza circulation is there a modelled increased risk of pandemic influenza infection associated with prior receipt of seasonal vaccine.

Background

Recent Canadian research has suggested that individuals who had received the seasonal influenza vaccination were at a higher risk of being infected with pandemic influenza H1N1 2009 (pH1N1) than unvaccinated individuals [1]. Four different studies from Canada reported that, compared to no vaccination, prior vaccination with seasonal vaccine increased the odds of infection with pH1N1 from 1.4 to 2.5. The authors proposed several explanations for these unexpected findings which were further discussed by Viboud and Simonsen [2]. Similar, but weaker, findings were found in several studies from the United States (US) with non-significant odds ratios above 1 [3-5]. In contrast to the Northern hemisphere experience, a study in the Southern hemisphere (Victoria, Australia) found no risk associated with receipt of seasonal vaccine with an age-adjusted odds ratio of 0.97 [6]. All of these studies only used data from the 'first wave' of the pH1N1 outbreak covering the period March-July 2009 and hence our model focuses on this time frame as well.

People infected with one strain of influenza will, in general, have immunity to this strain and will have partial immunity (cross-immunity) to strains that emerge by mutation from the infecting strain. The level of cross-immunity will diminish with increasing number of amino acid differences between strains [7]. New pandemic strains are characterized by minimal host immunity. It has been postulated that a 'short-lived strain transcending immunity' after any influenza infection may exist [8]. Modelling studies have demonstrated that only with the inclusion of this short-lived strain transcending immunity do the models reproduce the slender phylogenetic tree structure [9] of influenza [8,10-14]. The mean duration of this

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hypothesised immunity is unclear but values in the range 3-6 months give realistic results in the models, and are supported by the available experimental and epidemiological literature, well summarized in Ferguson et al. 2003 [8].

Although previously demonstrated in animal models (see references in [15]) the concept of heterotypic and heterosubtypic temporary immunity is very difficult to demonstrate in observational studies of humans, because it is rare to find sequential or contemporaneous circulation of different influenza types or sub-types. The 2009 pH1N1 outbreak was one such opportunity. Prior to the

Method

The model is based on a standard SIR (Susceptible,

$$\frac{dT_1^1}{dt} = \gamma I_1^1 - \delta T_1^1 \tag{8}$$

$$\frac{dT^1}{dt} = \gamma I^1 - \delta T^1 \tag{9}$$

$$\frac{dT_1^1}{dt} = \gamma I_1^1 - \delta T_1^1 \tag{10}$$

$$\frac{dT}{dt} = \gamma I - \delta T \tag{11}$$

For example, equation (1) states that unvaccinated individuals (S^{12}) can be either infected by seasonal influenza infectious individuals $(I_1^1 + I_1^1)$ or pandemic strain infectious individuals $(I^1 + I)$ equation (3) states that the proportion of individuals only susceptible to the pandemic strain (S^2), which is originally a proportion of

70% [22]. The different timings of the seasonal and pan-

wave of pH1N1 infection and so mostly restrict the analysis to cases where the delay from the usual influenza season to the pandemic strain introduction is less than 5 months. One case is run for a delay of 240 days to demonstrate the case in the Northern hemisphere in jurisdictions where there was no substantial first wave and only a second wave (for example many parts of Europe).

Of interest is the effect on the odds ratio of the timing of the introduction of the pandemic strain and the level

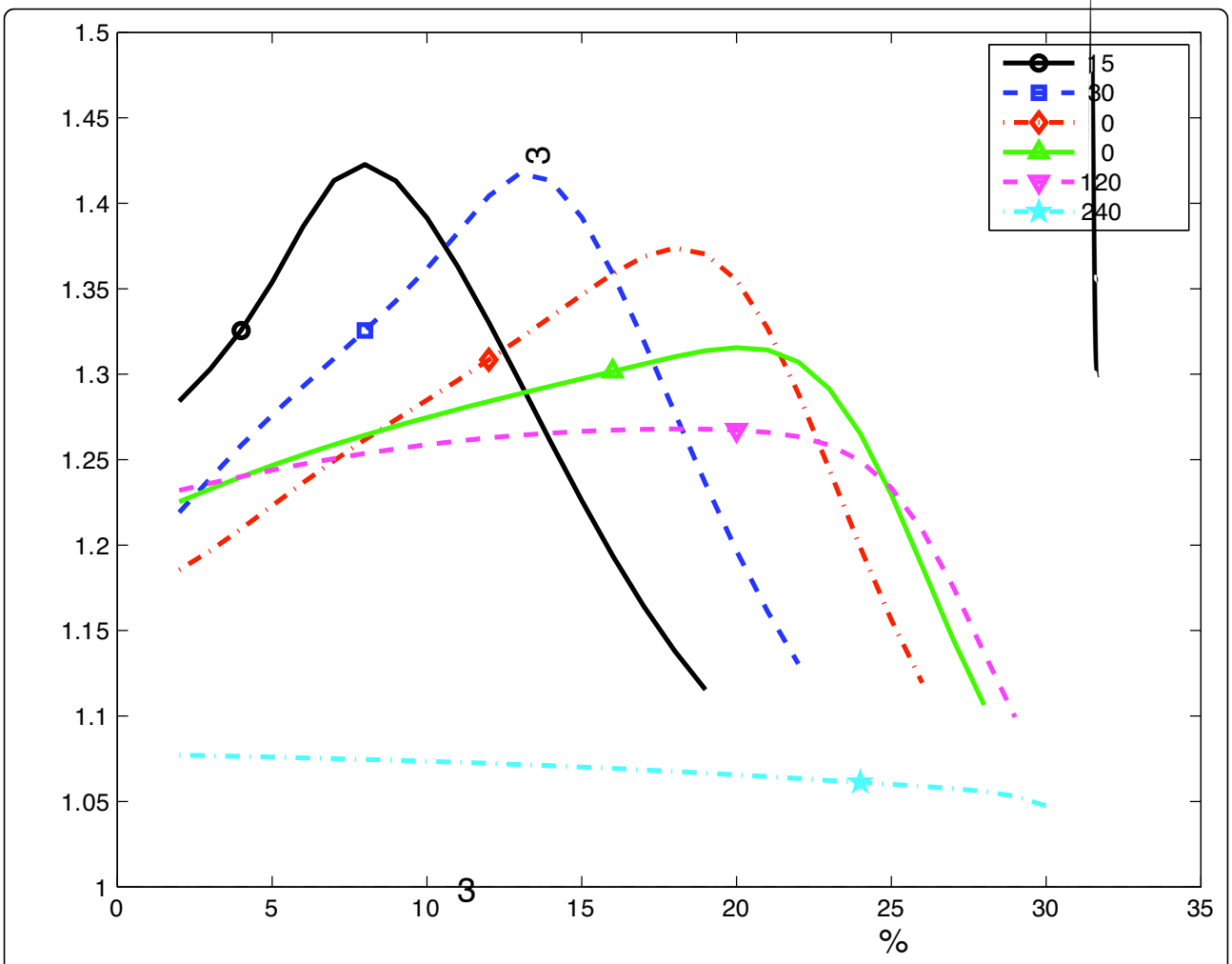

Figure 3 Odds ratio for six different seasonal strain delays with R_0 = 1.5. Odds ratio versus effective vaccination coverage for six different delays from seasonal strain introduction to pandemic strain introduction. All calculations are with R_0 = 1.5 and $1/\delta$ = 120 days. Delays of 120 days or less correspond to a first wave scenario, the delay of 240 days corresponds to a second wave only scenario. The symbols on the lines are to aid in differentiating the line types and not a specific data point of interest.

delays. This suggests that in those jurisdictions the apparent risk from the seasonal vaccination may not be observed since the odds ratio is close to 1. We are not aware of any studies published that investigate this second wave scenario.

As demonstrated in Figure 3 for each delay less than or equal to 120 days there is an effective vaccination coverage for which the odds ratio is a maximum. This is the effective vaccination coverage where the apparent risk of the seasonal vaccination is strongest. As the effective vaccination coverage increases beyond this maximum point the seasonal epidemic is smaller due to the higher vaccination coverage. This smaller epidemic size means the proportion of unvaccinated individuals infected with the seasonal strain also decreases. The result of this is that the odds ratio decreases as the effective vaccination coverage increases in this region. When the effective vaccination coverage is increased further, the seasonal epidemic does not take off and hence vaccinated and unvaccinated individuals appear almost the same and the odds ratio tends to one. For all delays there is no modelled increased risk from vaccination when the effective vaccination coverage is above 30%, since effective vaccine coverage at this level (for example, 50% coverage with a vaccine that was 60% effective or 60% coverage with a vaccine that was 50% effective) aborts the seasonal epidemic.

The odds ratio of vaccinated versus unvaccinated individuals also depends on the disease reproduction number. Shown in Figure 4 is the odds ratio versus effective vaccination coverage for 6 different basic reproduction numbers ranging from 1.3 to 1.8 [25] for a pandemic introduction delay of 60 days. The higher the reproduction number the higher the odds ratio and hence the

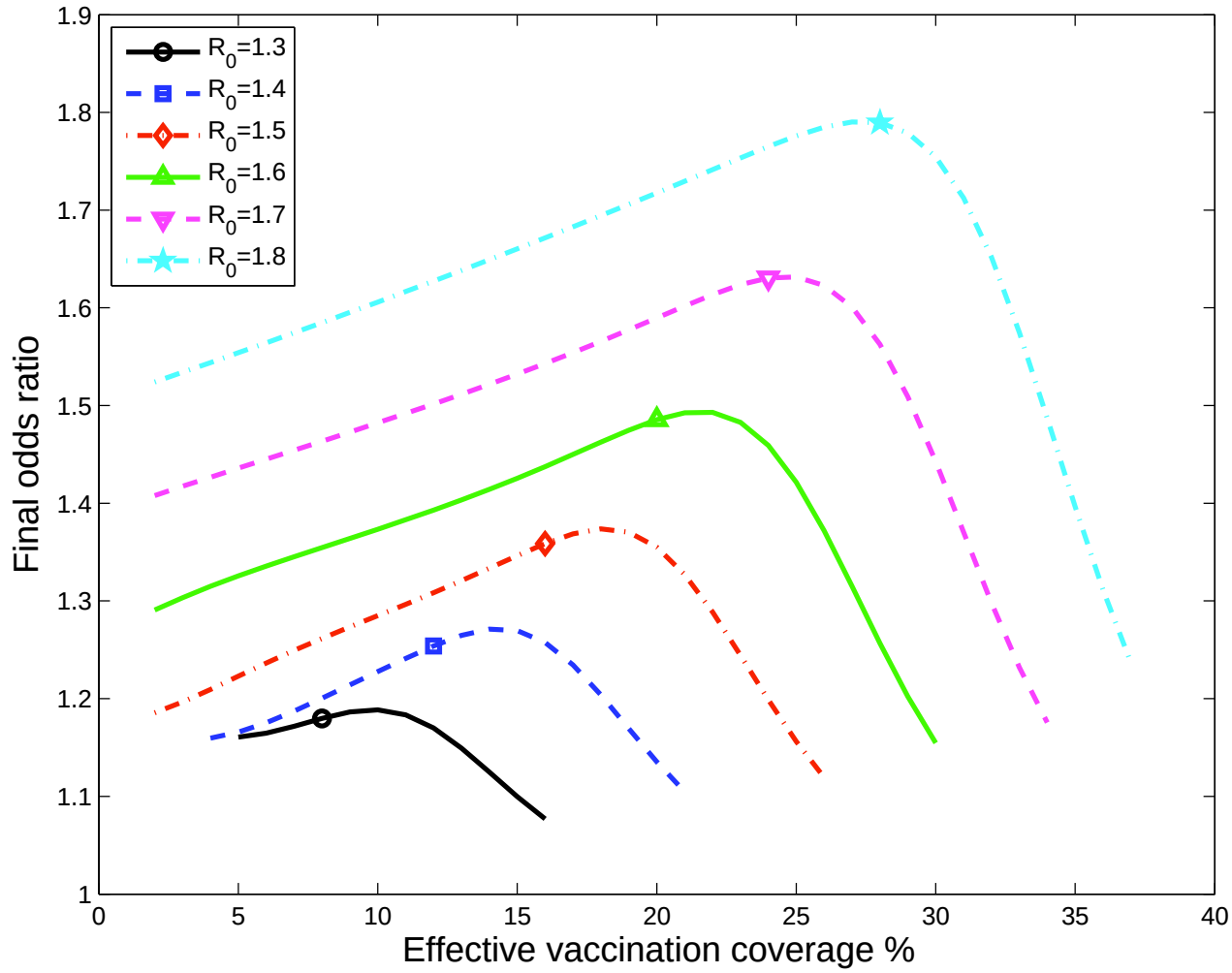

Figure 4 Odds ratio for six different R_0 values with 60 day delay. Odds ratio versus effective vaccination coverage for six different R_0 values. All calculations are with $1/\delta$ = 120 days and the delay from seasonal strain introduction to pandemic strain introduction of 60 days. The symbols on the lines are to aid in differentiating the line types and not a specific data point of interest.

greater apparent risk from the seasonal vaccination. This pattern is also seen over all delays considered from 15 to 240 days.

In the Canadian studies [1] vaccination coverage of around 30% was reported and vaccine effectiveness was estimated as 56% giving an effective vaccination coverage of approximately 17%. This is the region where there is maximum effect of the seasonal vaccination for a delay of the pandemic after the seasonal circulation of 60 to 90 days. In Canada the peak incidence of seasonal influenza occurred 11 weeks (77 days) before the first notified cases of pH1N1. The model gives maximum value of the odds ratio from 1.15 to 1.75 over the range of plausible reproduction numbers, delay between the introduction of seasonal and pandemic influenza and effective vaccination coverage. These estimates are consistent with the lower end of estimates from the Canadian studies. However, if the cases of pandemic influenza were predominantly in children, the reproduction number could be higher than 1.8 [29]. In the Canadian studies, the Quebec sample comprised 44% children with pH1N1 infection and the Ontario study 61%. If we used a value of R = 2.0 in our model, consistent with values reported for school children in Japan [29], with a delay of 70 days and effective vaccination coverage of 17%, both consistent with observations from Canada, we estimate an odds ratio of 2.0 for the risk of pH1N1 infection following receipt of seasonal vaccine.

Over a wide range of parameter values the maximum odds ratio occurs for effective vaccination coverage in the range 15-25%. This range will be generated if vaccination coverage is 20-40% and vaccine effectiveness is 50-70% [22,28]. We could therefore expect to see an apparent harmful effect of vaccination in the Northern

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