"Wait and see" vaccinating behavior during a pandemic: a game theoretic analysis†

Samit Bhattacharyya[1], Chris T. Bauch[1,2]

1 Department of Mathematics and Statistics, University of Guelph, Guelph, Canada

2 Department of Clinical Epidemiology and Biostatistics, McGill University, Montreal, Canada

∗ **E-mail: sbhattac@uoguelph.ca**

† **Running Title: "Wait and see" vaccination strategies**

Abstract

During the 2009 H1N1 pandemic, many individuals adopted a "wait and see" approach to vaccinating until further information was available on the course of the pandemic and emerging vaccine risks. This behaviour implies two sources of strategic interactions between individuals: both perceived vaccine risk and the probability of becoming infected decline as more individuals become vaccinated. Here we analyze the outcome of these two strategic interactions by combining game theory with a mathematical model of disease transmission during an outbreak of a novel influenza strain. We include a case where perceived vaccine risk declines according to the cumulative number of individuals vaccinated. A common Nash equilibrium strategy exhibited by this model is a "wait and see" strategy where some individuals delay the decision to vaccinate, relying on the herd immunity provided by early vaccinators who also act as "guinea pigs" that validate the safety of the vaccine. The occurrence of "wait and see" strategies leads to a higher disease burden than occurs under socially optimal vaccine coverage. The model also exhibits both feedback and feed-forward processes. Feedback takes the form of individuals adjusting their vaccinating behaviour to accommodate changing transmissibility or risk parameters. Among other effects, this causes in the epidemic peak to occur at approximately the same time across a broad range of R_0 values. Feed-forward takes the form of high initial perceived vaccine risk perpetuating high perceived vaccine risks (and lower vaccine coverage) throughout the remainder of the outbreak, when perceived risk declines with the cumulative number vaccinated. This suggests that any effect of risk communication efforts at the start of a pandemic outbreak will be amplified compared to the same level of risk communication effort distributed throughout the outbreak, since any reductions in initial perceived risk will also result

in reduced perceived risk throughout the outbreak.

Author Summary

During the 2009 H1N1 pandemic, postponing vaccination until further information was available on the course of the outbreak and emerging vaccine risks was a very common psychology. This behaviour implies two sources of strategic interactions between individuals: perceived vaccine risk at any time was a function of how many individuals had already acted as "guinea pigs" by accepting the vaccine earlier, and these earlier vaccinators also provided herd immunity to later vaccinators. Hence, both perceived vaccine risk and the probability of becoming infected decline as more individuals become vaccinated. Here we amalgamate game theory with a mathematical model of infectious disease transmission to analyze the strategic interactions of vaccine behaviour during a pandemic outbreak of a novel influenza strain. We study the numerical solutions of the system to gain insight into dynamic interplay between vaccinating behaviour, disease transmission, and risk perception during the outbreak. We find that the system exhibits both feed-forward and feedback mechanisms. Feed-forward mechanisms take the form of initially elevated levels of perceived vaccine risk perpetuating elevated perceived vaccine risk through the outbreak. This suggests that imparting accurate and useful vaccine safety information for a new vaccine before and during a pandemic outbreak is crucial.

Introduction

The recent emergence of pandemic (H1N1) 2009 highlighted the vulnerability of human populations to emerging infectious diseases [1–3]. During the pandemic, vaccines were quickly developed to mitigate transmission of the novel H1N1 influenza strain [4]. However, many individuals hesitated to vaccinate. The reasons for this are numerous and variable [5,6], but a leading reason was concern about side effects [7]. This concern may have been exacerbated by the fact there were no large safety studies upon which to base such conclusions for this particular vaccine, even though very similar vaccines had previously been demonstrated to be safe [8–11]. In the face of such uncertainties, many individuals adopted a "wait and see" strategy: deferring a decision to vaccinate until more information on vaccine risks and disease epidemiology was available [12].

The possibility of a "wait and see" approach to vaccinating during a pandemic outbreak creates two potential sources of strategic interactions between individuals. Firstly, individuals who choose to vaccinate early in the pandemic provide herd immunity that protects individuals who wait until later to vaccinate, or who do not vaccinate at all. The strategic interaction between individuals as a result of herd immunity in the context of voluntary immunization programs has previously been studied with mathematical models for the case of vaccinating decisions made over relatively long timescales [13–23], but not in the case of vaccinating behaviour during a single outbreak. Moreover, the use of a novel vaccine that has not been tested in a large group may cause individuals to have elevated perception of vaccine risk, at least until a sufficient number of persons have been safely vaccinated. This gives rise to a second source of strategic interactions during a pandemic: those who vaccinate early in the pandemic essentially act as "guinea pigs", providing formal or informal information on vaccine safety that can be used by those who prefer to "wait and see". This source of strategic interaction in vaccine decision making has also not been characterized in a mathematical modelling framework.

The strategic interplay between individual behaviour and disease dynamics, informed by perceived vaccine and infection risks, can be modeled and analyzed using game theory [24]. Game theory describes how individuals act in strategic interactions, where their payoff depends on the decisions of other individuals. Game theory often involves finding the Nash equilibrium of the system. In the context of populations games, this is a strategy such that no sufficiently small group of individuals can achieve a higher payoff by adopting a different strategy [25–27]. The Nash equilibrium is, therefore, considered to be stable, and the strategy that the population is expected to adopt.

Here we construct a game theoretic model of vaccinating behaviour during the course of a single outbreak of pandemic influenza in a population, where strategic interactions arise both through herd immunity and through the potential for declining perceived vaccine risk as a function of increased vaccine coverage. Disease dynamics are described by a compartmental Susceptible-Infectious-Recovered (SIR) model. We consider a case where perceived vaccine risk is constant throughout the outbreak and we compare this to a case where perceived vaccine risks declines in proportion to the cumulative number of individuals vaccinated. The latter case reflects greater availability of information (either formally or informally) upon which to base vaccinating decisions as more individuals become vaccinated. Among other possibilities, we allow individuals to adopt a "wait and see" strategy of delaying vaccination either until the vaccine risk is better understood, or in the hopes that enough other individuals will vaccinate

to make their having to vaccinate unnecessary. We compute the Nash equilibrium and compare it to socially optimal strategies of uptake during the outbreak for a range of scenarios. Our objective is to gain insights into possible strategic mechanisms that may operate during a pandemic outbreak, and possible vaccinating behaviour patterns that may therefore evolve.

Model

In the following subsections, we describe the behavioral submodel that governs individual vaccinating decisions given information on risks and disease prevalence, and the transmission submodel that governs disease transmission as it depends on vaccinating behaviour during the outbreak. We also describe the algorithm used to determine the Nash equilibrium vaccine coverage.

Behavior submodel: The behavior submodel is formulated as a population game, where the payoff to an individual depends on the average behaviour of the population [23, 28]. Vaccination is voluntary (i.e. individuals are not coerced to vaccinate in any way) and individuals do not pay for vaccination, as was the case in many countries during the 2009 influenza pandemic. The players of the game are individuals in the population, all of whom are eligible for being vaccinated. The strategy set is

$$\{k|0 \leq k \leq 53\}. \tag{1}$$

where $k = 0$ is a strategy of vaccinating before the outbreak starts, such that the individual is immune by the time the outbreak begins; $k = 53$ is a strategy of never vaccinating; and for all other values $1 \leq k \leq 52$ in the set, k is the week that the individual vaccinates. For instance, $k = 1$ denotes that the individual vaccinates during the first week of the outbreak. As indicated, vaccine is administered in the population on a specific day of each week for instance through a weekly immunization clinic. (Assuming weekly rather than daily administration maintains the strategy set at a manageable size.) This strategy set defines a frequency distribution of strategies in the population:

$$\Phi = \{\phi_k : 0 \leq \phi_k \leq 1, \phi_k \text{real}\} \qquad \forall k = 0, \ldots, 53. \tag{2}$$

where ϕ_k is the proportion of the population playing strategy k, and $\sum_{k=0}^{53} \phi_k = 1$.

Each individual receives a baseline payoff L in the absence of disease or vaccine: this represents

baseline expected health before risks from the disease or the vaccine are taken into account. In the case where perceived vaccine risk is constant during the outbreak, vaccinating at any time incurs a penalty r_{vac} due to perceived probability of adverse events from vaccination. The efficacy of the vaccine is ϵ, and successfully immunized individuals are fully protected two weeks after vaccine administration. Thus, if any individual receives a vaccine on week k, the vaccine will only start working from week $k+2$ onward. Likewise, contracting infection incurs a penalty r_{inf} in non-vaccinated individuals and individuals unsuccessfully vaccinated.

Let $\rho_{\leq k}$ be the probability that a susceptible person is infected during or before week k when the distribution of strategies in the population is Φ, and likewise let $\rho_{>k}$ be the probability of infection after week k. Let $\Pi_k(\Phi)$ denote the payoff to an individual playing k when the distribution of strategies in the population is Φ. Then the payoff $\Pi_k(\Phi)$ is given by

$$\Pi_k(\Phi) = \begin{cases} L - r_{vac} - r_{inf}\rho_{>0}(1-\epsilon), & \text{for } k = 0, \\ L - r_{vac} - r_{inf}\rho_{\leq k+1} - r_{inf}\rho_{>k+1}(1-\epsilon), & \text{for } 1 \leq k \leq 52, \\ L - r_{vac} - r_{inf}\rho_{\leq 52}, & \text{for } k = 53, \end{cases} \tag{3}$$

where the use of subscript $k+1$ occurs because of the two week period before vaccines provide fully protective immunity in a vaccinated person. The quantities $\rho_{\leq k+1}$ and $\rho_{>k+1}$ are determined from the transmission submodel according to a calculation described in the appendix.

We also define and explore a second case where perceived vaccine risk declines as more individuals become vaccinated. Initially, perceived risk is elevated, reflecting hesitation to use a vaccine that has not undergone post-licensure population-based safety studies. As more individuals choose to become vaccinated without experiencing significant adverse events, the perceived risk begins to decline in inverse proportion to the cumulative number of individuals vaccinated, until at a certain point it comes into alignment with the actual vaccine risk. Hence we define the perceived vaccine risk at each week k, $r^k_{vac} : k \to (0,1)$ as

$$r^k_{vac} = \begin{cases} \frac{b}{cV+d}, & \text{if } \ V < \frac{a}{r_{acvac}} \\ r_{acvac}, & \text{otherwise} \end{cases} \tag{4}$$

where $V = N\sum_{j=0}^{k}\phi_j$, $a, b, c, d \in \mathbb{R}$, and r_{acvac} denotes the actual risk of vaccine. For the case where perceived vaccine risk declines during the outbreak, the function r^k_{vac} replaces the parameter r_{vac} in equation (3). The model assumptions, strategy set, and payoff functions are otherwise identical to the case where perceived vaccine risk is constant throughout the outbreak. We note that the perceived vaccine risk at the time of vaccination determines payoff and hence behaviour, not the actual vaccine risk r_{acvac} that eventually becomes known–the actual vaccine risk may determine actual health impacts but it is perceived vaccine risk early in the outbreak that determines behaviour and hence vaccinating patterns in the population. We also note also that r^k_{vac} implies a strategic interaction since its value depends on how many individuals have vaccinated beforehand.

The Nash equilibrium distribution for this game is the distribution of strategies

$$\Phi^* = \{\phi^*_k : 0 \leq \phi^*_k \leq 1, \phi^*_k \text{real}\} \qquad \forall k = 0, \ldots, 53$$

such that any small group of individuals adopting a different strategy, and thus shifting the distribution Φ^*, thereby receive a lower payoff. To define the Nash equilibrium, recall that ϕ^*_k is the proportion of the population that adopts strategy k when the population distribution is Φ^*. Now suppose that a fraction $(1-f)$ of these individuals continue playing strategy k, but a fraction f play some strategy $\tilde{k} \neq k$. Hence we have the following changes in the population distribution Φ^*:

$$\phi^*_k \to \phi^*_k(1-f) \quad \equiv \quad \phi^{alt}_k, \tag{5}$$

$$\phi^*_{\tilde{k}} \to \phi^*_{\tilde{k}} + f\phi^*_k \quad \equiv \quad \phi^{alt}_{\tilde{k}}, \tag{6}$$

and the distribution of strategies is otherwise unchanged. We denote the new population distribution as Φ^{alt}. We define Φ^* to be a strict Nash equilibrium distribution if

$$\Pi_{\tilde{k}}(\Phi^{alt}) < \Pi_k(\Phi^*), \tag{7}$$

for all $\tilde{k} \neq k$ and for sufficiently small f. This means that Φ^* is a Nash equilibrium distribution if no small fraction f of individuals playing a given strategy can achieve a higher payoff by adopting a new strategy $\tilde{k} \neq k$. The payoff functions depend upon the probabilities of being infected for an individual who has or has not vaccinated by week k, which are computed from the transmission submodel.

Transmission submodel: Disease transmission in the population is described by a Susceptible-Infectious-Recovered (SIR) model which is modified to distinguish between vaccinated and unvaccinated susceptible individuals (Figure 1) [29,30]. Weekly vaccination in the population gives rise to an impulsive system of differential equations, where disease transmission follows the SIR model in-between periods of vaccine administration, and vaccination is introduced as an impulse to the system of ODEs once per week. Because the vaccine is not fully efficacious, a fraction of vaccinated population remain susceptible to the disease. We denote the number of vaccinated, yet susceptible, individuals by S_{vac}. Accordingly, the transmission model equations are given by

$$\begin{aligned} \frac{dS}{dt} &= -\beta\frac{SI}{N}, \\ \frac{dS_{vac}}{dt} &= -\beta\frac{S_v I}{N}, \\ \frac{dI}{dt} &= \beta\frac{(S+S_v)I}{N} - \gamma I, \\ \frac{dR}{dt} &= \gamma I, \end{aligned} \tag{8}$$

where β denotes the transmission rate, γ denotes the recovery rate, and $N = S + S_{vac} + I + R$ denotes the total population size. The number vaccinated in week k is $V_k = N\phi_k$, so a proportion ϵV_k of individuals who vaccinate in week k are moved to the recovered class R while the remaining $(1-\epsilon)V_k$ are moved to the compartment S_{vac}.

Algorithm for determining Nash equilibrium : To identify candidates for the Nash equilibrium, we used a simulated annealing algorithm that begins with an initial set $\Phi = \{\phi_k\}$ of vaccine coverages for all strategies 0 to 53 such that $\sum \phi_k = 1$. Under this vaccine coverage, we simulate the SIR model for a full outbreak and compare the payoff for each strategy. Then, the distribution of individuals strategies in the population, Φ, was adjusted such that individuals moved to adopt strategies that were more successful. For instance, if the payoff to vaccinate in some week k exceeded the payoff to vaccinate in the preceding week $k-1$, then a fraction of individuals were moved from the $k-1$ strategy to the k strategy. Then, the SIR model was simulated again and the process was repeated, each time moving individuals such that the constraint $\sum \phi_k = 1$ is continued to hold and individuals moved toward strategies of higher

payoff. For mixed Nash equilibriua, this algorithm resulted in Φ such that the payoff is the same for each strategy k, and this distribution was taken to be the candidate for the Nash equilibrium. To ensure that the algorithm converged to the Nash candidate, the values of ϕ_k were periodically disturbed to prevent convergence to a local minimum (simulated annealing). This final Nash equilibrium candidate was then tested by challenging it with randomly selected alternative strategies being played by a small group in the population and comparing the total payoffs for the small group versus the remainder who continued to play the Nash equilibrium strategy. If the challenging groups always received a lower payoff, then the Nash candidate was taken to be the Nash equilibrium.

Results

The Nash equilibrium vaccine coverage in each week of the pandemic can vary greatly depending on parameter values and the feedback between disease prevalence and individual vaccinating behaviour. In the following subsections, we first describe results for the case where perceived vaccine risk is constant over the course of the outbreak. We then describe the case where perceived vaccine risk declines as the number of vaccinated individuals increases. Baseline parameter values appear in Table 1 and these are the values used in all simulations except when specified otherwise.

Case of constant vaccine risk

For the case where vaccine risk $r_{_{vac}}$ is constant throughout the outbreak, some typical examples of the Nash equilibrium vaccine coverage in each week, and the corresponding epidemic curve, are shown in Figure 2 for several values of vaccine efficacy ϵ and disease risk $r_{_{inf}}$. For the case of higher disease risk, the most widely adopted strategy is $k = 0$ (advance vaccination before the outbreak) for both high and low vaccine efficacy, and a small proportion of the population vaccinate within the first five weeks. The outbreak is curtailed due to vaccination and the peak of the outbreak occurs in week 3. In contrast, for the case of lower disease risk, the most widely adopted strategy is $k = 2$, and the epidemic peak is larger but also occurs later. Moreover, a larger proportion of population chooses never to vaccinate when disease risk is low. Thus, a lower disease risk means more individuals adopt a "wait and see" strategy, resulting in a larger outbreak that peaks later. This delaying behaviour occurs even though the perceived vaccine risk is constant throughout the outbreak. The higher vaccine efficacy scenarios are qualitatively similar

to the lower vaccine efficacy scenarios, however lower vaccine efficacy results in higher overall vaccine coverage and fewer pure non-vaccinators. This paradoxical effect occurs because when the vaccine is not sufficiently efficacious, infection transmission is less affected. The reduced strength of herd immunity means more individuals want to vaccinate and thus free-riding on herd immunity does occur as much.

Predictably, the overall Nash equilibrium vaccine coverage increases, and vaccination occurs sooner, as vaccine risk declines or disease risk increases (Figure 3). The Nash equilibrium coverage for zero vaccine risk is purely advance vaccination, whereas in case of zero infection risk, the Nash equilibrium coverage is simply non-vaccination. Advance vaccination only occurs for very low values of the vaccine risk (this is relatively insensitive to changes in disease risk). For most values of vaccine and disease risk in these ranges, the dominant mode of behavior is delaying vaccination by up to 6 weeks.

An important question when considering the impact of individual choice on vaccine coverage is whether rational behaviour results in suboptimal health outcomes. To address this question it is necessary to compare the total burden due to disease and vaccine adverse events under the Nash equilibrium versus the total burden under a defined socially optimal strategy that provides the most benefit to the population as a whole. Previous models of vaccination games for endemic infections have often shown that disease burden under the Nash equilibrium is higher than under the social optimum due to free-riding [31], but whether this will hold for a vaccination game where individuals make strategic decisions in the course of a single outbreak has not been investigated.

Here, the social optimum is defined as the vaccine coverage such that the sum total burden in the whole population from either vaccine adverse events or infection is minimized. We analyzed the total burden under the Nash equilibrium versus the socially optimal strategies and compared the corresponding vaccine coverage. For a wide range of values of the vaccine risk r_{vac}, the total burden is higher under the Nash equilibrium than the social optimum (Figure 4A). This occurs because the Nash equilibrium strategy typically involves at least some portion of the population adopting a "wait and see" strategy. However, "wait and see" is never socially optimal because it would involve first exposing part of the population to the risk of being infected and then vaccinating them anyway. Hence under the social optimum, individuals either receive advance vaccination or are never vaccinated. This pattern of vaccinating is seen in the proportion of individuals being vaccinated in advance ($k = 0$) as a function of r_{vac} for the Nash equilibrium and the social optimum. As r_{vac} increases, the proportion of the population receiving advance vaccination declines under both the Nash equilibrium and the social optimum, but it declines more under

the Nash equilibrium because individuals begin adopting "wait and see" strategies (Figure 4B). For sufficiently high vaccine risk r_{vac}, advance vaccine coverage is zero under both the Nash equilibium and the social optimum because the risk of the vaccine r_{vac} now outweighs the risk of disease r_{inf} and hence there is no incentive to vaccinate from either the rational individual perspective or the socially optimal perspective.

The Nash equilibrium vaccine coverage also depends on the basic reproductive ratio R_0, which is the average number of secondary infections produced by a single infected person in an otherwise susceptible population (Figure 5). As R_0 increases, advance and early vaccination ($k < 3$) becomes more common. This occurs because individuals faced with a more transmissible pathogen will tend to choose to vaccinate earlier. In contrast to the shift in vaccine coverage in response to higher R_0, the location of the epidemic peak does not change as R_0 changes: it remains at approximately 3-4 weeks for all values of R_0 evaluated. This is interesting, because in the absence of vaccination, higher R_0 causes the epidemic to peak sooner (Figure 5, first column). The relative constancy in the location of the epidemic peak despite changing R_0 for the case where individuals vaccinate strategically is due to a feedback mechanism: higher R_0 also stimulates more individuals to adopt advance or early vaccination to fend off infection, and this tends to delay the peak, counteracting the effect of higher R_0. This shows that vaccinating behaviour may regulate disease prevalence through feedback mechanisms, as a function of disease severity and vaccine risk perception.

Case of declining vaccine risk

So far we have considered the case of constant vaccine risk over time. However, if the vaccine is new, the perceived vaccine risk may initially be elevated, as occurred in the 2009 H1N1 pandemic [7, 8, 10, 11]. In this subsection, we consider the case where the perceived vaccine risk decreases as the cumulative number of individuals vaccinated increases during the course of the outbreak.

The parameter a in equation (4) controls how quickly perceived vaccine risk declines as more individuals become vaccinated. Higher values of a result in slower declines in perceived vaccine risk and later alignment of perceived risk with the actual risk, r_{acvac} (Figure 6A). For higher values of a, more individuals vaccinate early in the outbreak (Figure 6B) which in turn decreases the incidence of infection (Figure 6C). For $a = 2.5$, there are two peaks in Nash equilibrium coverage over the course of the outbreak. The first peak occurs due to rapid decline in perceived vaccine risk, whereas the second peak is due to delays

caused by free-riding on herd immunity.

If these simulations are run again with identical parameters except the perceived risk is held constant at r_{acvac} throughout (as in the first part of the Results) instead of declining gradually to r_{acvac}, then the Nash equilibrium coverage strategy is primarily advance vaccination and disease incidence is much reduced (Figure 6D). Hence, even when Nash equilibrium strategies are not socially optimal, the implications of variable initial perceived risk are significant. Therefore, rapid communication of vaccine safety information (through the media and other sources) can play a valuable role in aligning perceived risks with actual probable vaccine risks more quickly and thus ensuring timely vaccination during a pandemic outbreak.

The initial level of perceived vaccine risk is also an influential determinant of long-term outcomes (Figure 7). For a given value of a, a higher initial perceived risk results in a lower Nash equilibrium coverage and higher perceived risk throughout the outbreak. This is due to a feedforward mechanism: a higher initial perceived risk means that fewer individuals become vaccinated in the early weeks of the outbreak. Hence there is less information upon which safety inferences can be made and fewer individuals seek vaccination subsequently. As a result, perceived risk falls more slowly and Nash equilibrium coverage is lower, when initial perceived risk is higher (Figure 7). Hence, initially high perceived vaccine risk can perpetuate high perceived vaccine risk throughout the outbreak, resulting in lower vaccine coverage and larger proportion of individuals avoiding vaccination altogether (Figure 7). This effect further emphasizes the importance of early and timely risk communication: the fact that elevated initial perceived risk can suppress vaccine uptake throughout the outbreak also means that the effect of any risk communication efforts started early in the outbreak will be amplified, producing dividends throughout the outbreak.

Social optimum and Nash equilibrium vaccine coverages can also be compared for the case of declining vaccine risk. As noted previously, the socially optimal strategy when vaccine risk is constant throughout the outbreak is advance vaccination of some portion of the population and non-vaccination of the remainder (Figure 4). However, if public health decision makers adopt a conservative approach and do not have large databases to assess vaccine safety, then a socially optimal strategy might be to ramp up vaccine coverage more gradually. For the case where vaccine risk declines over time (and we assume that both immunization program decision-makers and individuals are acting on the same value of vaccine risk r^k_{vac}), the socially optimal coverage requires some delay in vaccine coverage (Figure 8A). However, the delay is still much less than the delay under the Nash equilibrium for the same parameter values (Figure 8C) and the overall coverage is higher. As a result, the outbreak size is still much larger under the Nash

equilibrium than the social optimum (Figure 8B, D).

The negative feedback that results in conservation of the location of the epidemic peak for various R_0 values in the case of constant vaccine risk over time is retained when vaccine risk declines over time (Figure 9). However, vaccine uptake can decline in the early weeks and then surge as individuals adjust their perceived vaccine risk downward (Figure 9), as was observed in Figures 6 and 7.

Discussion

Here we analyzed strategic interactions among individuals making vaccination decisions during an outbreak of pandemic influenza. Previous models have analyzed such strategic interactions in the context of endemic infections over longer timescales, but not over the course of a single outbreak. We assumed administration of a new vaccine not previously tested in large population-based safety studies, causing the perceived vaccine risk to initially be elevated. However, the perceived vaccine risk can decline in proportion to the cumulative number of individuals vaccinated. As a result, the model system exhibits two sources of strategic interactions: individuals who vaccinate early provide herd immunity for individuals who decide to "wait and see" (free-ride), and they also validate the safety of the vaccine for individuals who "wait and see". The strategic interaction through herd immunity operates solely through negative feedback, with more early vaccinators creating herd immunity that discourages subsequent vaccinating. In contrast, the strategic interaction through declining perceived risk of the vaccine operates initially through a feed-forward mechanism: having more early vaccinators validates the safety of the vaccine and encourages later vaccination. However, the effect of this feedforward mechanism is again blunted through negative feedback, since the resulting increase in vaccination will also increase herd immunity and then operate to suppress subsequent vaccination.

As a result of the differing nature of strategic interactions during the course of an outbreak of a novel pathogen where the vaccine is also novel, a range of phenomena are possible. The model predicted the possibility of a "wait and see" Nash equilibrium strategy, where free-riding individuals are encouraged to delay vaccination if enough other individuals become vaccinated before them. This occurs because pure advance vaccination is often not a Nash equilibrium: pure advance vaccination precludes an outbreak, which thus makes the payoff to free-ride by not vaccinating at all–or at least to "wait and see"–much higher. This occurs even when the vaccine risk is constant during the outbreak but is more likely to

occur if vaccine risk declines during the outbreak as more individuals become vaccinated. Pure advance vaccination is only a Nash equilibrium for sufficiently high disease risk and/or sufficiently low vaccine risk, such that the vaccine is essentially more dangerous than the disease. For certain parameter values, we found it was possible for vaccine coverage to initially decline as the outbreak proceeded, but then surge once enough individuals vaccinated to convince the rest of the population that the vaccine risk is low. Also, we found that the negative feedback associated with herd immunity tends to conserve the location of the epidemic peak as the basic reproductive ratio R_0 is changed: higher transmissibility encourages earlier vaccination which in turns tends to offset early epidemic peaks caused by increased R_0. This conservation of the location of the epidemic peak was due to the adjustment of individual behaviour to meet changing epidemiological conditions caused by differing transmissibility or by reactions of other individuals to perceived vaccine risk.

We found that socially optimal vaccine coverage involved earlier vaccination, and higher vaccine coverage, than the Nash equilibrium strategy regardless of whether vaccine risk was constant or declining. As a result, the total burden due to infection and/or vaccine adverse events was higher under the Nash equilibrium than the social optimum (since delaying behaviour on account of exploiting herd immunity is never socially optimal). This echoes previous game theoretical models for endemic disease suggesting that the outcomes of individual choice under strategic interactions for infectious diseases generally do not align with what is socially optimal. However, the results also suggest ways to minimize the impact in the case of a pandemic outbreak. Feedforward mechanisms imply that an initially elevated perceived vaccine risk will perpetuate higher perceived risk through most of the outbreak. Similarly, it was observed that early vaccination is much more common under the Nash equilibrium when vaccine risk is at its actual value from the start of the outbreak, instead of declining gradually to the actual value as perceived risk declines. These two observations imply that any effect of risk communication efforts at the start of a pandemic outbreak will be amplified and yield much greater dividends than the same level of risk communication effort distributed throughout the outbreak, since any reductions in initial perceived risk will also result in reduced perceived risk throughout the outbreak.

Immunization has long played an essential role in reducing morbidity and mortality for many communicable diseases worldwide, and it resulted in complete eradication of smallpox. At the same time, it has been one of the most divisively polemic issues in health care since vaccination was first introduced in the 1800s. Over the past 60 years, health behaviour research has contributed to an understanding of how

and why people make decisions to accept or reject vaccines, especially with respect to the introduction of new vaccines. This kind of research continues to be crucial, especially given the role of individual choice in phenomena such as Measles-Mumps-Rubella vaccine and polio vaccine scares in recent years. Parameterization of vaccine and disease risks using empirical data, and validation of the model against time series of actual vaccine coverage during the 2009 H1N1 pandemic, would be valuable for validating such models and understanding how they may be useful for planning for future pandemics. With better empirical validation and continued development of theory, it is possible that mathematical models of the interaction between disease transmission and individual vaccinating behaviour may contribute to the toolbox that is used to protect the health of the public. The present model has illustrated strategic mechanisms operating during a pandemic outbreak that may contribute to determining patterns of vaccine uptake over time, and has suggested several ways in which early risk communication is crucial.

Acknowledgments

S. Bhattacharyya was supported through an internship from the CIHR Pandemic Outbreak Team Leader Grant (PTL-97126), Division of Mathematical Modeling, British Columbia Centre for Disease Control (BCCDC).

References

1. Fraser C, Donnelly C, Cauchemez S, et al (2009) Pandemic potential of a strain of influenza A (H1N1): Early findings. Science 324: 1557-61.

2. Munster V, Wit E, Judith M, et al (2009) Pathogenesis and transmission of swine-origin 2009 A (H1N1) influenza virus in ferrets. Science 325: 481-483.

3. Yang Y, Halloran JSM, et al (2009) The transmissibility and control of pandemic influenza A (H1N1) virus. Science 326: 729-33.

4. Hebert P, MacDonald N (2009) The H1N1 vaccine race: Can we beat the pandemic? CAMJ 181(8): E125.

5. Maurer J, Pinesa L, Harrisa K (2010) Perceived seriousness of seasonal and A (H1N1) influenzas, attitudes toward vaccination, and vaccine uptake among US adults: Does the source of information matter? Preventive Medicine 51(2): 185-187.

6. Brown K, Kroll J, et al (2010) Omission bias and vaccine rejection by parents of healthy children: Implications for the influenza A/H1N1 vaccination programme. Vaccine 28(25): 4181-4185.

7. HSPH (2009) Harvard School of Public Health Survey finds just 40% of adults "absolutely certain" they will get H1N1 vaccine. HSPH press Release http://www.hsph.harvard.edu/news/press-releases/2009-releases/survey-40-adults-absolutely-certain-h1n1-vaccine.html.

8. Strum L, Mays R, Zimet G (2005) Parental beliefs and decision making about child and adolescent immunization: From polio to sexually transmitted infections. J Dev Behav Pediatr 26(6): 441-452.

9. Wroe A, Turner N, Salkovskis P (2004) Understanding and predicting parental decisions about early childhood immunizations. Health Psychol 23: 33-41.

10. Streefland P (2001) Public doubts about vaccination safety and resistance against vaccination. Health Policy 55: 159-172.

11. Gellin B, Maibach E, Marcuse E (2000) Do parents understand immunizations? a national telephone survey. Pediatrics 106: 1097-1102.

12. OPHLA (2009) Ontario Public Health Libraries Association: pH1N1 flu virus (human swine influenza) information resources, october 5 http://www.ophla.ca/pdf/H1N120100427-0507.pdf.

13. Reluga T (2010) Game theory of social distancing in response to an epidemic. PLoS Comp Biol 6(5): e1000793.

14. Funk S, Gilad E, Jansen V (2010) Endemic disease, awareness, and local behavioural response. J Theor Biol 264: 501-9.

15. d'Onofrio A, Manfredi P (2010) Vaccine demand driven by vaccine side effects: dynamic implications for SIR diseases. J Theor Biol 264: 237-52.

16. Vardavas R, Breban R, Blower S (2007) Can influenza epidemics be prevented by voluntary vaccination? PLoS Comp Biol 3(5): 0796-0802.

17. Manfredi P, Posta P, d'Onofrio A, Salinelli E, Centrone F, et al. (2009) Optimal vaccination choice, vaccination games, and rational exemption: an appraisal. Vaccine 28(1): 98-109.

18. Coelhoand F, Codeco C (2009) Dynamic modeling of vaccinating behavior as a function of individual beliefs. PLoS Comp Biol 5(7): 1-10.

19. Basu S, Chapman G, Galvani A (2008) Integrating epidemiology, psychology, and economics to achieve HPV vaccination targets. Proc Natl Acad Sci USA 105: 19018-19023.

20. d'Onofrio A, Manfredi P, Salinelli E (2007) Vaccinating behaviour, information, and the dynamics of sir vaccine preventable diseases. Theor Popul Biol 71(3): 301-17.

21. Chen F (2006) A susceptible-infected epidemic model with voluntary vaccinations. J Math Biol 53: 253-72.

22. Bauch C (2005) Imitation dynamics predict vaccinating behaviour. Proc R Soc Lond B 272: 1669-1675.

23. Bauch C, Earn D (2004) Vaccine and the theory of games. Proc Natl Acad Sci USA 101: 13391-13394.

24. Smith J (1982) Evolution and the theory of games, volume 89. 15-23 pp.

25. Nash J (1950) Equilibrium points in n-person games. Proc Nat Acad Sci USA 36(1): 48-49.

26. Alexrod R (1984) The Evolution of Cooperation. Basic Books, New York.

27. Sigmund K, Hofbauer J (1998) Evolutionary Games and Population Dynamics.

28. Neumann V, Morgenstern O (1944) Theory of Games and Economic Behavior. Princeton Univ. Press, Princeton.

29. Anderson R, May R (1982) Population biology of infectious diseases. Springer-Verlag, Berlin, New York, Heidelberg.

30. Anderson R, May R (1991) Infectious diseases of humans. Oxford University, Oxford.

31. Bauch C, Galvani A, Earn D (2003) Group-interest versus self-interest in smallpox vaccination policy. Proc Natl Acad Sci USA 100: 10564-10567.

32. Gojovic M, Sander B, Fisman D, Murray D, Bauch C (2009) Modelling mitigation strategies for pandemic (h1n1) 2009. CMAJ DOI:10.1503/cmaj.091641.

A Determination of probability of infection $\rho_{\leq k+1}$ and $\rho_{>k+1}$

Let the proportion of the population that is susceptible (respectively, infected) before the first week be denoted by S_0 (respectively, I_0).

Now, proportion of population get vaccine at week-1 is ϕ_1 and this implies that susceptible on day-1 is $S_1 = S_0(1-\phi_1)$ and thus probability of being infected on day-1 is $P_1 = \lambda_1 S_1$, where $\lambda_1 = \beta I_0$.

Similarly, susceptible on day-2 is $S_2 = S_1 - P_1$ and probability of being infected on day-2 is $P_2 = \lambda_2 S_2$, where $\lambda_2 = \beta I_1$. Thus we can obtain P_3, P_4,...,P_7, etc. So, sum of the probability at the end of first week

$$\begin{aligned} P_{wk-1} &= P_1 + P_2 + ... + P_7 \\ &= S_0(1-\phi_1)[\lambda_1 + \lambda_2(1-\lambda_1) + ... + \lambda_7(1-\lambda_6)...(1-\lambda_1)]. \end{aligned}$$

Again, proportion of population get vaccine at the week-2 is ϕ_2. So similarly, we obtain sum of the probability at the end of second week

$$\begin{aligned} P_{wk-2} &= P_8 + P_9 + ... + P_{14} \\ &= S_0(1-\phi_1)(1-\phi_2)\{(1-\lambda_7)...(1-\lambda_1)\}[\lambda_8 + \lambda_9(1-\lambda_8) + ... + \lambda_{14}(1-\lambda_{13})...(1-\lambda_8)]. \end{aligned}$$

Thus generalizing the formulation, we obtain the sum of the probability of infection in week k is given by

$$\begin{aligned} P_{wk-k} &= P_{7(k-1)+1} + P_{7(k-1)+2} + ... + P_{7k} \\ &= S_0\{(1-\phi_1)(1-\phi_2)...(1-\phi_k)\}\{(1-\lambda_{7(k-1)})(1-\lambda_{7(k-1)-1})...(1-\lambda_1)\} \\ &\quad [\lambda_{7(k-1)+1} + \lambda_{7(k-1)+1}(1-\lambda_{7(k-1)+1}) + ... + \lambda_{7k}(1-\lambda_{7k-1})...(1-\lambda_{7(k-1)+1})], \end{aligned} \tag{9}$$

where $P_{7k} = \lambda_{7k} S_0(1-\lambda_{7k-1})...(1-\lambda_1)(1-\phi_1)...(1-\phi_k))$ is the probability of infection at week k, $\lambda_i = \beta I_{i-1}/N$ denotes the force of infection and ϕ_k denotes vaccination coverage at week k. Hence, the cumulative probabilities $\rho_{\leq k+1}$ and $\rho_{>k+1}$ are defined by $\rho_{\leq k+1} = \sum_{j=1}^{(k+1)} P_{wk-j}$ and $\rho_{>k+1} = \sum_{j=k+2}^{52} P_{wk-j}$.

Tables

Table 1. Baseline parameter values

Parameters	values/ranges	References
Total Population (N)	100,000	–
Contact rate (β)	0.6 day^{-1}	[32]
Recovery rate (γ)	0.33 day^{-1}	[32]
Baseline payoff (L)	1	–
Risk of vaccine ($r_{_{vac}}$)	0.0005	–
Risk of infection ($r_{_{inf}}$)	0.001	–
Efficacy of vaccine (ϵ)	0.75	–
a	see the text	–
b	0.15	–
c	0.015	–
d	10	–

Figure Legends

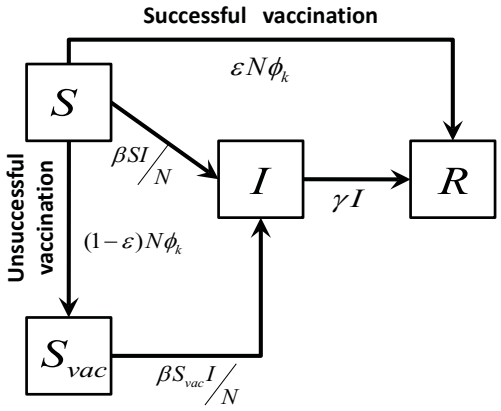

Figure 1. Schematic diagram of epidemiological process between several compartments.

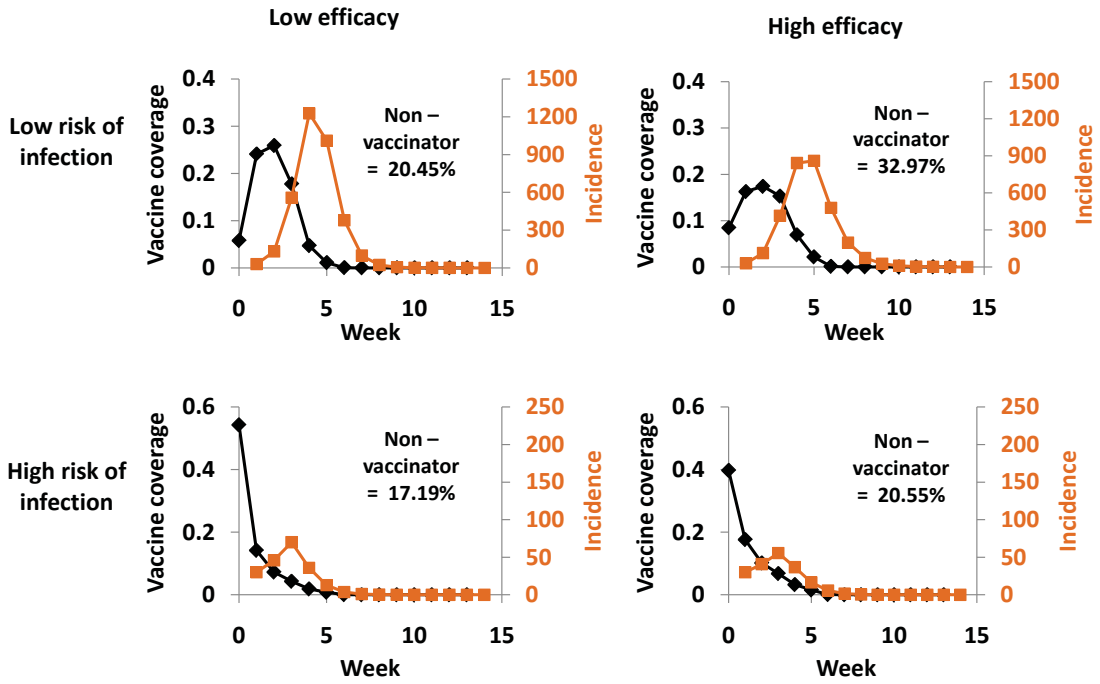

Figure 2. Nash equilibrium vaccine coverage over weeks for low ($r_{inf} = 0.0006$) and high ($r_{inf} = 0.03$) disease risk, and low ($\epsilon = 0.6$) and high ($\epsilon = 0.9$) efficacy of vaccine. Incidence is per 100,000 populations. Percentage in the inset of each figure indicates the proportion of population choosing pure non-vaccination strategy.

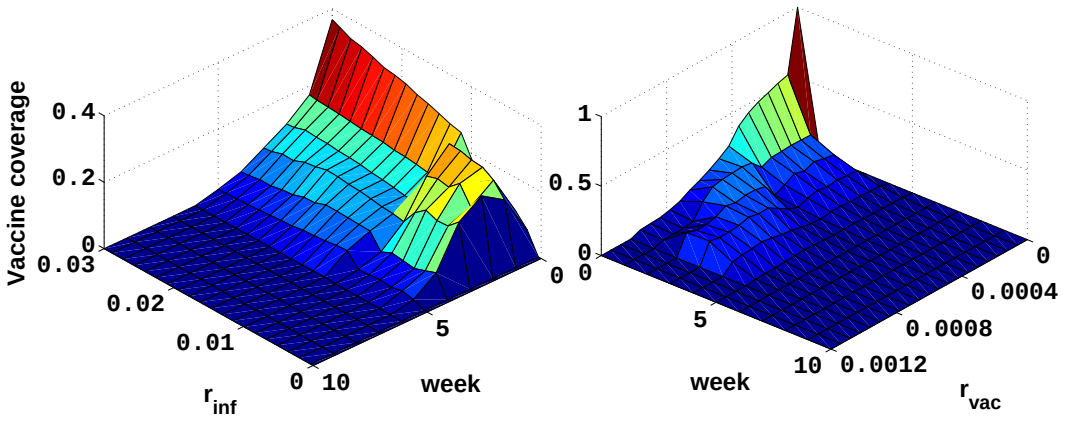

Figure 3. Nash equilibrium vaccine coverage at different disease risk (r_{inf}) (left panel) and different vaccine risk (r_{vac}) (in the right panel).

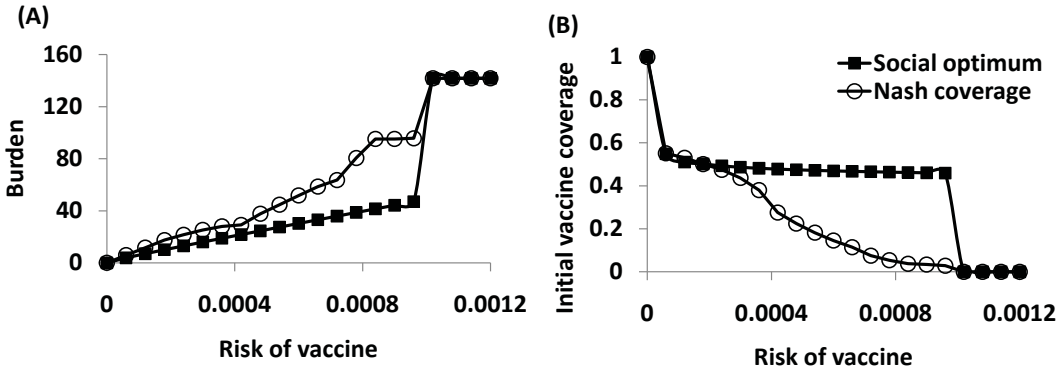

Figure 4. Nash equilibrium vaccine coverage and social optimum for constant perceived risk of vaccine. (A) total burden due to disease and vaccine for both Nash and non-Nash coverage and (B) corresponding initial vaccination coverage.

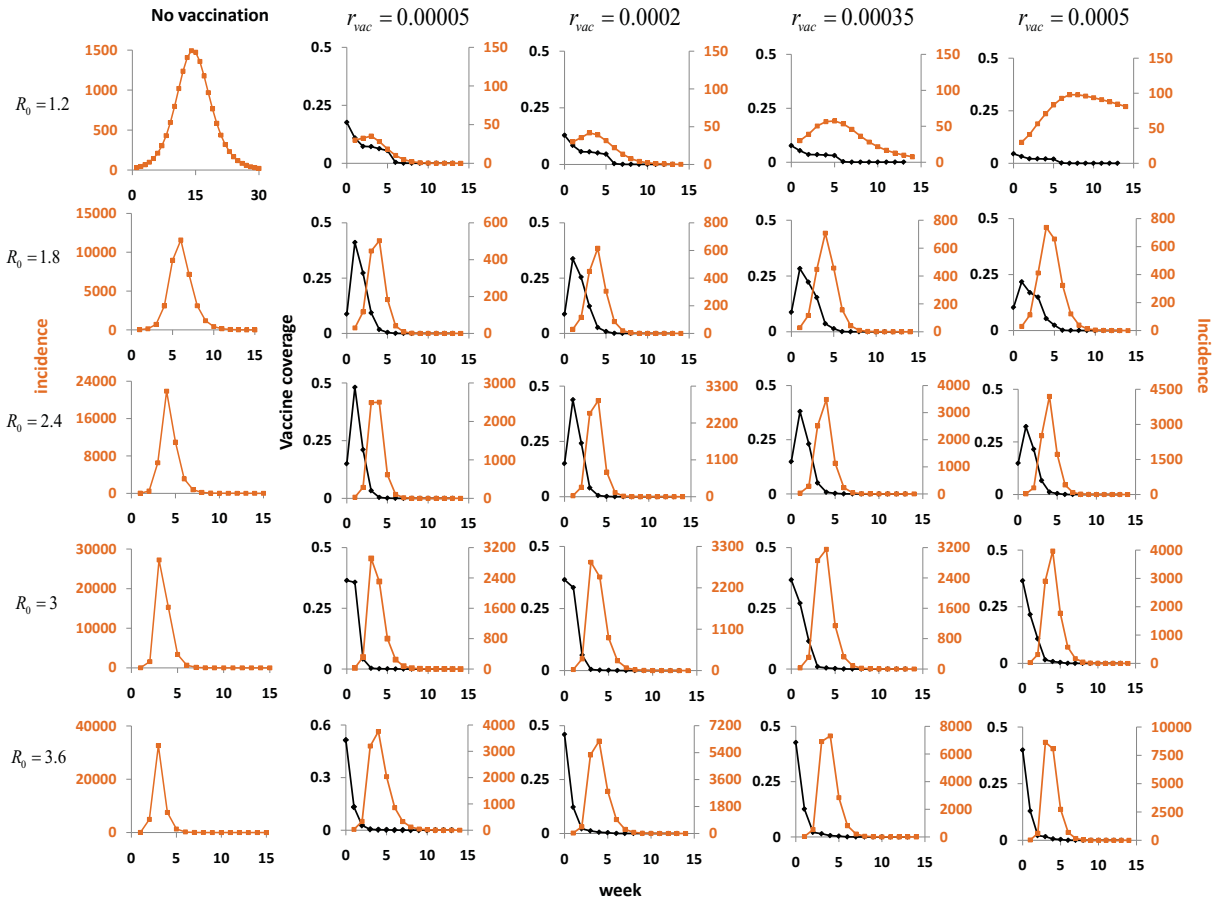

Figure 5. Nash equilibrium vaccine coverage and incidence at different R_0 and for constant risk of vaccine over the weeks. The first column indicates the incidence in absence of vaccination.

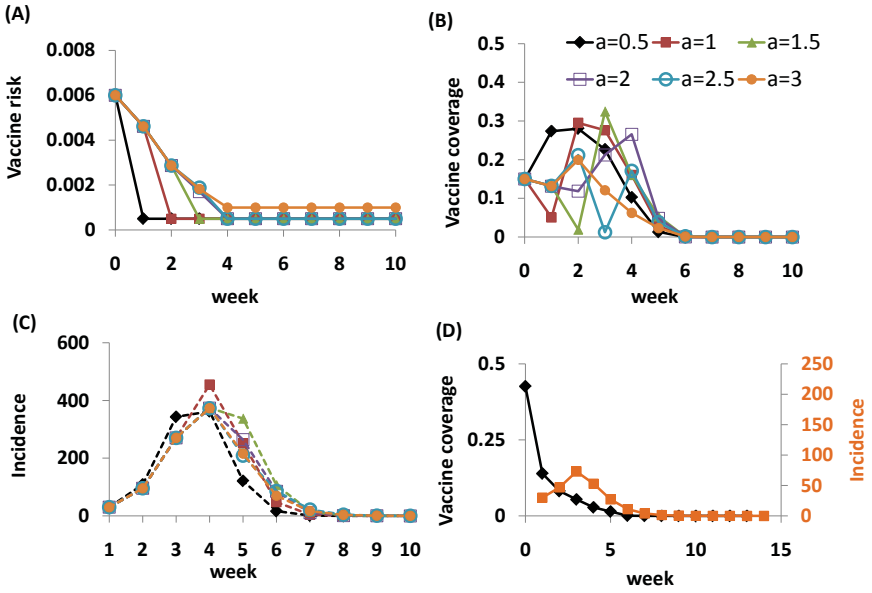

Figure 6. Nash equilibrium vaccine coverage at variable perceived risk of vaccine. (A) Variable vaccine risk over weeks for different values of a in the risk function and (B) corresponding Nash equilibrium vaccine coverage and (C) disease prevalence. The incidence is per 10,000 populations and $r_{inf} = 0.02$. Figure (D) indicates the vaccine coverage in the same parameter setup as in (B) except the vaccine risk is constant = 0.0005 during the entire period of disease outbreak.

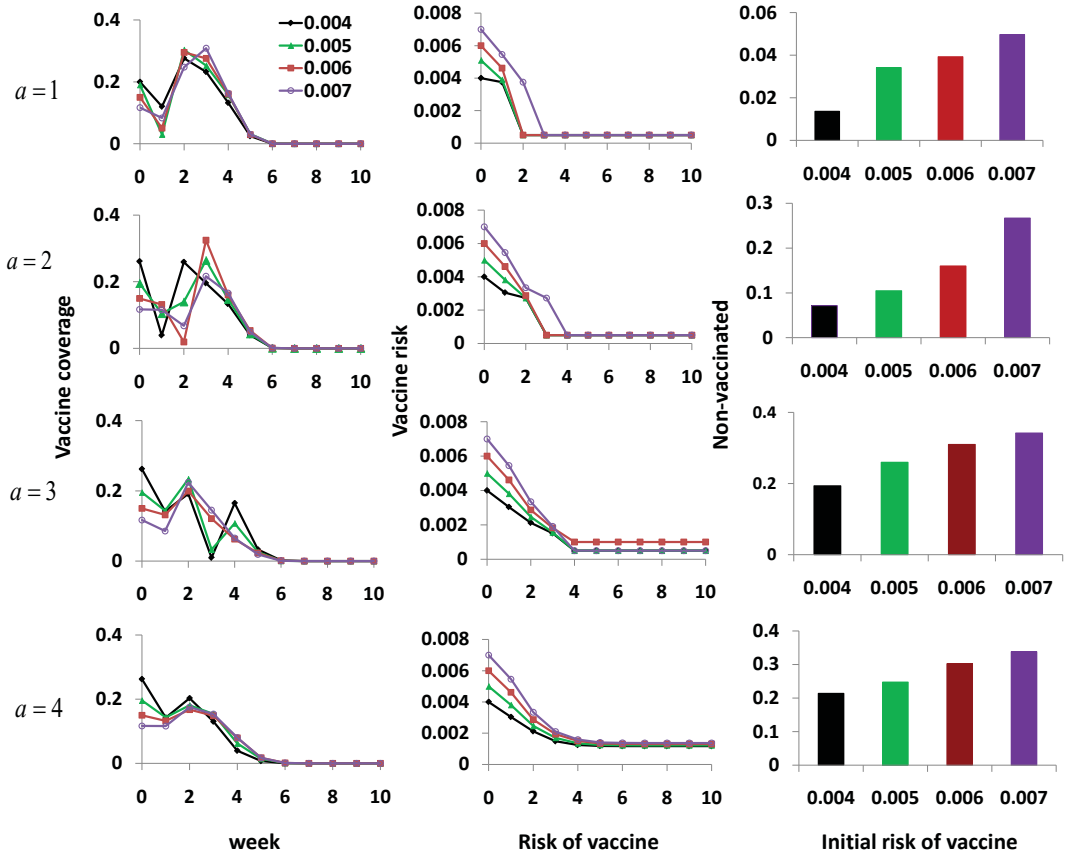

Figure 7. Nash coverage at different initial risk and for different a values. First column exhibits Nash equilibrium vaccine coverage, second column indicates corresponding variable vaccine risk and third column shows the proportion of population choose non-vaccination if initial vaccine risk is different. The parameter values are same as in Figure 6. The third panel of the figure indicates that the mean vaccine coverage decreases with higher initial risk perception.

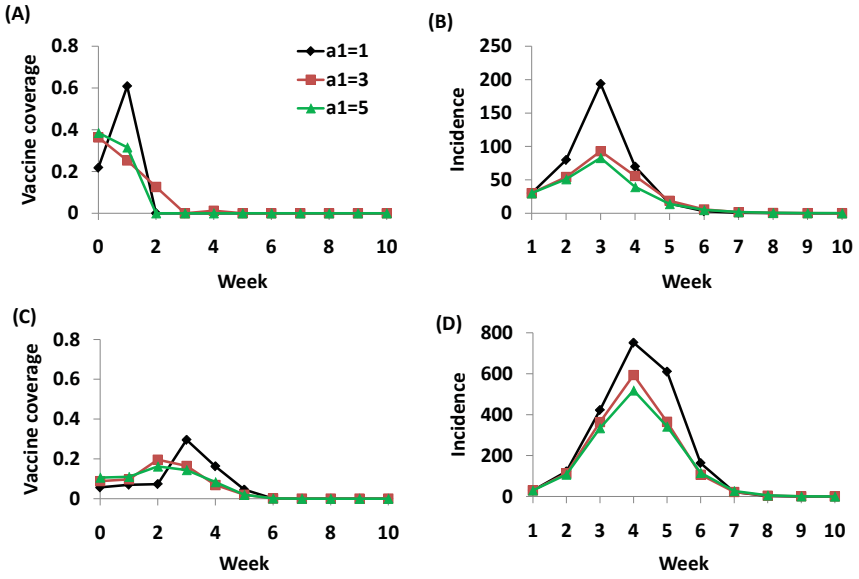

Figure 8. Social optimum and Nash equilibrium vaccine coverage at variable perceived risk of vaccine. (A) Social optimum and (C) Nash equilibrium vaccine coverage when vaccine risk varies over weeks depending on earlier coverage. (B) & (D) exhibit corresponding disease incidence. The parameter values are same as in Figure 6.

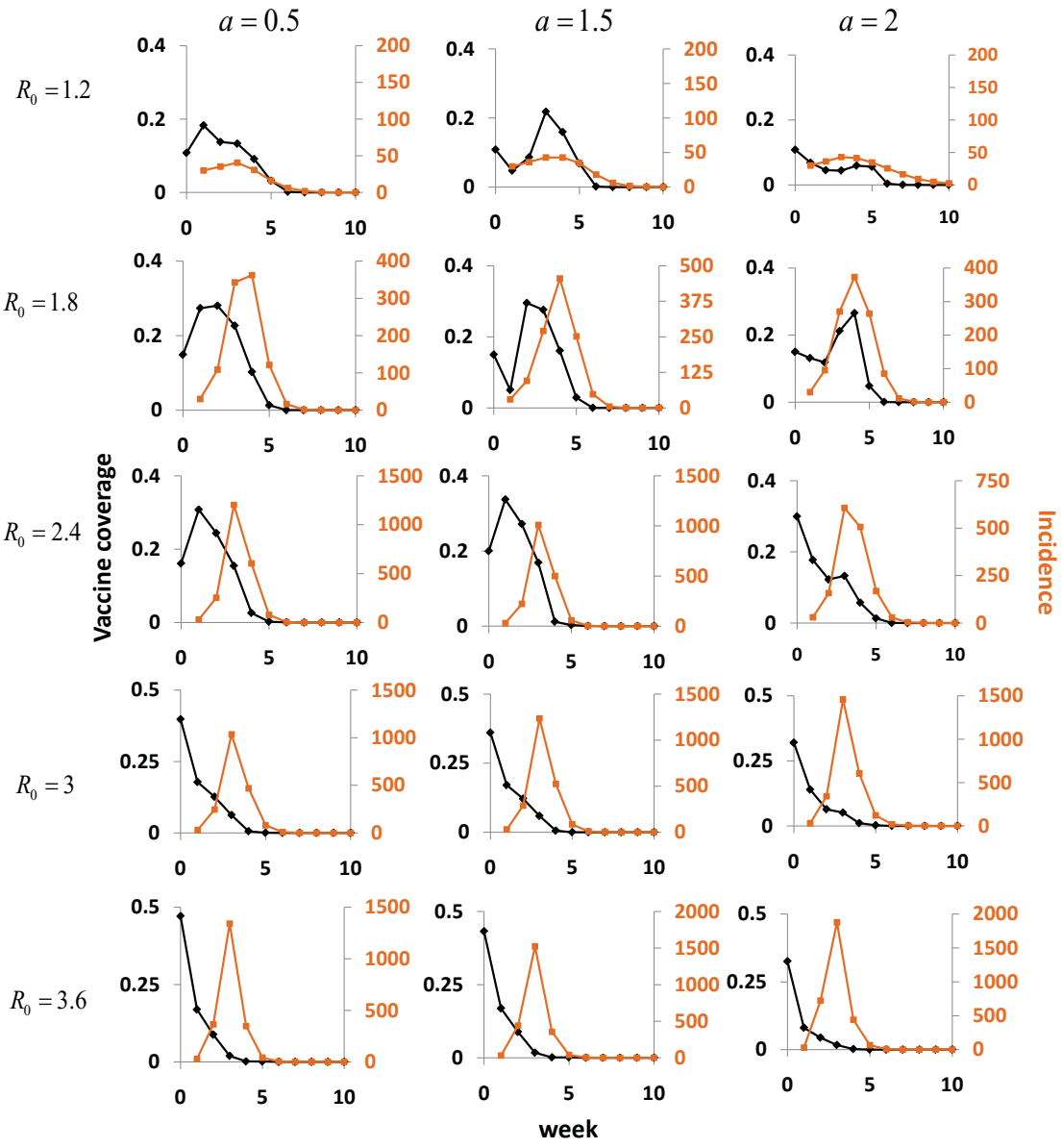

Figure 9. Nash equilibrium vaccine coverage at different R_0 and for variable risk of vaccine over the weeks. The parameter values are same as in Figure 6.