Long-standing influenza vaccination policy is in accord with individual self-interest but not with the utilitarian optimum

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Influenza vaccination is vital to reducing infection-mediated morbidity and mortality. To maximize effectiveness, vaccination programs must anticipate the effects of public perceptions and attitudes on voluntary adherence. A vaccine allocation strategy that is optimal for the population is not necessarily optimal for an individual. For epidemic influenza, the elderly have the greatest risk of influenza mortality, yet children are responsible for most of the transmission. The long-standing recommendations of the Centers for Disease Control follow the dictates of individual self-interest and prioritize the elderly for vaccination. However, preferentially vaccinating children may dramatically reduce community-wide influenza transmission. A potential obstacle to this is that the personal utility of vaccination is lower for children than it is for the elderly. We parameterize an epidemiological game theoretic model of influenza vaccination with questionnaire data on actual perceptions of influenza and its vaccine to compare Nash equilibria vaccination strategies driven by self-interest with utilitarian strategies for both epidemic and pandemic influenza. Our results reveal possible strategies to bring Nash and utilitarian vaccination levels into alignment.

Vaccination is the principal strategy for reducing the public health burden of influenza. However, a fundamental but oft-neglected component of implementing an optimal community vaccination program is human psychology, which influences adherence to vaccination recommendations. The utilities of vaccination decisions for individuals and for their communities are governed by the interplay between epidemiological and social systems. An individual's vaccination decisions are driven by their perceptions of the epidemiological system. Individual decisions collectively determine the level of population immunity and thus the magnitude of an epidemic.

Vaccination protects not only those who are vaccinated, but also others in the community who are thereby less likely to be infected. Unmitigated pursuit of self-interest can lead to suboptimal vaccination coverage for a community (1, 2). Previous studies have applied game theory to vaccination under the assumption that individuals are fully rational decision makers with perfect and complete knowledge (1, 2). However, our psychological data reveals that there are significant discrepancies between individuals' perceptions of influenza and its vaccine and the epidemiological facts. Here we parameterize a game theoretic epidemiological model of influenza vaccination with empirically collected psychological data to incorporate perceptions of influenza epidemiology and vaccination (Methods).

The policy of the Centers for Disease Control (CDC) has been to prioritize the elderly for influenza vaccination (3), because they are at highest risk of influenza mortality. However, most transmission occurs between children and within the adult workforce as a consequence of frequent contact with greater numbers of individuals at school and work, respectively (4-11). Thus, influenza vaccination targeted at the young can dramatically reduce community-wide transmission (4, 12, 13).

Here we show that the discordance of vaccination incentives between the young (who perpetuate epidemics) and the elderly (who are at greatest risk of influenza morbidity and mortality) obstructs utilitarian vaccination.

In a game-theoretic context, individuals seek to maximize their personal utility, which is a trade-off between anticipated benefits and costs, discounted by the diminished value of the future relative to the present. Accordingly, survey data indicates that individuals attempt to minimize their perceived risks (14). For example, the decision to vaccinate is positively associated with perceived vaccine effectiveness, and is negatively associated with perceived side effects (14, 15). People are also more likely to vaccinate if they perceive a high likelihood or severity of influenza (16). Thus, an individual's decisions may be affected by discrepancies between perceived and actual risks. Survey studies have found that people often believe that diseases are less risky than their respective vaccines (17, 18). Some parents believe that childhood vaccination is not necessary because other parents have vaccinated their children and because childhood diseases are under control (18), indicating at least a conceptual understanding of the indirect protection that is attained from the vaccination of others via herd immunity.

We broadly define vaccine costs to include both direct costs and anticipated risks. For influenza vaccination, costs to individuals include monetary cost, opportunity costs associated with time and inconvenience of vaccine administration, and potential adverse health effects. The actual medical risks of influenza vaccination are generally minor. Potential adverse effects include arm soreness (19), rhinorrhea, nasal congestion and fever (20). However, public perceptions of risk may be elevated beyond actual risks. There has been public concern about a reputed causative link between the influenza vaccine and Guillain–Barré syndrome, a disorder of the peripheral nervous system that can lead to paralysis and even death. It was reported that one such case correlated with every 100,000 swine-influenza vaccines given in 1976 (21). Subsequent studies estimate that the risk of Guillain–Barré syndrome has dropped to approximately one case per million vaccinations (22). There has also been widespread public concern that thimerosal, a mercury-containing preservative, could have adverse effects including neuro-developmental disorders (23). Our survey data suggests that risks associated with influenza vaccination are over-estimated by the public compared to actual risks estimated in epidemiological studies. Thus, we predict an effect of overestimated vaccine risks on the optimality of vaccine demand.

Without public health intervention, vaccination choices of individuals are expected to tend toward the Nash equilibrium, at which no individuals can improve their utility by switching to a different strategy (24). When driven by self-interest, an individual's utility is not increased by its contribution to herd immunity. However, the positive externality of herd immunity does improve the utilitarian vaccination strategy, which is defined as the strategy that achieves the highest population utility. Thus, the utilitarian strategy generates higher utilities, both for the community and for the individual, on average. Nevertheless, the utilitarian strategy may not be socially stable, because at the utilitarian level of vaccination "free-riders" who do not vaccinate but benefit from herd immunity can yield a higher utility than "cooperators" who vaccinate.

Previous epidemiological game theoretic studies have neither considered populations with heterogeneous incentives, nor influenza vaccination. Calculating mixed-strategy Nash equilibria requires simultaneously determining the best response strategy for each individual in the population, dependent upon the strategy of every other individual, an operation that is recalcitrant to analytical solution. Thus, we have developed a Monte Carlo algorithm for determining both Nash equilibria and utilitarian vaccination strategies. We reveal the impact of perceived vaccine cost and risk on the discrepancy between Nash equilibria and utilitarian vaccination strategies. Relative to utilitarian

vaccination against epidemic influenza, we predict that much more vaccine will be desired by the elderly and much less vaccine sought by the young, at the expense of the community overall. We find that the utilitarian and Nash strategies are in closer alignment during a pandemic than during an epidemic.

To determine the likely impact of improved education about influenza and its vaccine, we compare actual epidemiological parameter values with perceived parameter values obtained from our psychological data. We reveal common misperceptions of influenza epidemiology, some of which reduce the discrepancy between utilitarian and Nash vaccination levels and others of which act against utilitarian vaccination. Interestingly, the vaccination threshold beyond which transmission is eliminated can be achieved with lower incentives if the public misestimates certain epidemiological parameters identified in our survey.

Results

Questionnaire results. Questionnaire results are reported for 595 university employees. The questionnaire results are not necessarily a representative sample of the US population at large.

Subjective perceptions of parameters. We examined whether people misperceive key epidemiological parameters for influenza. Mean responses for questionnaire items of interest are shown in Table 1 along with actual epidemiological values for each variable. Single sample t-tests indicate whether mean perceived values differ significantly from the actual values. The data indicate that people greatly overestimate the incidence of influenza infection and underestimate vaccine efficacy. They tend to overestimate the incubation period and underestimate the duration of vaccine protection. They only slightly overestimate the duration of the infectious period.

Some questionnaire items used 5-point Likert response scales, and thus it was difficult to compare participants' responses to an objectively correct value. In some cases, however, it was nevertheless possible to establish that participants misperceived parameters. One item asked, "How likely do you think it is that the flu shot would cause a person to have a severe reaction?" The mean response was 2.06 on a scale from 1 (not at all likely) to 5 (very likely). A response of 2 corresponds to "a little likely." The normatively correct response is "very unlikely" and thus the 70% of participants who gave a higher response were overestimating vaccine risk. Accordingly, we examined model output with vaccine risk elevated by varying degrees above the actual risk.

Predictors of vaccination. Older participants were more likely to be vaccinated ($r=0.30$, $N=595$, $p<.0001$). Among participants aged 65 and older ($n=35$), 71% were vaccinated, compared to 47% among younger participants ($n=560$). 38% ($N=215$) of the adults in the survey had one or more children under age 18 living in their household. In only 15% of these households were any children vaccinated, a rate that is significantly lower (OR = 1.31, 95CI 1.22 – 1.42) than that among parents themselves (42%). Thus, the questionnaire study reveals a vaccination pattern that parallels the CDC guidelines, with high vaccination rates for the elderly, moderate rates for younger adults, and low rates for children. This vaccination pattern corresponds more closely to a Nash equilibrium than to a utilitarian strategy identified by our model. As an indication that vaccination decisions are driven by perceived risks and benefits, vaccination was positively associated with perceived likelihood of infection ($r=0.37$, $N=595$, $p<.0001$) and perceived vaccine efficacy ($r = 0.29$, $p<.0001$), and negatively associated with perceived adverse effects of the vaccine ($r= -0.29$, $p<.0001$).

Model results

Epidemic influenza. For the perceived parameters of epidemic influenza, the utilitarian strategy is to allocate all vaccine to the young (Fig 1A). However, Nash vaccination levels for the young are much lower than those that are optimal for the community for a given vaccine cost. Conversely, vaccination demand by the elderly is much higher than that of the utilitarian strategy. Nash and utilitarian vaccination by the young falls exponentially with greater vaccine cost (a function of the severity and probability of all potential costs and risks), while Nash vaccination by the elderly is inelastic to increasing cost over the wide range examined (Fig 1A).

When both age groups are vaccinated according to the Nash equilibrium, levels of disease incidence and mortality are significantly higher than when vaccination adheres to the utilitarian strategy (Fig 1B). For the current vaccine cost (value of 1 on the log scale of the X-axis), 170 more infections and 2 more deaths within a population of a million occur if vaccination is guided by the Nash equilibrium than if vaccination adheres to the utilitarian strategy. If the vaccine were 10 times more costly (as was the case for the swine influenza vaccine in 1976), further reduced vaccination levels are predicted by the Nash solution that would cause 43144 more infections and 24 more deaths per million individuals than would the utilitarian optimum.

For actual epidemiological parameters of epidemic influenza, there are also differences in vaccination levels between the utilitarian optimum and Nash equilibria (Fig 2A). Furthermore, vaccination levels are lower for actual parameters than for perceived parameters, because people tend to greatly overestimate their infection probability (Figs 1A & 2A). Nash vaccination of the elderly in Fig 2A reveals the trade-off between vaccine cost and risk of infection. At low vaccine costs, all elderly seek vaccination. However, at higher vaccine costs, the demand for vaccination drops slightly. This dip occurs until the decline in herd immunity resulting from the concomitantly falling vaccination of the young generates a rebound in vaccine demand by the elderly. The lower actual infection probability results in lower incidence and mortality than when our model is parameterized with perceived values, particularly at high vaccine costs (Figs 1B & 2B).

Another comparison of interest is the Nash solution based on perceived parameters (Figure 1A) relative to the utilitarian solution based on epidemiological parameters (Figure 2B). Because the utilitarian solution is the normatively optimal solution (often determined at a policy level), one might argue that it should be based on best estimates of epidemiological parameters. The Nash solution, in contrast, represents the self-interested behavior of individuals who act according to their own beliefs. When the Nash equilibrium is calculated using perceived parameters, the discrepancy between the Nash and utilitarian vaccination levels is reduced. That is, in the Nash solution the self-interest that reduces vaccination of the young is to some extent offset by the overestimation of infection risk.

Reducing vaccine cost promotes vaccination at the Nash equilibrium (Fig 1A, 2A). Based on actual epidemiological parameters, 77% vaccination of the young would eliminate both perpetuated transmission and mortality. For perceived parameters this vaccination level is achieved by reducing the vaccine cost to 10% of the current cost. For actual parameters, vaccination of the young to the 77% threshold is predicted to occur at 0.9% of the current cost.

Pandemic influenza. For pandemic influenza, as for epidemic influenza, utilitarian vaccination is achieved by vaccinating the young. The Nash and utilitarian vaccination strategies of complete vaccination for the young are in alignment over a range of lower vaccine costs (Fig 3A). At both the utilitarian optimum and the Nash equilibrium, the elderly are not vaccinated, unless the vaccine cost is

low. In the pandemic case, the young have more incentive to vaccinate than the elderly. The young vaccinate up to a level of herd immunity at which point the elderly have no incentive to vaccinate.

Elevations in infection incidence (Fig 3B, 1B) at the Nash equilibrium relative to the utilitarian strategy during a pandemic are lower than those for epidemic influenza for a given vaccine cost. The greater virulence of pandemic influenza boosts incentives to vaccinate. However, pandemic influenza's higher case fatality proportion results in greater mortality for pandemic influenza than for epidemic influenza (Fig 3B, 1B).

Discussion

Community-wide protection is optimally achieved by vaccinating the proportions of the population most responsible for influenza transmission, i.e. the young (4, 12, 13). However, we found that this utilitarian strategy faces obstacles in population adherence if individuals act according to self-interest, because the personal utility of vaccination is lower for the young than for the elderly.

We identified two sources of discrepancies that affect vaccination levels for both epidemic and pandemic influenza. First, discrepancies generated by discordant incentives to vaccinate between the young and the elderly lead to misalignments between Nash and utilitarian vaccination levels. For epidemic influenza, in both our model and survey results, the young tend to under-vaccinate and the elderly to over-vaccinate, relative to the utilitarian strategy, paralleling CDC recommendations. The differences between utilitarian and Nash vaccination strategies arise because the positive externalities of indirect protection via herd immunity effects are encompassed in the optimization of the utilitarian strategy, but only an individual's internalized costs and benefits come into play at the Nash equilibrium. Herd immunity is fundamental to reducing the public health burden of infectious diseases, but creates an incentive for individuals to "free-ride" on the vaccination of others. Consequently, the overall level of population vaccination is lower at the Nash equilibrium than at the utilitarian community optimum. Thus, the current CDC policies that focus on the elderly are reinforced by self-interest, but are not the most effective for curtailing transmission and minimizing influenza morbidity and mortality.

For a pandemic avian influenza outbreak, Nash and utilitarian strategies are in closer alignment, relative to an epidemic outbreak. During pandemics, the young are responsible for most transmission, but they also experience disproportionately more severe infection (5, 25, 26). Hence, individual and community incentives are in greater accord than for epidemic influenza. Although a pandemic vaccine will likely be of higher cost and risk than a typical influenza vaccine, the Nash vaccine demand is probably above the number of avian influenza vaccine doses that will be available during a pandemic.

A second source of discrepancy that affects vaccination levels is between perceived and actual epidemiological parameters. We revealed that misperceptions of some epidemiological parameters promote vaccination while others discourage vaccination. For a given vaccine cost, vaccination levels under both the Nash equilibrium and the utilitarian optimum are actually lower for realistic epidemiological parameters than for perceived parameters. People greatly overestimate influenza infection probability, and vaccine risks, while they underestimate influenza vaccine efficacy. Thus, education about actual infection probabilities without education about actual vaccine efficacy and risks could actually expand the discrepancy between Nash and utilitarian vaccination levels.

We found that the threshold of vaccination at which perpetuated transmission is terminated could be achieved with a higher cost of vaccination for perceived parameters than for actual epidemiological parameters. For perceived parameters, vaccination of the young to this threshold is predicted to occur at 10% of the current cost. For actual parameters, the vaccine must be reduced to

less than 1% of its current cost in order to achieve this critical vaccination level. Thus, for a given vaccine cost, less incentive is required (or a higher cost permitted) to promote vaccination for the inaccurately perceived parameters identified in our survey.

Achieving these reductions in vaccine costs and real or perceived risks might be accomplished in a combination of ways. Convenience of vaccination is positively associated with the decision to vaccinate (27). To make vaccination more convenient, one approach would be to provide vaccination in schools. The Advisory Committee on Immunization Practices recommends removal of administrative and financial obstacles (28). Greater vaccine availability and initiation of Medicare reimbursement are credited with increasing population vaccination levels (29).

Our survey results indicate that vaccine demand is positively correlated with perceived vaccine efficacy. However, we found that people perceive a lower influenza vaccine efficacy than is actually the case. The discrepancy between utilitarian and Nash strategies is exacerbated by elevated perceptions of vaccine risk. Indeed, people report apprehension about side effects as a primary deterrent to receiving influenza vaccination (20, 30). For both epidemic and pandemic influenza, aligning the Nash and utilitarian strategies could be promoted by public education to counteract the current overestimation of vaccine risks. Additionally, replacement of thimerosal, the mercury-containing preservative, might allay concerns about vaccine safety, whether or not these concerns are overestimated.

We examined the interaction between disease transmission and social decision-making, with specific application to influenza infection and vaccination. We found that influenza vaccination driven by self-interest and promoted by current CDC recommendations compromises utilitarian programs that would minimize transmission, disease incidence and mortality for the young, the elderly and overall. We also identified discrepancies between predictions generated using perceived and actual parameters that reveal the importance of parameterizing models of vaccine uptake with psychological data. Ultimately, policy makers must balance public health, social, economic and ethical considerations when developing optimal public health policies (31). Assessing the interplay among biological systems, decision-making processes and social influences will generate more accurate predictions of vaccination-related decisions, which should facilitate improved interventions.

Methods

Questionnaire

In order to establish empirical parameters for the model, we analyzed survey responses from the Health Promotion at Work (HPAW) longitudinal study of university employees (15, 27, 32). 673 participants indicated whether they had received a flu shot during fall 2001 and answered a variety of other questions. For a more complete description of the study and procedures, see (15). The questionnaire items employed in the parameterization of our model are summarized in Table 1. We compared predictions when the epidemiological model is parameterized using point estimates of psychological questionnaire data reflecting the perceptions that inform individuals' decisions regarding influenza vaccination to when the model is parameterized using epidemiological estimates from published data. The epidemiological estimates are equivalent to the decisions of rational individuals with complete knowledge.

Model

Our epidemiological game theoretic analysis consists of four main components. We first developed an age-structured and seasonal epidemiological model of influenza transmission and vaccination at the population level. The dynamics of young and elderly susceptible, vaccinated, naturally immune, latently infected and infectious compartments of the population are described by this model. We then used infection prevalence outputted by the epidemiological model to parameterize a Markov process description (33, 34) of vaccination decisions at the level of the individual and resulting probabilities of vaccination and infection. Thirdly, we calculated expected utilities of all possible vaccination decisions, based on cost data (Table 2). Finally, a Monte Carlo algorithm parameterized with these utilities was used to determine the convergently stable Nash equilibria. Please see the supporting information for a detailed description of the model equations and methodology.

1. *Epidemiological population model*

To capture the seasonal timing of vaccination and the annual cycle of influenza epidemics, we combined a discrete-time model of vaccination with a differential equation model of a seasonal influenza epidemic (35). The population was divided into two age classes: one containing all individuals below age 65, and the other containing all individuals age 65 and older. Age classes were parameterized from US census data: 88% of the population is under 65 years and 12% of the population is 65 years or older (36). The older age class corresponds to the CDC's defined target group for vaccination (3). We assumed that parents make decisions in the best interest of their children.

Vaccinated individuals become infected at a fraction of the rate of susceptible individuals. We found from our questionnaire study that perceived vaccine efficacy against infection is 34% (Table 1), compared to actual values of 80% protection among individuals younger than 65 (10, 37) and 60% for the elderly (38). Upon infection, individuals enter a latency period, the perceived duration of which is 4 days (Table 1), compared to an actual value of 1.2 days (39). Latently infected individuals proceed to become infectious. The perceived duration of the infectious period is 5 days (Table 1), which is close to the actual value of 4-5 days (40). It is assumed that recovered individuals are fully protected against further infection for the remainder of the influenza season.

We assumed, as is suggested by time series of influenza incidence (41), that the incidence follows an annual pattern with a winter seasonal increase that is an order of magnitude above baseline summer incidence. The perceived annual infection probability was 0.48 (Table 1), compared to an actual infection probability of 0.15 (42) for epidemic influenza and of 0.5 for pandemic influenza (derived from refs. (5, 25, 26) and 1918 census data). The model incorporated the finding that younger individuals are twice as likely to transmit influenza to others (9, 10). For epidemic infection, younger and older individuals are equally likely to contract infection, while for pandemic influenza, the attack rate in the young is increased three-fold relative to epidemic influenza (5, 25, 26). The case fatality proportion for epidemic influenza is typically 0.3% for the elderly and 0.03% for the young (5, 10). The case fatality proportion for pandemic influenza is 5% for the elderly and 2% for the young (5).

Vaccination was assumed to occur each fall, three months before transmission reaches its maximum. It was assumed that vaccination reduces the likelihood of infection as well as disease severity in the event of infection, consistent with epidemiological data (Table 2). Since influenza rapidly evolves new antigenic variants (43), immunity tends to wane from one year to the next. People perceive that vaccine protection lasts for 8 months (Table 1), which would confer protection for the duration of an influenza season. On average, a fraction of all individuals choose to vaccinate each fall. We modeled the dynamics of waning immunity and vaccination as an instantaneous event each fall.

2. *Individual model of vaccination and infection*

Our epidemic model described the average population dynamics of vaccination and influenza transmission, but the infection future of an individual is stochastic. Therefore, using output of infection prevalences from our population-level epidemic model, we parameterized a Markov process for an individual's decision dynamics. This process predicts annual probabilities of vaccination and infection for an individual within an age class.

We tracked the susceptible, resistant, and vaccinated states that an individual can occupy. Consistent with our population-level model, we divided the year into a vaccination phase followed by an influenza-season phase. During the vaccination phase, transitions among epidemiological model states depend upon both the probability that an individual's immunity wanes due to viral evolution and the probability that an individual chooses to vaccinate. For a susceptible individual, the annual infection probability was calculated from the equilibrium solution of the epidemic model as the number of susceptible individuals at the end of the influenza season divided by the number of susceptible individuals at the beginning of the influenza season. Similarly, for a vaccinated individual, the probability of infection was calculated as the number of vaccinated individuals at the end of the influenza season divided by the number at the beginning. Individuals who were resistant at the beginning of the influenza season remained resistant for the duration of the influenza season. We produced a matrix of transition probabilities for an individual during the vaccination phase based on these features of influenza transmission.

3. *Utility calculation*

The individual-level model predicted the probability of future infection and vaccination events. We then used Markov process theory (34) to calculate an individual's expected utility of a vaccination decision by summing the products of the discounted costs and probabilities for each possible event. We assumed an annual discount rate of 3% (44). The population's overall utility, then, is a weighted average of the utilities for each age class, with weights given by the proportion of the total population in each class.

During the influenza season, susceptible and vaccinated individuals pay expected costs of infection (Table 2) in proportion to their risk of infection. Age-specific costs of infection were calculated as the sums of varying severities of outcomes, including loss of work, treatment, outpatient visits, hospitalization and mortality, multiplied by their respective probabilities (5, 10, 45-51) (Table 2). In contrast to the CDC's analysis of infection costs (10), we generally assumed that all individuals value their life equally, irrespective of their age, although we also compare with a lower valuation of elderly life consistent with the CDC's analysis of infection costs (10) (Fig S1). If vaccinated people are infected, they are less likely to have serious complications, i.e. outpatient visits to a doctor, hospitalization, and mortality (10) (Table 2). Thus, we parameterized the utility calculations with age-specific distributions of vaccine efficacy in reducing influenza morbidity and mortality (10, 37, 38, 52-60) for infected individuals. Vaccination costs include the cost of the vaccine ($14), associated travel expenses ($4) and time cost to the individual ($16) (47, 61), as well as probabilities and average treatment costs of each adverse event ($3.25) (5, 10, 49)**,** giving a total actual vaccination cost of $37.26. We varied the cost of vaccination to determine the impact of inaccurate perceptions of costs/risks and/or changes in actual cost.

Previous studies of vaccination games have used less flexible utility calculations. By combining deterministic models of macroscopic population dynamics with stochastic models of an individual's dynamics, we employed of a powerful reformulation of population games for the study of

game theoretic decision-making. The flexibility of this approach will facilitate the future incorporation of potentially complex factors such as host heterogeneity and geographical variation.

4. *Calculation of Nash equilibria*

We then used our utilities of vaccination decisions to calculate convergently stable Nash equilibria of the population game in which individuals of a given age class choose vaccination rates under the assumption that individuals act to maximize their personal utility. For some simple problems in homogeneous populations, calculations of Nash equilibria are achieved through single parameter optimization. No such simplification is available, however, for age-structured populations with two or more strategy-parameters. Other methods rely on the calculation of local derivatives, which cannot be analytically obtained in closed form for our model. Thus, we have adapted a Monte Carlo algorithm(62) to calculate ρ_A and ρ_B at the Nash equilibrium.

At the Nash equilibrium, no individual can improve their expected utility by changing their vaccination probability. Thus, the utility of vaccination is equal to the utility of vaccine refusal for each age class. We found solutions to the equations through minimization of the squared difference between utilities of vaccination refusal versus acceptance for each age class over the parameter solution space. Random perturbations of the proposed vaccination probabilities were drawn sequentially for each class from triangular distributions that add or subtract at most 0.01. For each iteration, perturbations were accepted when the ratio of the proposed to current squared difference in the specific age class was greater than uniform variates between 0 and 1. The algorithm tended to converge on the solution within approximately 100 iterations. The best result from 10000 iterations of this algorithm was considered a numerical solution. We verified the algorithm on a simplified version of our model, and found that its estimate of the Nash equilibrium was the same as that determined algebraically. Additionally, solutions were examined by further manual perturbation and by starting from different initial conditions to ensure that each solution was a global rather than a local equilibrium. For any given set of parameters, only one Nash equilibrium was observed. To find the utilitarian optimum, the search procedure was the same, but the optimization criterion was the maximization of the population utility.

We are grateful for valuable comments on the manuscript from J Townsend, D Thomas, S Basu, J Medlock and E Poolman. AG was funded by the James McDonnell Foundation and the John Simon Guggenheim Memorial Foundation. TR was funded by Notsew Orm Sands Foundation.

1. Bauch, C. T., Galvani, A. P. & Earn, D. J. D. (2003) *PNAS* **100,** 10564-10567.
2. Reluga, T. C., Bauch, C. & Galvani, A. P. (2006) *Mathematical Biosciences* **204,** 185-198.
3. Smith, N. M., Bresee, J. S., Shay, D. K., Uyeki, T. M., Cox, N. J. & Strikas, R. A. (2006) *MMWR* **55,** 1-41.
4. Brownstein, J. S., Kleinman, K. P. & Mandl, K. D. (2005) *Am. J. Epidemiol.* **162,** 1-8.
5. Glezen, W. P. (1996) *Epidemiol. Rev.* **18,** 64-76.
6. Monto, A. S. & Ullman, B. M. (1974) *JAMA* **227,** 164-169.
7. Glezen, W. P. & Couch, R. B. (1978) *N. Engl. Med.* **298,** 587-592.
8. Fox, J. P., Hall, C. E., Cooney, M. K. & Foy, H. M. (1982) *Am. J. Epidemiol.* **116,** 212-227.
9. Taber, L. H., Paredes, A., Glezen, W. P. & Couch, R. B. (1981) *J. Hyg. (Lond.)* **86,** 303-313.
10. Meltzer, M. I., Cox, N. J. & Fukuda, K. (1999) *Emerg. Infect. Dis.* **5,** 659-671.
11. Viboud, C., Bjornstad, O. N., Smith, D. L., Simonsen, L., Miller, M. A. & Grenfell, B. T. (2006) *Science* **312,** 447-451.

12. Monto, A. S., Davenport, F. M., Napier, J. A. & Francis, T., Jr. (1969) *Bull. World Health Organ.* **41,** 537-42.
13. Halloran, M. E. & Longini Jr., M. (2006) *Science* **311,** 615-616.
14. Chapman, G. B. & Coups, E. J. (1999) *Prev. Med.* **29,** 249-262.
15. Chapman, G. B. & Coups, E. J. (2006) *Health Psychol.* **25,** 82-90.
16. Brewer, N. T., Chapman, G. B., Gibbons, F. R., Gerard, M., McCaul, K. & Weinstein, N. D. (in press) *Health Psychology*.
17. Smailbegovic, M. S., Laing, G. J. & Bedford, H. (2003) *Child Care. Hlth. Dev.* **29,** 303-11.
18. Asch, D. A., Baron, J., Hershey, J. C., Kunreuther, H., Meszaros, J., Ritov, I. & Spranca, M. (1994) *Med. Decis. Making* **14,** 118-23.
19. Couch, R. B. (2000) *N. Engl. Med.* **343,** 1778-1787.
20. Nichol, K. L., Lind, A., Margolis, K. L., Murdoch, M., McFadden, R., Hauge, M., Magnan, S. & Drake, M. (1995) *N. Engl. Med.* **333,** 889-893.
21. Ahmed, F., Singleton, J. A. & Franks, A. L. (2001) *N. Engl. Med.* **345,** 1543-1547.
22. Lasky, T., Terracciano, G. J., Magder, L., Koski, C. L., Bellesteros, M., Nash, D., Clark, S., Haber, P., Stolley, P. D., Schonberger, L. & Chen, R. T. (1998) *N. Engl. Med.* **339,** 1797-1802.
23. CDC (1999) *MMWR* **48,** 996-998.
24. Nash, J. F. (1950) *PNAS* **36,** 48-49.
25. Simonsen, L., Clarke, M. J., Schonberger, L. B., Arden, N. H., Cox, N. J. & Fukuda, K. (1998) *J. Infect. Dis.* **178,** 53-60.
26. Reichert, T. A., Simonsen, L., Sharma, A., Pardo, S. A., Fedson, D. S. & Miller, M. A. (2004) *Am. J. Epidemiol.* **160,** 492-502.
27. Capolongo, M. J., DiBonaventura, M. D. & Chapman, G. B. (2006) *Ann. Behav. Med.* **31,** 288-296.
28. CDC (1999) *MMWR* **48,** 1-15.
29. CDC (1994) *MMWR* **43,** 771-773.
30. CDC (2004) *MMWR* **53,** 1012-1015.
31. Galvani, A. P., Medlock, J. & Chapman, G. (in press) *Science*.
32. DiBonaventura, M. D. & Chapman, G. B. (2005) *Psychol. Health.* **20,** 761-774.
33. Bellman, R. (1957) *Dynamic programming* (Princeton University Press, Princeton, NJ).
34. Howard, R. A. (1960) *Dynamic Programming and Markov Processes* (MIT Press, Cambridge, MA).
35. Reluga, T. (2004) *Theor. Popul. Biol.* **66,** 151-161.
36. U.S. Bureau of the Census (2000).
37. Demicheli, V., Jefferson, T., Rivetti, D. & Deeks, J. (2000) *Vaccine* **18,** 957-1030.
38. Govaert, T. M., Thijs, C. T., Masurel, N., Sprenger, M. J., Dinant, G. J. & Knottnerus, J. A. (1994) *JAMA* **272,** 1661-1665.
39. Longini, I., Nizam, A., Xu, S., Ungchusak, K., Hanshaoworakul, W., Cummings, D. A. T. & Halloran, E. M. (2005) *Science* **309,** 1083-1087.
40. Longini, I. M., Halloran, M. E., Nizam, A. & Yang, Y. (2004) *Am. J. Epidemiol.* **159,** 623-633.
41. Simonsen, L., Clarke, M. J., Williamson, G. D., Stroup, D. F., Arden, N. H. & Schonberger, L. B. (1997) *Am. J. Public Health* **87,** 1944-1950.
42. Treanor, J. (2004) *N. Engl. Med.* **350,** 218-220.
43. Bush, R., Bender, C., Subbarao, K., Cox, N. & Fitch, W. (1999) *Science* **286,** 1921-1925.
44. Gold, M. R., Siegel, J. E. & Weinstein, M. C. (2001) *Cost-effectiveness in Health and Medicine* (Oxford University Press, Oxford, UK).

45. Campbell, D. S. & Rumley, M. A. (1997) *J Occupational Environ Med* **39,** 408-414.
46. Government, U. (1996) *The Federal Register* **61,** 46301-46302.
47. Haddix, A. C., Teutsch, S. M., Shaffer, P. A. & Duet, D. O. (1996) *Prevention Effectiveness* (Oxford University Press, New York, NY).
48. Kavet, J. (1977) *Am. J. Public Health* **67,** 1063-1070.
49. Office of Technology Assessment, U. S. C. (1981) *Cost effectiveness of influenza vaccination* (Government Printing Office, Washington, D. C.).
50. Serfling, R. E., Sherman, I. L. & Houseworth, W. J. (1967) *Am. J. Epidemiol.* **86,** 433-441.
51. U.S. Bureau of the Census (1997) *Statistical abstract of the United States*, Washington, D. C.).
52. Arden, N. H., Patriarca, P. A. & Kendal, A. P. (1986) in *Options for the Control of Influenza* (Alan R. Liss, Inc., New York, NY).
53. Bridges, C. B., Thompson, W. W., Meltzer, M. I., Reeve, G. R., Talamonti, W. J., Cox, N. J., Lilac, H. A., Hall, H., Klimov, A. & Fukuda, K. (2000) *JAMA* **284,** 1655-1663.
54. Monto, A. S., Hornbrook, K. & Ohmit, S. E. (2001) *Am. J. Epidemiol.* **154,** 155-160.
55. Mullooly, J. P., Bennett, M. D., Hornbrook, M. C., Barker, W. H., Williams, W. W., Patriarca, P. A. & Rhodes, P. H. (1994) *Ann. Intern. Med.* **121,** 947-952.
56. Neuzil, K. M., Dupont, W. D., Wright, P. F. & Edwards, K. M. (2001) *Pediatr. Infect. Dis. J.* **20,** 733-740.
57. Nichol, K. L., Wuorenma, J. & von Sternberg, T. (1998) *Arch. Intern. Med.* **158,** 1769-1776.
58. Palache, A. M. (1997) *Drugs* **54,** 841-856.
59. Patriarca, P. A., Weber, J. A., Parker, R. A., Hall, W. N., Kendal, A. P., Bregman, D. J. & Schonberger, L. B. (1985) *JAMA* **253,** 1136-1139.
60. Wilde, J. A., McMillan, J. A., Serwint, J., Butta, J., O'Riordan, M. A. & Steinhoff, M. C. (1999) *JAMA* **281,** 908-913.
61. Jefferson, T. & Demicheli, V. (1998) in *Textbook of influenza*, eds. Nicholson, K. G., Webster, R. G. & Hay, A. J. (Blackwell Science, London, UK), pp. 541-547.
62. Johannesson, H., Townsend, J. P., Hung, C.-Y., Cole, G. T. & Taylor, J. W. (2005) *Genetics* **171,** 109-117.

Fig 1A) Probability of vaccination against epidemic influenza by young and elderly when vaccination levels are at the Nash equilibrium and at the utilitarian optimum for perceived parameters, with increasing vaccine cost relative to actual cost ($37.26). Note that vaccine cost is on a log scale, so a value of 1 represents its actual cost. B) Annual infection incidence and mortality when vaccination levels are at the Nash equilibrium and at the utilitarian optimum for perceived parameters of epidemic influenza, with increasing vaccine cost.

Fig 2A) Probability of vaccination against epidemic influenza by young and elderly when vaccination levels are at the Nash equilibrium and at the utilitarian optimum for actual parameters, with increasing relative vaccine cost. B) Annual infection incidence and mortality when vaccination levels are at the Nash equilibrium and at the utilitarian optimum for actual parameters of epidemic influenza, with increasing vaccine cost.

Fig 3A) Probability of vaccination against pandemic influenza by young and elderly when vaccination levels are at the Nash equilibrium and at the utilitarian optimum, with relative increasing vaccine cost. Parameters were as in the perceived epidemic case, except that the probability of infection was assumed higher and biased towards the young (see Methods). B) Annual infection incidence and

mortality when vaccination levels are at the Nash equilibrium and at the utilitarian optimum for pandemic influenza, with increasing vaccine cost.

Model description

We first describe our age-structured compartmental differential equation model for influenza transmission that incorporates an annual pulse of vaccination. The asymptotic dynamics of this model are calculated and then used to construct models of Markov decision processes (1) that describe an individual's annual probability of becoming infected based on their annual vaccination decision. The utilities of individual behaviors are then calculated using these infection probabilities and estimates of expected costs of becoming infected and vaccinated. Since an individual's utility of vaccination depends on both the individual's decision and the population's average behavior, it is necessary to formulate the study of utilities as a population game. Monte Carlo methods parameterized with the calculated utilities are employed to determine Nash equilibria and utilitarian strategies.

1. *Epidemiological population model*

To capture the seasonal timing of vaccination and the annual cycle of influenza epidemics, we combined a discrete-time model of vaccination with a continuous-time seasonal influenza epidemic model (2). We divided the population into two age classes: age class A containing all individuals below age 65, and age class B containing all individuals age 65 and older. Age classes were parameterized from US census data: 88% of the population is under 65 years (A) and 12% of the population is over 65 years (B) (3). The older age class corresponds to the CDC's defined target group for vaccination (4). We assumed that parents make decisions in the best interest of their children.

In our model, individuals in each age class j are subdivided among susceptible (S_j), vaccinated (V_j), latently infected (E_j), infectious (I_j), and resistant (R_j) states. Susceptible individuals become infected at a rate $\lambda_j(t)$ equal to the force of infection, defined below (Eq. 2). Vaccinated individuals become infected at a fraction (1-ε_j) of the rate of susceptible individuals, where ε_j is the efficacy of vaccine. We found from our questionnaire study that perceived vaccine efficacy against infection is 34% (Table 1), compared to actual values of 80% protection among individuals younger than 65 (5, 6) and 60% for the elderly (7). Upon infection, individuals enter a latency period, the perceived duration of which is $1/\sigma = 4$ days (Table 1), compared to the actual value of 1.2 days (8). Latently infected individuals proceed to become infectious, and infectious individuals recover at rate δ. The perceived duration of the infectious period is 5 days (Table 1), which is close to the actual value of 4-5 days (9). It is assumed that recovered individuals are fully protected against further infection for the remainder of the influenza season. The transmission dynamics are thus described by the following equations:

$$\dot{S}_j = -\lambda_j(t)S_j, \qquad (1a)$$

$$\dot{V}_j = -\lambda_j(t)(1-\varepsilon_j)V_j \qquad (1b)$$

$$\dot{E}_j = \lambda_j(t)[S_j + (1-\varepsilon_j)V_j] - \sigma E_j, \qquad (1c)$$

$$\dot{I}_j = \sigma E_j - \delta I_j, \qquad (1d)$$

$$\dot{R}_j = \delta I_j. \qquad (1e)$$

We used a standard-incidence form for the force of infection $\lambda_j(t)$,

$$\lambda_j(t) = a_j\left(\beta_A(t)\frac{I_A}{N} + \beta_B(t)\frac{I_B}{N}\right), \qquad (2)$$

where $N = 10^6$, a reasonable population size for a typical large city. We assumed, as is suggested by time series of influenza incidence (10), that the incidence follows an annual pattern with a winter seasonal increase that is an order of magnitude above baseline summer incidence. Annual oscillations were incorporated using sinusoidal rates of transmission $\beta_j(t) = m_j + b_j \sin(2\pi t)$ with mean m_j and amplitude b_j. The rates of transmission were parameterized according to perceived and actual annual infection probabilities, respectively. The perceived annual infection probability was 0.48 (Table 1), compared to an actual infection probability for epidemic influenza of 0.15(11) and 0.5 for pandemic influenza (derived from (12-14) and 1918 census data). Younger individuals are twice as likely to transmit influenza to others $(m_A = 2m_B)$ (5, 15). To obtain the perceived annual infection probability of 0.48, $m_A = 8.86\times10^{-6}$ and $m_B = 4.43\times10^{-6}$, with $b_A = b_B = 150$ and a period of 1 year. For epidemic infection, younger and older individuals are equally likely to contract infection ($a_A = a_B = 1$), while for pandemic influenza, the attack rate in the young is increased three-fold relative to epidemic influenza ($a_A = 3$ and $a_B = 1$) (12-14). The case fatality proportion for epidemic influenza is typically 0.3% for the elderly and 0.03% for the young (5, 12). The case fatality proportion for pandemic influenza is 5% for the elderly and 2% for the young (12).

Vaccination occurs each fall, three months before transmission reaches its maximum. It was assumed that vaccination reduces the likelihood of infection and disease severity in the event of infection, consistent with epidemiological data (Table 2). Since influenza rapidly evolves new antigenic variants (16), immunity tends to wane from one year to the next $(\phi = 1)$. People perceive that vaccine protection lasts for 8 months (Table 1), which would confer protection for the duration of an influenza season. On average, a fraction $\bar{\rho}_j$ of all individuals choose to vaccinate each fall. We modeled the dynamics of waning immunity and vaccination as an instantaneous event each fall. Here we use a prime to denote the state variables immediately after vaccination:

$$S_j' = (1-\bar{\rho}_j)S_j + \phi(1-\bar{\rho}_j)V_j + \phi(1-\bar{\rho}_j)R_j, \qquad (3a)$$

$$V_j' = \bar{\rho}_j S_j + (1-\phi+\phi\bar{\rho}_j)V_j + \phi\bar{\rho}_j R_j, \qquad (3b)$$

$$E_j' = E_j, \qquad (3c)$$

$$I_j^{'} = I_j, \qquad (3d)$$

$$R_j^{'} = (1 - \phi) R_j. \qquad (3e)$$

The seasonal dynamics of influenza incidence converge to a periodic solution that repeats annually. We denoted this periodic solution for class j as $\left(S_j^*, V_j^*, E_j^*, I_j^*, R_j^*\right)$. It solves System (1), over the interval [0,1] with boundary conditions

$$S_j^*(0) = (1-\overline{\rho}_j)S_j^*(1) + \phi(1-\overline{\rho}_j)V_j^*(1) + \phi(1-\overline{\rho}_j)R_j^*(1), \qquad (4a)$$

$$V_j^*(0) = \overline{\rho}_j S_j^*(1) + (1-\phi+\phi\overline{\rho}_j)V_j^*(1) + \phi\overline{\rho}_j R_j^*(1), \qquad (4b)$$

$$E_j^*(0) = E_j^*(1), \qquad (4c)$$

$$I_j^*(0) = I_j^*(1). \qquad (4d)$$

$$R_j^*(0) = (1-\phi)R_j^*(1). \qquad (4e)$$

2. *Individual model of vaccination and infection*

Systems (1) and (3) give the average population dynamics of vaccination and influenza transmission, but the dynamics of an individual's state are stochastic. Using System (1), we parameterized a Markov process for an individual's decision dynamics. Since residences in the latent and infectious states are brief, we did not need to follow residences in these states in utility calculations. Thus, we tracked the susceptible, resistant, and vaccinated states that an individual may occupy, $\left(S_j^*, V_j^*, R_j^*\right)$, in vector form. The cost of infection was incorporated in the transition costs as susceptible or vaccinated individuals became infected and then resistant via acquired immunity from infection.

Consistent with our modeling assumptions in Equations 1-8, we divided the year into a vaccination phase followed by an influenza-season phase. During the vaccination phase, transitions among epidemiological model states depended upon both the probability that an individual's immunity waned due to viral evolution (ϕ) and the probability that an individual chose to vaccinate (ρ_j). The matrix of transition probabilities for an individual during the vaccination phase is:

$$\mathbf{q}_j^*(\text{vacc}) = \begin{bmatrix} 1-\rho_j & (1-\rho_j)\phi & (1-\rho_j)\phi \\ \rho_j & 1-(1-\rho_j)\phi & \rho_j\phi \\ 0 & 0 & 1-\phi \end{bmatrix}. \qquad (5)$$

During the influenza season, almost all individuals who are infected will become resistant. For a susceptible individual, the probability of infection was calculated from the equilibrium solution of the epidemic model as the number of susceptible individuals at the end of the influenza season divided by the number of susceptible individuals at the beginning of the influenza season. For a vaccinated

individual, the probability of infection was calculated as the number of vaccinated individuals at the end of the influenza season divided by the number at the beginning. Individuals who are resistant at the beginning of the influenza season remain resistant for the duration of the influenza season. The matrix of transition probabilities during the influenza season is

$$\mathbf{q}^*_j(\text{flu}) = \begin{bmatrix} \frac{S^*_j(1)}{S^*_j(0)} & 0 & 0 \\ 0 & \frac{V^*_j(1)}{V^*_j(0)} & 0 \\ 1-\frac{S^*_j(1)}{S^*_j(0)} & 1-\frac{V^*_j(1)}{V^*_j(0)} & 1 \end{bmatrix}. \quad (6)$$

Given the probabilities $\mathbf{p}_t$ that an individual is susceptible, vaccinated, or resistant immediately prior to vaccination in year t, the probabilities that they are in these states immediately prior to vaccination in year $t+1$ are given by the matrix equation

$$\mathbf{p}_{t+1} = \mathbf{q}^*_j(\text{flu})\ \mathbf{q}^*_j(\text{vacc})\ \mathbf{p}_t. \quad (7)$$

3. *Utility calculation*

The utility of an individual's vaccination strategy is calculated by summing the discounted costs associated with vaccination (Eq. 8) and infection (Eq. 9) over all possible infection and vaccination histories, where the histories are weighted according to their likelihood using the transition matrix (Eq. 5 and 6). The cost of infection was incorporated into the transitions for both susceptible and vaccinated individuals who are infected and become resistant. During the vaccination phase, an individual does not directly incur costs associated with the loss of immunity, but incur costs of vaccination, ν_j, in proportion to their probability of vaccination. The individual's expected vaccination cost is given by the vector. The cost of vaccination to an individual is the same irrespective of their resistance state, because individuals will not know their level of resistance.

$$\mathbf{f}_j(\text{vacc}) = [\rho_j \nu_j, \rho_j \nu_j, \rho_j \nu_j]. \quad (8)$$

During the influenza season, susceptible and vaccinated individuals pay expected costs of infection (Table 2) in proportion to their risk of infection, so the infection cost vector is:

$$\mathbf{f}_j(\text{flu}) = \left[c_{S,j}\left(1-\frac{S^*_j(1)}{S^*_j(0)}\right), c_{V,j}\left(1-\frac{V^*_j(1)}{V^*_j(0)}\right), 0 \right], \quad (9)$$

where $c_{S,j}$ is the cost of infection for susceptible individuals and $c_{V,j}$ is the cost of infection for vaccinated individuals of age j. Age-specific costs of infection were calculated as the sums of varying severities of outcomes, including loss of work, treatment, outpatient visits, hospitalization and mortality, multiplied by their respective probabilities (5, 12, 17-23) (Table 2). In contrast to the CDC's analysis of infection costs (5), we generally assumed that all individuals value their life equally, irrespective of their age, although we also compare with a lower valuation of elderly life consistent with the CDC's analysis of infection costs (Fig S1), that is \$74,146 versus \$1,045,278. If vaccinated people are infected, they are less likely to have serious complications, i.e. outpatient visits to a doctor, hospitalization, and mortality (5) (Table 2). Thus, we parameterized the utility calculations with age-specific distributions of vaccine efficacy in reducing influenza morbidity and mortality (5-7, 24-32) for infected individuals. Vaccination costs include the cost of the vaccine (\$14), associated travel expenses (\$4) and time cost to the individual (\$16) (19, 33), as well as probabilities and average treatment costs of each adverse effect (\$3.25) (5, 12, 21)**,** giving a total actual vaccination cost of \$37.26. We varied the cost of vaccination to determine the impact of inaccurate perceptions of costs/risks and/or changes in actual cost.

From these assumptions, the Bellman equation (1, 34) for the annual utility $\mathbf{u}_j(t)$ of each possible initial state (susceptible, vaccinated, or resistant) after t years recursively is given by:

$$\mathbf{u}_j(t) = [\theta\, \mathbf{u}_j(t-1)\ \mathbf{q}^*_j(\text{flu}) + \mathbf{f}_j(\text{flu})]\mathbf{q}^*_j(\text{vacc}) + \mathbf{f}_j(\text{vacc}), \qquad (10)$$

where θ is the annual discount rate of 3% (35). We assumed individuals adopt an infinite planning horizon, such that:

$$\mathbf{u}_j(\infty) = [\,\mathbf{f}_j(\text{flu})\mathbf{q}^*_j(\text{vacc}) + \mathbf{f}_j(\text{vacc})\,][\,\mathbf{I} - \theta\,\mathbf{q}^*_j(\text{flu})\mathbf{q}^*_j(\text{vacc})\,]^{-1}\ . \qquad (11)$$

We did not incorporate the aging of individuals, but this simplification should have not significantly affected our results of annual probabilities of vaccination.

If individuals have an equal probability of initially occupying the susceptible, vaccinated, or recovered states over an infinite planning horizon, the utility to an individual in age class j is:

$$U_j = \mathbf{u}_j(\infty)\left[\frac{1}{3},\frac{1}{3},\frac{1}{3}\right]^T. \qquad (12)$$

The population's overall utility $\overline{U}$ is a weighted average of the utilities to each age class j, with the weights given by the proportion of the total population in each class:

$$\overline{U} = 0.88U_A + 0.12U_B. \qquad (13)$$

Previous studies of vaccination games have used less flexible utility calculations. By combining deterministic models of macroscopic population dynamics with stochastic models of an individual's dynamics, we employed of a powerful reformulation of population games for the study of game theoretic decision-making. The flexibility of this approach should facilitate the future incorporation of potentially complex factors such as host heterogeneity and geographical variation.

Calculation of Nash equilibria

We then used our utilities of vaccination decisions to calculate convergently stable Nash equilibria of the population game in which individuals are choose vaccination rates under the assumption that individuals act to maximize their personal utility. For some simple problems in homogeneous populations, calculations of Nash equilibria are achieved through single parameter optimization. No such simplification is available, however, for age-structured populations with two or more strategy-parameters. Other methods rely on the calculation of local derivatives, which cannot be analytically obtained in closed form for our model. Thus, we have adapted a Monte Carlo algorithm(36) to calculate ρ_A and ρ_B at the Nash equilibrium.

At the Nash equilibrium, no individual can improve their expected utility by changing their vaccination probability. Thus, the utility of vaccination (U_V) is equal to the utility of vaccine refusal (U_N) for each age class. We found solutions to the equations through minimization of the squared difference between utilities of vaccination refusal versus acceptance for each age class over the parameter solution space. Random perturbations of the proposed $\bar{\rho}$ were drawn sequentially for each class from triangular distributions that add or subtract at most 0.01. For each iteration, perturbations were accepted when the ratio of the proposed to current squared difference in the specific age class was greater than uniform variates between 0 and 1. The algorithm tended to converge on the solution within approximately 100 iterations. The best result from 10000 iterations of this algorithm was considered a numerical solution. We verified the algorithm on a simplified version of our model, and found that its estimate of the Nash equilibrium was the same as that determined algebraically. Additionally, solutions were examined by further manual perturbation and by starting from different initial conditions to ensure that each solution was a global rather than a local equilibrium. For any given set of parameters, only one Nash equilibrium was observed. At the Nash equilibrium, an individual's utility was observed to be independent of that individual's probability of vaccination. To find the utilitarian optimum, the search procedure was the same, but the optimization criterion was the maximization of the population utility.

Effect of variation in valuation of an elderly life

From the societal perspective, Meltzer et al. (5) estimated that the value of the life of an individual under 64 years is 1,045,278, compared with $74,146 for an individual over 65 years, due to differences in expected future earnings. It could be argued that this lower value for an elderly life is the appropriate measure to use when

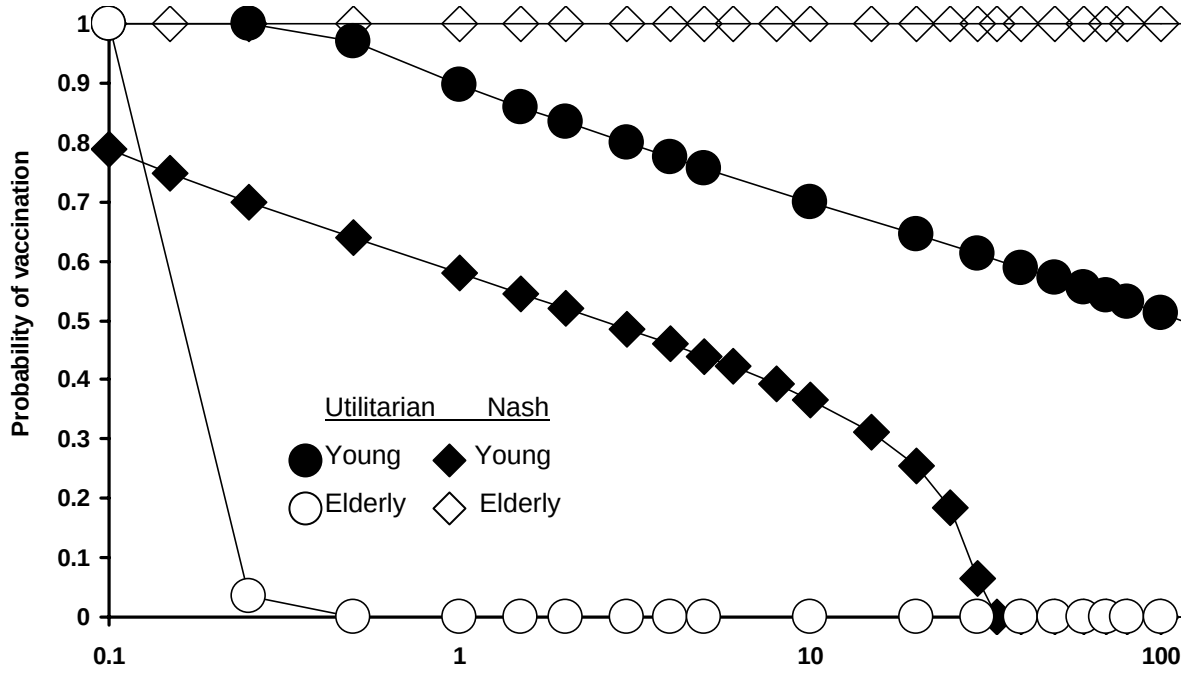
calculating the utilitarian strategy from a societal perspective. The result of this lower valuation of an elderly life is reduced vaccination of both young and elderly (Fig S1). The indirect protection of the elderly via vaccination of the young has reduced public health benefit when the lower valuation of elderly life is employed. The reduction is sufficiently small, for example 0.83 versus 0.9 for accurate vaccine costs, that the discrepancy between the utilitarian and Nash strategies remain significant.

References

1. Howard, R. A. (1960) *Dynamic Programming and Markov Processes* (MIT Press, Cambridge, MA).
2. Reluga, T. (2004) *Theor. Popul. Biol.* **66,** 151-161.
3. U.S. Bureau of the Census (2000).
4. Smith, N. M., Bresee, J. S., Shay, D. K., Uyeki, T. M., Cox, N. J. & Strikas, R. A. (2006) *MMWR* **55,** 1-41.
5. Meltzer, M. I., Cox, N. J. & Fukuda, K. (1999) *Emerg. Infect. Dis.* **5,** 659-671.
6. Demicheli, V., Jefferson, T., Rivetti, D. & Deeks, J. (2000) *Vaccine* **18,** 957-1030.
7. Govaert, T. M., Thijs, C. T., Masurel, N., Sprenger, M. J., Dinant, G. J. & Knottnerus, J. A. (1994) *JAMA* **272,** 1661-1665.
8. Longini, I., Nizam, A., Xu, S., Ungchusak, K., Hanshaoworakul, W., Cummings, D. A. T. & Halloran, E. M. (2005) *Science* **309,** 1083-1087.
9. Longini, I. M., Halloran, M. E., Nizam, A. & Yang, Y. (2004) *Am. J. Epidemiol.* **159,** 623-633.
10. Simonsen, L., Clarke, M. J., Williamson, G. D., Stroup, D. F., Arden, N. H. & Schonberger, L. B. (1997) *Am. J. Public Health* **87,** 1944-1950.
11. Treanor, J. (2004) *N. Engl. Med.* **350,** 218-220.
12. Glezen, W. P. (1996) *Epidemiol. Rev.* **18,** 64-76.
13. Simonsen, L., Clarke, M. J., Schonberger, L. B., Arden, N. H., Cox, N. J. & Fukuda, K. (1998) *J. Infect. Dis.* **178,** 53-60.
14. Reichert, T. A., Simonsen, L., Sharma, A., Pardo, S. A., Fedson, D. S. & Miller, M. A. (2004) *Am. J. Epidemiol.* **160,** 492-502.
15. Taber, L. H., Paredes, A., Glezen, W. P. & Couch, R. B. (1981) *J. Hyg. (Lond.)* **86,** 303-313.
16. Bush, R., Bender, C., Subbarao, K., Cox, N. & Fitch, W. (1999) *Science* **286,** 1921-1925.
17. Campbell, D. S. & Rumley, M. A. (1997) *J Occupational Environ Med* **39,** 408-414.
18. Government, U. (1996) *The Federal Register* **61,** 46301-46302.
19. Haddix, A. C., Teutsch, S. M., Shaffer, P. A. & Duet, D. O. (1996) *Prevention Effectiveness* (Oxford University Press, New York, NY).
20. Kavet, J. (1977) *Am. J. Public Health* **67,** 1063-1070.
21. Office of Technology Assessment, U. S. C. (1981) *Cost effectiveness of influenza vaccination* (Government Printing Office, Washington, D. C.).

22. Serfling, R. E., Sherman, I. L. & Houseworth, W. J. (1967) *Am. J. Epidemiol.* **86,** 433-441.
23. U.S. Bureau of the Census (1997) *Statistical abstract of the United States*, Washington, D. C.).
24. Arden, N. H., Patriarca, P. A. & Kendal, A. P. (1986) in *Options for the Control of Influenza* (Alan R. Liss, Inc., New York, NY).
25. Bridges, C. B., Thompson, W. W., Meltzer, M. I., Reeve, G. R., Talamonti, W. J., Cox, N. J., Lilac, H. A., Hall, H., Klimov, A. & Fukuda, K. (2000) *JAMA* **284,** 1655-1663.
26. Monto, A. S., Hornbrook, K. & Ohmit, S. E. (2001) *Am. J. Epidemiol.* **154,** 155-160.
27. Mullooly, J. P., Bennett, M. D., Hornbrook, M. C., Barker, W. H., Williams, W. W., Patriarca, P. A. & Rhodes, P. H. (1994) *Ann. Intern. Med.* **121,** 947-952.
28. Neuzil, K. M., Dupont, W. D., Wright, P. F. & Edwards, K. M. (2001) *Pediatr. Infect. Dis. J.* **20,** 733-740.
29. Nichol, K. L., Wuorenma, J. & von Sternberg, T. (1998) *Arch. Intern. Med.* **158,** 1769-1776.
30. Palache, A. M. (1997) *Drugs* **54,** 841-856.
31. Patriarca, P. A., Weber, J. A., Parker, R. A., Hall, W. N., Kendal, A. P., Bregman, D. J. & Schonberger, L. B. (1985) *JAMA* **253,** 1136-1139.
32. Wilde, J. A., McMillan, J. A., Serwint, J., Butta, J., O'Riordan, M. A. & Steinhoff, M. C. (1999) *JAMA* **281,** 908-913.
33. Jefferson, T. & Demicheli, V. (1998) in *Textbook of influenza*, eds. Nicholson, K. G., Webster, R. G. & Hay, A. J. (Blackwell Science, London, UK), pp. 541-547.
34. Bellman, R. (1957) *Dynamic programming* (Princeton University Press, Princeton, NJ).
35. Gold, M. R., Siegel, J. E. & Weinstein, M. C. (2001) *Cost-effectiveness in Health and Medicine* (Oxford University Press, Oxford, UK).
36. Johannesson, H., Townsend, J. P., Hung, C.-Y., Cole, G. T. & Taylor, J. W. (2005) *Genetics* **171,** 109-117.

Fig 1A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0.8
0.7
0.6
0.5
0.4
0.3
0.2
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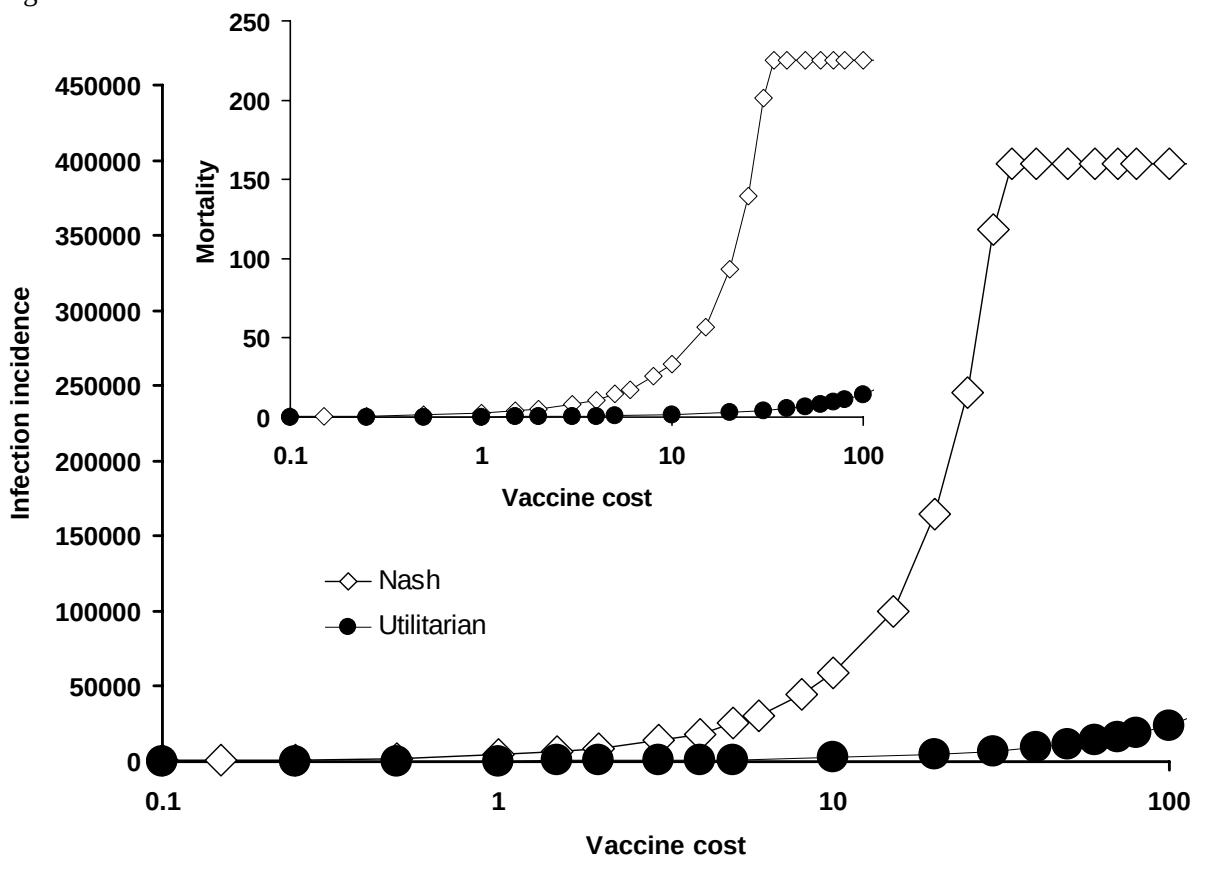
0
0.1
1
10
100
Utilitarian
Nash
Young
Young
Elderly
Elderly

Fig 1B


Infection incidence
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350000
300000
250000
200000
150000
100000
50000
0
0.1
1
10
100
Vaccine cost
Mortality
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150
100
50
0
0.1
1
10
100
Vaccine cost
Nash
Utilitarian

Fig 2A

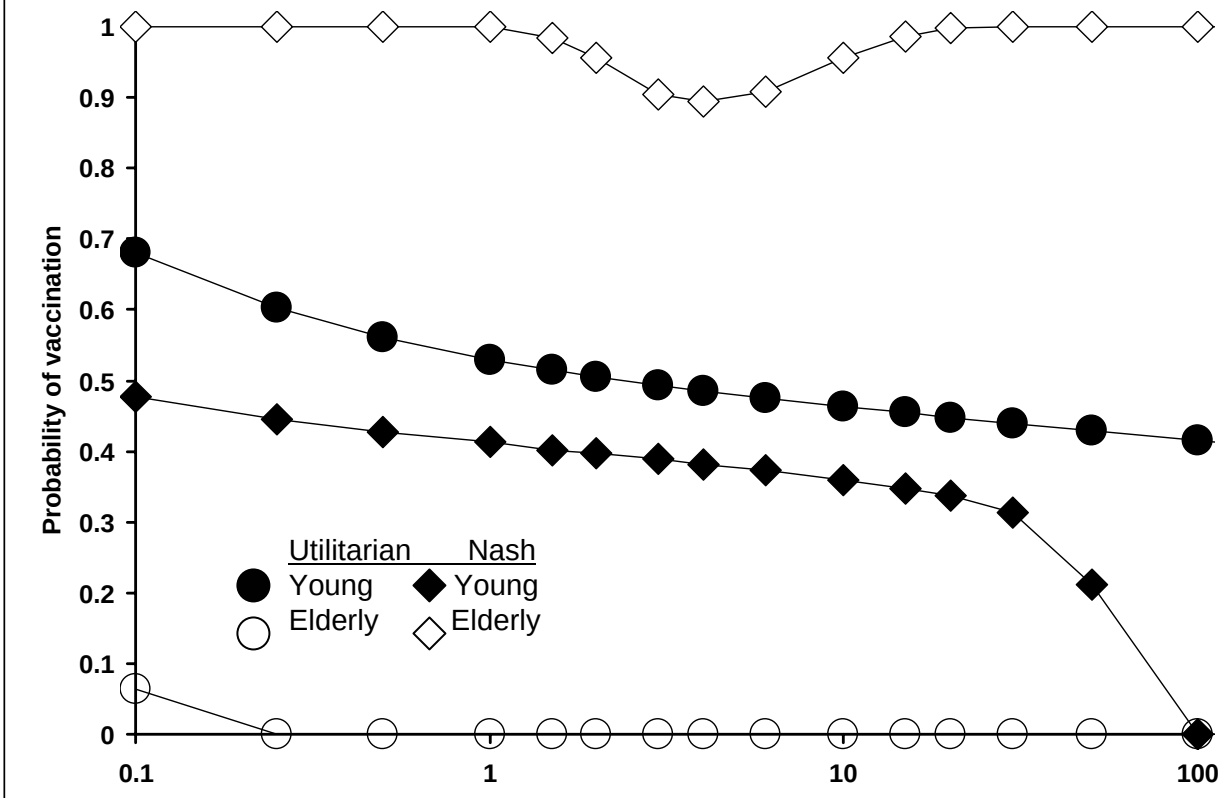
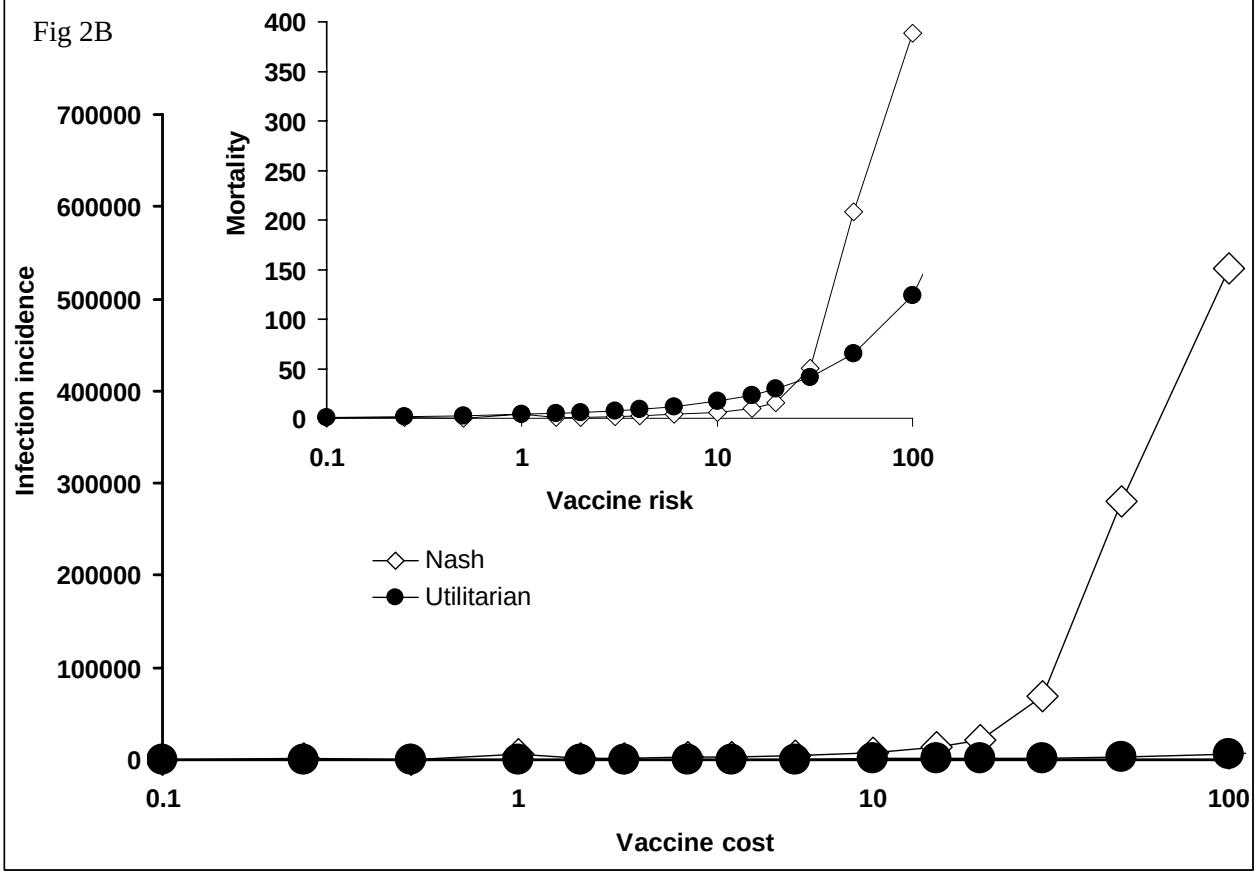

Probability of vaccination
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.1
1
10
100
Utilitarian
Nash
Young
Young
Elderly
Elderly

Fig 2B


Infection incidence
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600000
500000
400000
300000
200000
100000
0
0.1
1
10
100
Vaccine cost
Mortality
400
350
300
250
200
150
100
50
0
0.1
1
10
100
Vaccine risk
Nash
Utilitarian

Fig 3A

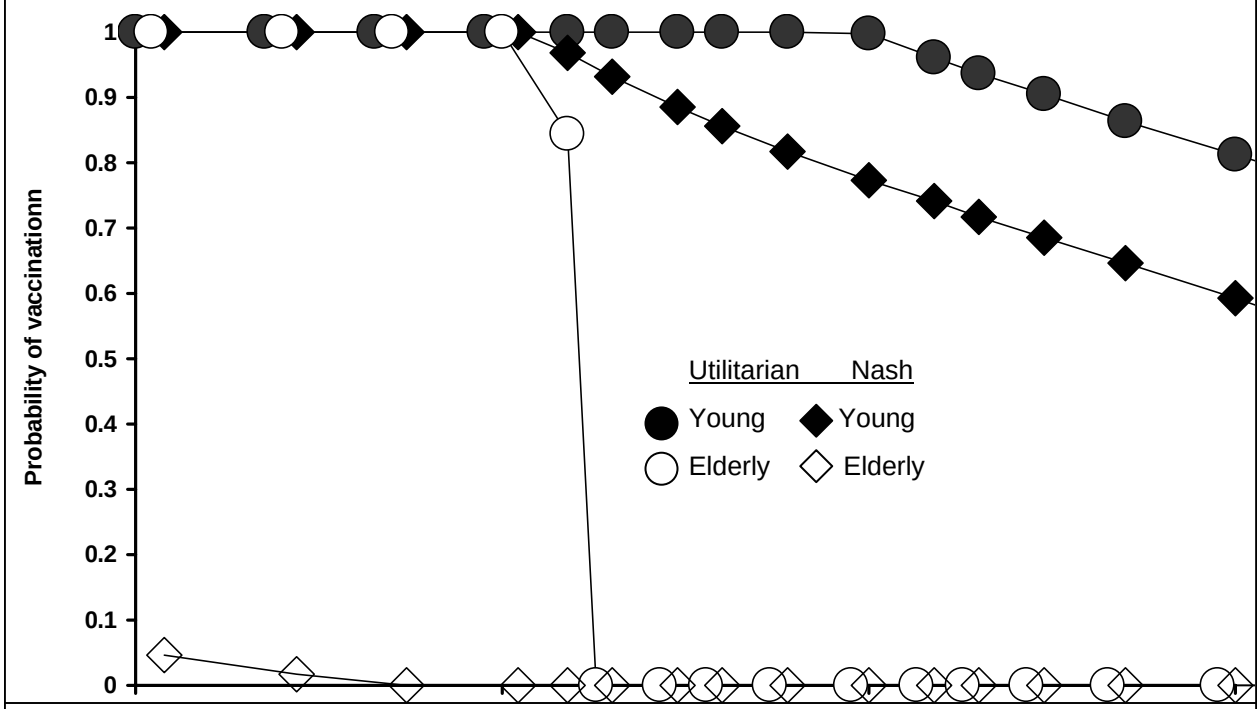
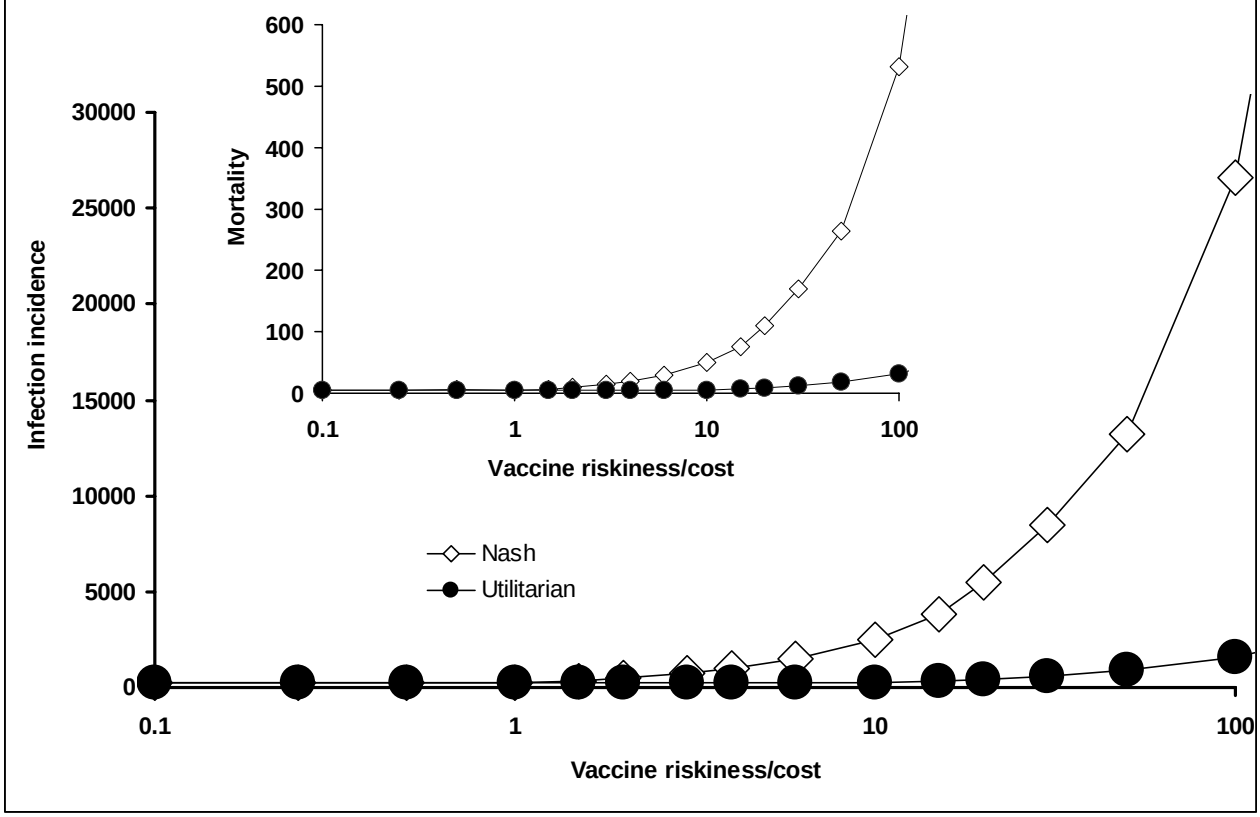
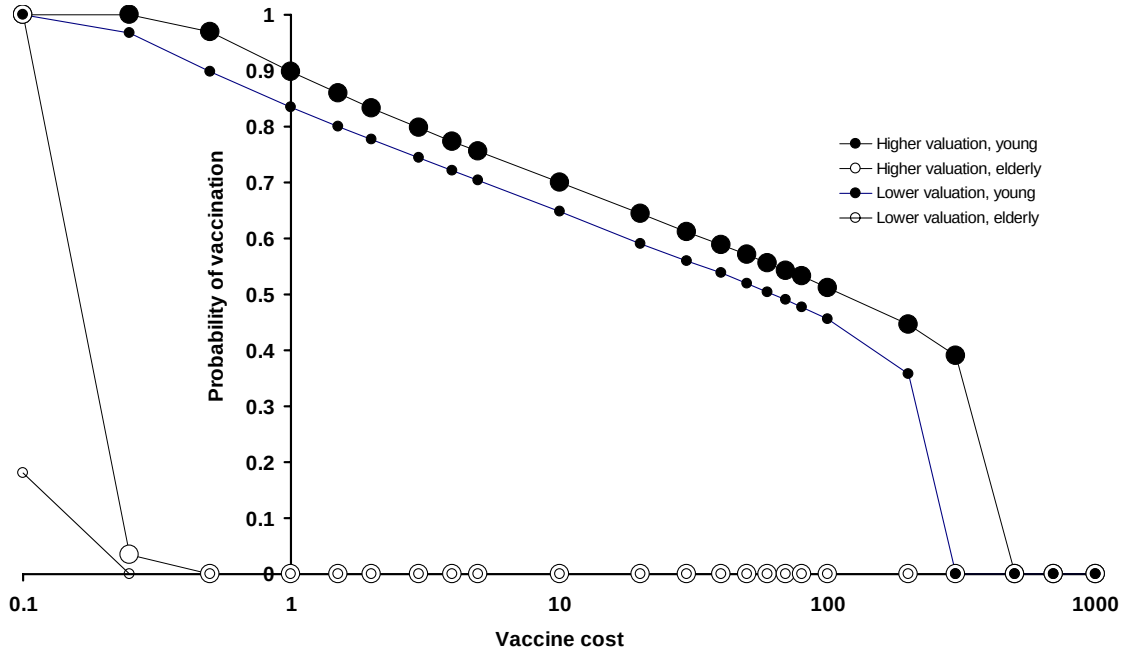

Probability of vaccinationn
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Utilitarian
Nash
Young
Young
Elderly
Elderly

Fig 3B


Infection incidence
30000
25000
20000
15000
10000
5000
0
0.1
1
10
100
Vaccine riskiness/cost
Mortality
600
500
400
300
200
100
0
0.1
1
10
100
Vaccine riskiness/cost
Nash
Utilitarian


Probability of vaccination
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.1
1
10
100
1000
Vaccine cost
Higher valuation, young
Higher valuation, elderly
Lower valuation, young
Lower valuation, elderly