Health Policy in the Face of Heterogeneous Externalities: the Case of Influenza Vaccination

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Abstract:

Heterogeneous treatments effects can lead to policies prioritizing groups with high estimated treatment gains. However, where there are treatment externalities, this strategy may not take advantage of large within and cross group gains because externalities are unmeasured. This paper illustrates the problem using the example of influenza vaccine. This is an ideal example to illustrate the case as externalities are large and heterogeneous across age, but existing evidence-based policy does not take these into account. Using a theoretical model of disease, this paper shows that due to heterogeneous externalities across age group, a zero-sum redistribution away from the typical "evidence-based" vaccination strategy leads to gains for all. The paper also illustrates the point by providing an empirical assessment of a particular policy: statutes allowing pharmacists to vaccinate. Using year-by-state variation in U.S. pharmacist statutes this paper shows that statutes lead to very little change in the overall vaccination rate but tip the age distribution of vaccination towards younger age groups and away from older age groups. Using estimates of the distributional change, the model shows that even though statutes made very little difference to overall vaccination, the change in distribution substantially lowers the rate of infection and other measures of loss from influenza.

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1. Introduction

Complications and death from influenza are more likely among the old, which parallels typical vaccination recommendations and coverage prioritizing the elderly. However, if these age groups are also the least able to levy positive vaccination spillovers, ironically this strategy may be the least effective way to reduce mortality among those same groups. Using a theoretical model of disease, this paper shows that due to heterogeneous spillovers across age group, a zero-sum redistribution away from the typical vaccination strategy leads to gains for all. The paper also provides a novel way to test this notion by setting up a model allowing for heterogeneous spillover effects across age groups and testing the effect of a particular vaccine policy change: that of allowing pharmacists to deliver vaccines.

Typical studies of the effect of vaccination generally cannot account for vaccine spillovers. For example, a standard randomized control study of the influenza vaccination randomizes the vaccine to a treatment and control groups (typically within a specific age group) and compares outcomes at the end of a flu season yielding an estimated treatment effect. However, there are three ways in which these estimated treatment effects may not take into account vaccine spillovers. The first it that herd immunity (or externality) effects from the vaccine can cause within study treatment spillovers from treated to control groups, thereby underestimating the effect of the vaccine within study. Secondly, herd immunity effects can cause cross-study treatment spillovers whenever treatment levels in the population differ across study, e.g., a study that is performed where population vaccination rates are low versus a study where population vaccination rates are high. Lastly, the typical study usually focuses on a particular age group, which then provides a within-age estimate of vaccine cost-effectiveness. This process ignores the difference in the size of spillovers across age group, which may be substantial. For example, vaccination in the elderly may prevent infections in themselves and in others, but the infections for themselves may be more costly (death, hospitalization more likely, etc.) making the within age cost effectiveness estimate large. On the other hand, vaccination in the young may prevent a higher number infections in themselves and others, but the infections for themselves are less costly (less death, hospitalization, etc.) making the within age cost effectiveness estimate relatively small. What this analysis misses is the value of the spillover effect across age group, which, in this example, is higher for the young and lower for the old.

To account for these types of herd immunity spillovers, I set up a model of disease dynamics that captures differences in the infection rate, vaccines efficacy and the cost of influenza across age groups, which I then use for three sets of analyses. First, I assess the optimal distribution of vaccination across age. Here, I find that for a given overall vaccination rate there is a wide range in infection, death and costs of influenza for different distributions of vaccines across age groups. I find that the optimal age-distribution of vaccines to prevent infections prioritizes vaccination among children, where the more substantial herd immunity effects levied by the young protect the overall population at a higher rate. In terms of death, I find that at very low levels of resources (i.e. vaccines that cover less than 5 percent of the population), it is optimal to vaccinate older age groups 65-69 and 70-74. This is because, death from influenza is more likely among the old and at these low resource levels, vaccination among other groups is not enough to levy substantial herd immunity effects for the old. On the other hand, as soon as resource levels of at least 5 percent are met, the optimal strategy shifts to vaccinating children. This is because vaccine levels are high enough here to levy substantial herd immunity effects for themselves and others. This stark result highlights the error of targeting vaccines to those with the highest illness costs while ignoring heterogeneous herd immunity effects.

Secondly, I use the model to compare actual vaccination rates in U.S. states over the seasons spanning 1997 to 2014. Here, I find that in all cases, vaccination is far from the optimal age-distribution, and moreover, is less favorable than an equal-share distribution of vaccines. This is largely because, for this time period, vaccination rates are highest among the elderly and lowest among children.

Lastly, I evaluate a particular vaccine policy, that of allowing pharmacists to vaccinate. Using variation in the adoption of pharmacy statutes, I find that the overall vaccination rate changed by a small 1.6 percentage points (representing a 6 percent change from base). While the overall change in vaccination is small, I find that pharmacy statutes lead to a sizable tilt in the age-distribution of vaccination: there are increases in the vaccination of children and adults age 30-39, but small decreases in vaccination for those over 50. Using the model to evaluate simulated outcomes for the pharmacy statue effects finds decreases in all outcomes measured. Specifically, there is a 13 percent fall in the infection rate, which is more than double the size of the increase in the vaccination rate and indicates substantial herd immunity effects for this policy. Furthermore, decomposing the total effect into that which is explained by the change in the age tilt of vaccination versus the overall increase in the scale of vaccination finds that 63 percent of the decrease in infections is due to the tilt in the age-distribution following pharmacy statutes.

The rest of the paper proceeds as follows. In section 2, I present a model of disease dynamics across age. I start with a simple model to fix ideas and then move to the extend model that allows for heterogeneity across multiple age groups. I conclude the model by providing a detailed description of the model parameters and a description of the disease outcomes, which include the infection and death rate as well as estimates of the cost and time loss associated with influenza (all of which vary across age group). In section 3, I provide an analysis on the optimal distribution of vaccines across age considering each outcome separately. I also include analysis of the outcomes that arise from an equal-share distribution of vaccines and the worst-case age-distribution. In Section 4, I describe vaccination rates in U.S. states for the period 1996-2014 and show how these compare within the model. In Section 5, I analyze the effect of pharmacy statues on vaccination and use simulated data to show the effect on each of the disease outcomes considered. Section 6 concludes.

2. Modeling Disease Dynamics

In order to assess actual and optimal vaccination rates, I develop a model that extends a standard Susceptible, Infectious, Recovered (SIR) model to incorporate vaccination and transmission mechanisms across age.[1] Intuition for the extended model may be best gained by looking at dynamics and policy implications of the standard model, which will lay the groundwork for extension to multiple age groups.

a. The SIR model

The SIR model describes the dynamics of infection with a contagious disease in a homogenous population over time by defining three states: susceptible to the disease, infected by the disease, or recovered from the disease. The dynamics are given as a set of nonlinear ordinary differential equations:

$$\frac{dS}{dt} = \frac{-\beta SI}{N}$$

[1] This model is based on the Kermack and McKendrick Susceptible-Infective-Removed (SIR) model of disease epidemics. Several variations of the model are shown in Geoffard and Philipson (1997); Francis (1997, 2004); and Boulier, Datta, and Goldfarb (2007).

$$\frac{dI}{dt} = \frac{\beta SI}{N} - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

where t is time, $S(t)$ is the number of susceptible people at time t, $I(t)$ is the number of infected people at time t, $R(t)$ is the number of people that have recovered from the infection and are no longer susceptible, and N is the population size. From the system, we can see that at each time period a fraction of the susceptible population becomes infected, which is determined by the size of the infection rate β and the current number of infectives. At the same time, a fraction of the infectives recover from the disease, which is determined by the recovery rate γ. Parameterizing the model with estimates of β and γ for a specific disease can allow us to see the evolution of infection over time, and a key factor in these dynamics is the ratio of β to γ, which is the so-called basic reproductive number, R_o. To see the summative power of R_o, note that the change in infectives in the first period is positive whenever $S(0)/N > \gamma/\beta$. This means that in a wholly susceptible population (i.e. $S(0) = N$), the disease will spread wherever $R_o \equiv \beta/\gamma > 1$, which is intuitive: in this case, $\beta/\gamma > 1$ implies that a single infection more than replaces itself with new infections next period. Note that as time progresses and a higher proportion of susceptibles are infected, $S(t)/N$ will eventually fall below γ/β, and the disease will cease to spread (implying that a fraction of the population remains susceptible even after an epidemic has past).

b. The role of vaccination in the SIR model

The critical role for vaccination in this model is to move people from the susceptible state to the immune state $R(0)$ thereby circumventing the infectious state, $I(t)$. Here, a higher vaccination rate among susceptibles means the number of ever-infected will fall, and, in fact, as we have seen above, if the vaccination rate reduces the proportion of initial susceptibles below γ/β, an epidemic is prevented altogether.

Consider the specific case of influenza. In this case, a standard estimate of the basic reproductive number is 1.44, which implies that an infected individual mixing in a wholly susceptible population, would, on average, infect 1.44 people (Hethcote 2000; Boulier, Datta, and Goldfarb 2007). Using this parameterization, the dynamics of this model imply that the number of infections occurring from one infection will fall to one when at most 69 percent of the population is susceptible to influenza (i.e., $1.44 \times 0.69 = 1$). In other words, to prevent an epidemic, the SIR model implies that more than 31 percent of the population would need to be vaccinated. This assumes vaccines deliver perfect immunity (e.g., the epidemic threshold rises as vaccine efficacy falls).

This result hints at the herd immunity effects of vaccination; at this epidemic threshold, for example, 31 percent of the population is protected through vaccination while the remaining 69 percent avoid infection due to the spillover effects from the vaccinated. Furthermore, at the margin, these herd immunity effects, like the total marginal effect of vaccination, are nonlinear and depend on the level of vaccination (e.g. around the 31 percent threshold, the marginal effect of vaccination drops off steeply because the spread of disease among remaining susceptibles begins to approach zero).

c. Extending the model to account for population heterogeneity

The above model is able to capture the dynamics of disease spread, the epidemic threshold, and, with some assumptions on the cost of each vaccine and infection, can determine the socially

optimal level of vaccination. But despite the apparent policy implications of the SIR model, it does not lend itself easily to policy action since it assumes both a homogenous population (meaning that the infection rate and recovery rate is constant across people), and that all infections are equal (e.g. there is no role for death or heterogeneity in the cost of infection across person). To see the limitations of these assumptions, consider the effect of moving vaccination rates from 0 to 10 percent in two different ways: first by vaccinating only children, and the second by vaccinating only the elderly. The homogeneity assumption implies that the change in the spread of disease is the same in either case even though there is strong evidence that children have higher instances of daily physical contact and higher vaccine efficacy rates. On the other hand, the equality of infections assumption implies there is no prescription to prioritize vaccination to those with the highest infection costs (e.g. the costs associated with hospitalization and death, which tend to be highest among the elderly). In the end, the model offers no way to balance the differential herd immunity effects coming from vaccinating different age groups with the differential costs associated with influenza infection across those same age groups. This is simply because it ignores differences in the effect of vaccination across age (which, importantly, includes herd immunity effects that are non-linear and heterogeneous across age).

In reality, the effectiveness of the influenza vaccine differs substantially across age group. This is a fact that features centrally in the structure of the literature on vaccine effectiveness and the policies regarding vaccine recommendations. Since most of the RCT literature on influenza vaccination is disaggregated across age group, vaccine policy recommendations (e.g. ACIP) have also tended to be stratified by age group. And because the costs of illness in these studies often include medical costs and mortality, those age groups with higher costs tend to yield higher cost effectiveness estimates and are often prioritized in policy recommendations. However, while meta-analysis of this literature reveals substantial differences in the effect of vaccination across age, each study, itself, focuses only on estimating the within-age effect of vaccination. Essentially, this ignores the effect of interaction across age groups, which will systematically impact estimates wherever there are substantial across-age spillovers. For example, the results from a RCT on influenza vaccination among the elderly might have very different results if, in the larger context, vaccination rates among the young are very high versus very low.

In order to account for differences in relevant vaccine parameters across age group and, at the same time, account for differential herd immunity effects across age group, I extend the standard SIR model in several important ways. First, I allow for the force of infection to vary across age groups. Here, disease spread is sensitive to different mixing patterns both within and across age groups, where contact rates across age groups are determined by large-scale survey data estimating the number of physical contact per day by age. Secondly, I explicitly model vaccination in the model and allow for vaccine efficacy to vary across age group, which captures the differential protection the vaccine offers to different age groups. Thirdly, I explicitly model death in where death conditional in influenza infection varies across age. Lastly, I model not only how infection rates respond to vaccination, I also evaluate the direct and indirect costs of infection by applying age specific costs estimates to the infection and death outcomes delivered by the model.

The model is described below. For each age group, *a,* of vaccine status v = [0,1] there are three possible states: susceptible $S_{av}(t)$, infected $I_{av}(t)$, and recovered $R_{av}(t)$. The dynamics of the model are given by the following system of differential equations:

$$\frac{dS_{av}}{dt} = -(1 - \mu_v \epsilon_{av})\beta\lambda_a \frac{S_{av}}{N}$$

$$\frac{dI_{av}}{dt} = (1 - \mu_v \epsilon_{av})\beta\lambda_a \frac{S_{av}}{N} - (\gamma I_{av} + \eta_{av} I_{av})$$

$$\frac{dR_{av}}{dt} = \gamma I_{av,}$$

which encompasses three sets of model dynamics: vaccine parameters, the force of infection, and removal parameters.

Vaccine parameters: μ_v and ε_{av} are the seasonal match rate for the vaccine and the age specific efficacy of the vaccine, respectively. These are set to zero for unvaccinated individuals, and they vary between [0,1] for the vaccinated (e.g. in the latter case, if they all equal one, then no vaccinated individual of any age will progress to infected or recovered state). In this way, the model makes no assumption that vaccines deliver perfect immunity. Instead it allows the dynamics to depend in the seasonal match rate (i.e. vaccine influenza strains do not always confer immunity to emergent strains) and differences in vaccine efficacy by age (i.e. older individuals have a weaker immune response to the vaccine and hence have a lower degree of protection).

Force of infection: the parameters β and λ_a describe the force of infection, where β is the probability of influenza transmission given contact with an infectious individual, and λ_a describes the average number of contacts with infectious people for age group *a* with all other age groups. Specifically, λ_a is given by:

$$\lambda_a = \sum_{\alpha=1}^{17} \phi_{a\alpha}(I_{\alpha 0} + I_{\alpha 1})$$

Here, the model allows for differential contact across age group by defining a contact matrix Φ, where, $\phi_{a\alpha}$ gives the contact rate for individuals in age group *a* with individuals of age group α. Therefore, λ_a describes the overall contact of *a* with other age groups by calculating the contact rate for each age pair multiplied by the number of infectives in age group α and summing this over all α.

Removal parameters: γ is the recovery rate from influenza, where $1/\gamma$ gives the average duration of the disease in periods (e.g. days). The parameter η_a is the age specific death rate from influenza.

Population: N is the total population size across all ages.

I use this model for two main types of analysis: the first is to document the optimal distribution of vaccination across age group for a given overall vaccination rate, and the second is to compare the optimal distribution of vaccines to actual vaccine rates for all U.S. states across the seasons running from 1997-2014.

d. Parameterizing the extended model

There are 17 age groups 0, 1–4, 5–9, 10–14, 15-17, 18-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75+, which are the finest gradations available for vaccination and

contact data. Population shares over age and the overall population size are calculated from data collected through The Surveillance, Epidemiology, and End Results (SEER) Program, which is a comprehensive source of population-based information in the United States. These are calculated as averages over the sample period of 1997-2014 and are displayed in Figure 1.

Age specific efficacy parameters, $\varepsilon_{a,}$ are gathered from the annual ACIP review on recommendations for influenza (Grohskopf, et al. 2016). The annual ACIP review surveys source literature on vaccine efficacy and summarizes results by age group. Efficacy parameters are displayed in Figure 2.

Instead of relying on assumptions about the mixing patterns of individuals across age groups, I calculate contact rates based on a survey of person-to-person contact from Mossong, et al. (2008). Mossong, et al.'s study provides a large-scale, cross-country survey approach to contact patterns relevant for infections transmitted by the respiratory route, with the main aim of improved parameterization of mathematical models. These results show that contact patterns are relatively similar across country, but that contact is highly positively assortative with age. Furthermore, the young have a much higher number of daily contacts in absolute terms, providing strong evidence against homogenous mixing. These patterns are shown in Figure 3, which provides a contour plot of the average numbers of contacts per person per day for all age groups. To calculate contact rates, $\phi_{a\alpha}$, I use the average contact numbers for age group a with age group α from Figure 3 and calculate rates by normalizing the average number of contacts by the proportion of the population in α. I then do the same normalization by the proportion of the population in a. To yield symmetry of the contact matrix I take the average of the two measures, i.e., $0.5(\phi_{a\alpha} + \phi_{\alpha a})$. Normalizing these numbers by using population shares, I arrive at the contract matrix needed to calculate λ_a for each age group. Lastly, in order to complete the set of parameters describing the force of infection, I reverse engineer the parameter β using a standard reproductive number for influenza, 1.44, and a standard estimate of the recovery rate, γ, of .24 (implying a duration of infectiousness of 1/.24=4.1 days).[2]

Since one aim of the model is to differentiate infections by their cost, I gather age specific cost measures for influenza. Molinari, et al. (2007) provides estimates of the annual economic burden of influenza epidemics for the U.S. population by age. Their analysis categorizes influenza infections into four care categories: not medically attended, outpatient care, inpatient care, and death, and provides probabilities and costs of care for each across age group. I use these data for two purposes. The first is to parameterize the death rates η_a (which are defined as the probability of death given an influenza infection), and the second is to provide estimates of the overall burden of disease in the model-simulated data. Mortality rates are given in Figure 4.

e. Outcome measures in the extended model

The extended model described above is able to generate disease dynamics for a given set of age specific vaccination rates, and at the end of the epidemic period, it can provide the proportion of individuals in each state.[3] One simple way to evaluate the impact of vaccination is to calculate to the proportion of ever-infected individuals, which would allow us to see how simulated infection

[2] Remember that in the simple SIR model $R_o = \beta/\gamma$ so that β could be recovered if R_o and γ are known. In the extended model, the derivation for β becomes $R_o\gamma$ multiplied by the maximum eigenvalue of the contact matrix. Effectively, this method sets β so that the reproductive number in the model is equivalent to 1.44.

[3] For instance, the number of individuals who avoid infection would be calculated as the sum of individuals in each of S_{av} at the end of the epidemic period. The epidemic period varies according to the vaccination rate but on average lasts about 90 days. All outcomes are evaluated at 10,000 periods to ensure the dynamics have played out completely.

rates respond to changes in vaccination (be it a change in the overall vaccination rate holding age-specific relative vaccination constant, or a redistribution of vaccination among age groups holding the overall vaccination rate constant, or a change in actual U.S. state vaccination rates over time).

While it is useful to analyze changes in the infection rate in response to changes in vaccination, comparing this outcome across different levels of vaccination implicitly treats all infections as equivalent. In order to capture the fact that there are strong age specific patterns in the cost of infections, I also calculate several other metrics of the loss from influenza. The first is the death rate, which is delivered explicitly by the model. The next set of objectives applies the cost estimates of influenza calculated by Molinari, et al. (2007). Aside from varying by age, these cost estimates are also specific to whether the infection occurs with/without death (e.g. the value of lost earnings would be the present value of all future earnings in the case of death, and the values of earnings for average days spent ill in the case of infection without death). The first metric in this set calculates the direct and indirect losses from influenza by including medical costs and estimates of the values of lost earnings for each age group. I term this the cost of influenza. The second loss metric is similar except, in the case of death, it uses a more comprehensive measure of loss, which is the value of a statistical life (including both the productivity and social value as a mortality loss). I term this the burden of influenza. The last loss metric measures time loss from influenza, which is a metric similar to the overall mortality rate but where sick days are also measured for survivors and where the overall loss of life-years is assigned in the case of death. Implicitly, this weights deaths among the young as more costly than the old. I term this as the time-cost of influenza.

In each measure described above, the overall loss is calculated as follows. First, for survivors of the disease, the age specific loss is calculated as expected loss using probability weights for three types of disease severity: cases of influenza that are not medically attended, cases that end up in outpatient care, and cases that end up in inpatient care (both the loss measures and the probability weights are age specific). For those who die, estimates of the age specific loss for each loss type are applied directly. Figure 5 shows the average loss for the three measures: cost, burden and time, and by type of infection: infection without death and infection with death. Including the loss metrics, this leaves us with 5 different outcomes with which to evaluate an influenza epidemic: the infection rate, the death rate, the cost of influenza, the burden of influenza, and the time-loss of influenza.

3. Optimization and the age distribution of vaccination

In this section, I use the extended model to describe the optimal distribution of vaccines across age group for all possible vaccination rates and for each outcome described above. For all simulations, I start with one infection in each of the age groups and document the resulting disease dynamics. To optimize over the age-distribution, I minimize each loss metric by choosing a vector of age-specific vaccination rates holding the overall vaccination rate constant. To get a sense of the range of loss across possible age-vaccination vectors, I also calculate the vector that maximizes the loss metric (i.e. for a given population vaccination rate, this is the distribution of vaccine across age that would lead to the worst outcome holding all else constant). For comparison, I also calculate the loss associated with the equal share age-distribution vector, where all age specific vaccination rates are equal. The results of this exercise are shown in Figure 6.

The figure shows that for a vaccination rate of zero, almost 40 percent of individuals will be infected with influenza at the end of the epidemic period. As the overall vaccination rate rises, the infection rate falls, but how quickly it falls depends on the distribution of vaccination across age.

For instance, in the equal share case the infection rate falls steadily until an overall vaccination rate of 40 percent is reached. At this point, an epidemic is circumvented and the marginal effect of additional vaccination falls close to zero. This point occurs at a much lower overall vaccination rate if vaccination is distributed to age groups optimally. In this case, the infection rate falls more steeply and the epidemic threshold is reached at an overall rate of 17 percent. If vaccines are distributed so as to maximize the infection rate, the infection rate slowly falls reaching a low only in the mid 90s (in this case, young children are left unvaccinated and infection is endemic in these age groups).

Figure 7 shows the age-specific vaccination rates in the maximum and minimum cases. Panel A plots vaccination rates among age groups that achieve the minimum infection rate. From this figure, we see that the first priority for vaccination is young school age children (age 5-9, and age 10-14). Not only do these children have some of the highest numbers of physical contacts (see Figure 3), they are also the most varied across the age distribution (notably to their peers and to adults age 30-39). Furthermore, vaccine efficacy rates are higher in younger age groups meaning that not only is the vaccine more protective among children, they are able to leverage this protective effect across a more varied group of contacts. Once a minimum level of 5 percent of the population is vaccinated, the optimal distribution prioritizes the age 5-9 year olds over 10-14 year olds. At 7 percent, it becomes optimal to raise vaccination rates among ages 15-17, then at 11 percent, ages 2-4. Finally, at 14 percent, vaccines are distributed to ages 18-24. At 17 percent, the vaccination rates depicted for these age groups are enough to prevent the spread of influenza in the population. After 17 percent, the optimal age-distribution rates are no longer unique, and vaccines can be distributed across age group in a variety of ways as long as children are featured heavily in the distribution. These additional vaccines, however, yield little effect since there is no longer any room for improvement on the infection rate.

The second panel in Figure 7 shows the age distribution rates that maximize the infection rate. Not surprisingly, distributing vaccines in this way calls for vaccination of the oldest age groups first; these age groups have lower contact rates and lower vaccine efficacy. In terms of infections, this means that centering a fixed supply of vaccines here will lead to the least amount of prevention. Note that this is not necessarily the case for death or other loss metrics. In these cases, the loss recognizes that infection among older groups is much more costly than infection among younger groups, and in this case it will be a matter of weighing the herd immunity effects delivered by the young versus the direct preventative effects of vaccines for the old.

To understand how this might differ if we differentiate the loss associated with infection across age, I perform the same analysis using the four types of loss described above: death, cost, burden and time. Figure 8 depicts the age-distribution rates that minimize and maximize the indicated loss metric. Here we can see that for the case of zero vaccination: the death rate would be 150 per 100,000, the per capita cost would be about $700 (this includes medical costs and the value of lost productivity), the per capita burden would be about $3000 (this is similar to the cost metric but measures loss from death as the value of a statistical life instead the productivity measure), and the per capita time loss is about 9 days.

Figure 9 depicts the age-distribution rates behind the minimized metric in Figure 8. Conditional on vaccine resources for at least 6 percent of the population, the optimal age-distribution for all loss metrics is similar to that of infection. This result occurs because, even though older age groups experience pricier infections on average, the herd immunity effects delivered by the young offer enough spillover protection for these older groups. But, in the case of death and time loss, this result is conditional on enough vaccine resources; specifically resources covering more than 5 percent of the population. In the case of death, for instance, the death rate is highest among the very old (see Figure 4) so at low vaccination rates, herd immunity effects from the young are not

large enough to protect the old, and here the optimal course of action is to protect the old directly. For death this means to scale up the vaccination of 65-69 year olds moving from 0 percent to 3 percent overall vaccination. At 3 percent, those 70-74 also become a priority. At 5 percent the optimal strategy switches to vaccinating the young to leverage the now large enough herd immunity effects for the rest of the population. In the case of time loss, there is a similar pattern. This loss metric is not as heavily weighted toward the old, i.e., this metric measures death according to the potential years of life lost (instead of treating all deaths a equivalent as with the death metric) and also measures the time loss for infections that do not lead to death. Here, we see that initially age 65-69 year olds are prioritized, but, again, at 5 percent the optimal strategy switches to vaccinating the young.

4. Vaccination in U.S. states from 1997-2014

a. Vaccination Data

This section compares actual age-distribution vectors in the U.S. for influenza seasons 1997-2014 to the strategies defined in section 6. To calculate vaccination rates over this time period, I use the Behavioral Risk Factor Surveillance System (BRFSS) to estimate rates for those 18+. The BRFSS is a large, annual, nationally representative cross-sectional survey that includes information on age, influenza receipt, and date of survey for years 1996 to 2014. I use the date of survey to assign influenza seasons to individuals: if the survey date occurred before October in year x, I assign season $(x-1)/x$ as the influenza season and I refer to it as season x. If the survey date occurred in October or later in year x, I assign $x/(x+1)$ as the influenza season and I refer to it as season $x+1$. To calculate vaccination rates for those under 18, I use the National Immunization Survey and the National Immunization Survey – Teen, which are a group of phone surveys used to monitor vaccination coverage among children 19-35 months, teens 13-17 years, and flu vaccinations for children 6 months-17 years. Because questions on influenza were only added after the vaccine was recommended for use in these age groups (i.e., 2003 for NIS and 2006 for NIS-Teen), I supplement this data with data from the National Health Interview Survey (NHIS). The NHIS includes information on influenza vaccination across all ages starting in 1996. Unfortunately, it does not include information on state. It can, however, be used to confirm that vaccination rates among children prior to date of recommendation were near zero. Figure 10 compares these datasets across time for all age groups. Here, because vaccination rates among children were near zero in the years not covered by NIS, I apply the NHIS rates to these age groups in these years.

b. Vaccination in U.S. compared to optimal vaccination

Vaccination data can be used to calculate the age-distribution of vaccination in each state and season. For each state-season pair, the resulting disease dynamics and outcomes can also be measured. Figure 11 performs this exercise for every state-season case and depicts the resulting infection rate. The minimized, equal share, and maximized vectors are also shown for comparison. Notably, all state-seasons lie above the equal-share line indicating that the actual age-distribution of vaccination in U.S. states over the last 17 years is less favorable in terms of infections than the a strategy that distributes vaccines equally across age groups. This is largely because in the early part of this time period, vaccination was emphasized more heavily for older age groups, and then recommendations began expanding to other groups. With this expansion, the overall vaccination rate began to rise. In the graph, we can see that points at lower vaccination rates are closer to the maximized line, and as the vaccination rate rises, age-distribution rates become more favorable and start to fall closer to the equal-share line. In all cases, the outcomes simulated from actual state-seasons lie far from the optimum.

The results in Figure 11 only consider infections, and we have seen that the loss associated with an infection has a strong age component. In fact, one main reason for the emphasis on vaccination for older ages was based on higher cost effectiveness of the vaccine against outcomes like hospitalization and death. To capture these differences, I look explicitly at death and the various loss metrics to compare these outcomes for each state-season case. Figure 12 shows these results. Here we can see that the cost, burden and time loss associated with influenza for state-seasons is, in all cases, less favorable than the equal-share distribution and is far from the optimal distribution. For death, those state-seasons with lower vaccination rates are more in line with that of the equal-share distribution (note that the vectors for each comparison are the same distance apart in all graphs, but the outcomes associated with those vectors are not necessarily). As the overall rate rises, the vector is increasingly less favorable compared to the equal-share line.

5. The effect of Pharmacy Statutes on vaccination and simulated outcomes

a. Vaccination

The above analysis shows that the effect of any policy on outcomes depends not only on how that policy impacts vaccination but also how it affects the age-distribution of vaccination. This section looks at the impact of a particular vaccine policy change that allows Pharmacists to provide vaccinations individuals. To assess the impact of Pharmacy Statutes (PS) on vaccination and outcomes, I first merge the vaccination data with information on the timing of PS for each state.[4] This allows me to estimate the difference-in-difference effect of PS on vaccination. To estimate the differential effect that PS has on the overall vaccination rate, I regress vaccination rates for each age, state and season on a dummy variable equal to one for all seasons and states where a pharmacy statute is in effect and zero otherwise. To account for time-invariant differences across state and state-invariant differences across season, I control for state and season fixed effects. To account for age specific differences in vaccination, I include age fixed effects, and to account for the impact of the change in ACIP recommendations for each age group across time, I include a dummy variable equal to one for all ages and seasons where the influenza was recommend. This isolates the change in vaccination that is specific to the time a place where a PS was put in place that is not explained by differences across state, season, age, or ACIP recommendation. All calculated age-state-season vaccination rates are weighted according to the survey weight, and all regressions are weighted by the population share in each cell. Standard errors are clustered at the state level.

The results of this analysis are given in the first column of Table 1. The first panel provides the overall effect of PS. The size of the effect is small at 1.6 percentage points (6 percent increase from the baseline mean). The implication of this change for outcomes is unclear even just considering the simple SIR model as a reference model: a 1.6 percentage point change could have a large or small effect on outcomes depending on the baseline rate, e.g., this change would have little effect on outcomes if it occurred from a baseline rate in excess of the epidemic threshold, but would have a larger effect at baseline vaccination rates below the threshold. In this case, the baseline rate (i.e. the average rate before pharmacy statutes) is 25 percent. This is below the epidemic threshold in the simple model so taking this model as given, the effect on outcomes would be to decrease the loss from influenza. That said, what the extended model shows us is that the epidemic threshold is not fixed, but rather it depends on the age-distribution of vaccination. So the size of the effect not only depends on the original age-distribution, but also on whether there has been a change in that age-distribution.

[4] Information on pharmacy statutes is obtained from a variety of sources: Blake, et al. (2003), Hammond, et al. (2003), Calomo, et al. (2004), Steyer, et al. (2004), Hogue, et al. (2006), and Turner, et al. (2007).

This means that the change in the age-distribution of vaccination can play a substantial role in the overall effect on outcomes (this could be true even if the overall change in rate was zero). To see the effect of PS on the age-distribution of vaccination, I rerun the model with a full set of PS-age interactions. The regression model then provides the differential effect of PS for each age group relative to the reference category (in this case age 0-1). The second panel of Table 1 reports these results. For ease of interpretation, instead of reporting the results as relative to the reference group, I provide contrast estimates comparing the differential effect of PS for each age group. A graphical depiction of these estimates is shown in Figure 13.

Here we see that aside from the fact that overall vaccination rates changed only slightly, this masks large differential effects by age. The largest effects of pharmacy statutes are among children. Those age 18-24 have little change, whereas the 30-34 and 35-39 group see an increase in vaccination. This could indicate that PS makes vaccination more convenient for children and their parents to receive the vaccine. Those over 50, on the other hand, have small decreases in vaccination, which fall more so as we move up the age groups. Overall these differences add up to a slight increase in the vaccination rate, but from what we have seen in the optimization analysis, the change in the age-distribution of vaccination is likely favorable since in encompasses higher vaccination in children and lower vaccination in the elderly.

b. Loss outcomes

The model provides the capability to assess the PS effect holding all else equal, and allows us decompose the effect of the policy into two parts: the age-distribution effect holding the overall rate constant (the tilt effect) and the effect of the increase in the overall rate holding the age-distribution constant (the scale effect). Together these add up to the total effect of the PS policy change. In order to assess these effects, I calculate outcomes for each state and season at baseline (i.e. cases where there are no pharmacy statutes in effect) using actual age-distribution vectors. These comprise the initial state-season outcomes. I then calculate two counterfactuals. The first is a zero-sum redistribution of vaccines along the lines of the PS age effects. To calculate this counterfactual, I adjust each state-season age-distribution vector by the estimated PS effects across age (shown in Figure 13), but scale the rates down across all age groups so that the overall vaccination rate remains unchanged. I call this the tilt effect because it changes the tilt of vaccination across age without changing the overall rate (i.e., a zero-sum redistribution). Once the age-distribution vectors are adjusted, I calculate counterfactual outcomes for all baseline state-seasons. In the second counterfactual, I rescale the age-distribution vectors in the post-PS case back up, to provide the final outcomes, which provides the total effect relative to the initial vectors. The scale effect is just the difference between the total effect and the tilt effect.

The effect of PS on outcomes is given in Table 1. The first column provides the effect for the infection rate. Here the total effect (both the tilt and scale effect) is estimated as a 3.5 percentage point decrease, which represents a 13 percent decrease in the rate. Comparing this to the 6 percent change in vaccination indicates substantial herd immunity effects. To see this note that if there were no spillovers from vaccination, a 6 percent increase in vaccination implies that the maximum effect on infections would be 6 percent.[5] The fact that the change in infections is 13 percent, 2.2 times higher than the change in vaccination, implies substantial herd immunity effects (i.e., each vaccination is estimated to prevent more than one infection). In fact, the tilt

[5] This maximum assumes that each of the newly vaccinated 6 percent would have been be infected without vaccination, but all are now prevented at a efficacy rate of 100 percent. In other words, each vaccine prevents one exactly one infection. The actual change in the infection rate assuming zero spillovers is likely much lower than 6 percent accounting for a more reasonable attack rate and measure of efficacy.

effect shows that there are substantial herd immunity effects from a simple zero-sum redistribution of vaccines along the lines of the PS age effects. Here the impact of redistributing vaccines holding the overall change constant delivers a decrease in infection of 2 percentage points or an 8 percent decrease from baseline. Furthermore, in the case of infections, most of the size of the effect is due to the change in tilt: 63 percent of the effect is due to tilting the age-distribution and the remaining 37 percent is due to the scaling up the overall rate.

The second panel of Table 1 shows the effects by age and Figure 15 represents these effects a percent changes. From the figure, we can see that there are large decreases in infection for younger children, but even more noteworthy is that the effects are negative for all age groups even though some of these older age groups experienced a decrease in vaccination. A large part of this effect is due to the change in tilt, which is also negative in all cases. This means that even where total vaccine resources are held constant, there are substantial gains from immunization.

The remainder of Table 1 shows the effect of PS on other loss metrics. The total effect of PS is negative across all age groups and all loss metrics indicating that even though the change in overall vaccination is small, the model indicates that PS effect had a substantial effect on the loss from influenza.

6. Conclusion

This paper shows that because of differential herd immunity effects across age, the impact of vaccination policy can have ambiguous effects on disease outcomes because a. the marginal effect of vaccination is non-linear and hence depends on baseline rates, and b. the marginal effect of vaccination is differential across age group which means, overall, it is not agnostic to changes in the age-distribution of vaccines. To illustrate this I set up a model that accounts for differences in the force of infection, where disease spread is sensitive to different mixing patterns both within and across age groups. Secondly, the model accounts for differences in vaccine efficacy across age group in order to capture the differential protection the vaccine offers to different age groups. Thirdly, I explicitly model death in the model where death conditional in influenza infection varies across age. Lastly, I model not only how infection rates respond to vaccination, I also evaluate the direct and indirect costs of infection by applying age specific costs estimates to the infection and death outcomes delivered by the model.

The model allows me to assess optimal vaccine distribution across age, to compare actual state-season vaccination vectors to the optimal rates, and to assess the impact of pharmacy statues, which had little effect on the overall vaccination rate but a sizable effect on relative vaccination across age.

The results show that for a given vaccination rate there is a wide range of infection rates and other loss outcomes between the age-distribution that distributes vaccines optimally, the age distribution that distributes vaccines in equal shares, and the age-distribution that distributes vaccines in the worst possible way. Moreover, actual vaccination in U.S. states in the last 17 years is less favorable than the equal-share distribution across all loss metrics considered. Finally, looking at the effect of pharmacy statutes on vaccination shows that the overall vaccination rate increased only slightly but that the it tilted vaccination towards young children and away from age groups over 50. Using the model to assess the counterfactual effects on outcomes shows that despite the small change in vaccination, there were substantial changes in outcomes. For instance, the decrease in infections was 2.2 times the size of the change in vaccination indicating large herd immunity effects. A substantial part of this effect was due to the tilt in vaccination alone, meaning that improvements in outcomes can be delivered with no additional resources needed. Unless the cost of vaccination differs substantially across age group, this is a free lunch.

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Table 1 - The effect of Pharmacy Statutes on vaccination and simulated loss outcomes

	Vaccination (rate)			Simulated Loss Outcomes: Infection (rate)			Death (per 100,000)			Cost ($2003)			Burden ($2003)			Time (days)		
Panel A: Pharmacy Statute Effect Overall																		
	Estimate		S.E.	Total	Tilt		Total	Tilt		Total	Tilt		Total	Tilt		Total	Tilt	
Overall	0.016	***	(0.005)	-0.035	-0.022	63%	-3.8	0.3	-	-35	-14	40%	-125	-31	25%	-0.37	-0.09	24%
Basline Mean	0.253			0.270	0.270		55.3	55.3		345	345		1419	1419		4.14	4.14	
Percent Change	6%			-13%	-8%		-7%	0%		-10%	-4%		-9%	-2%		-9%	-2%	
Tilt/Total																		
Panel B: Pharmacy Statute Effect by Age (estimates are given as contrasts between PS=1 and PS=0)																		
Age 0-1	0.198	***	(0.015)	-0.081	-0.062	77%	-1.5	-1.2	79%	-56	-44	78%	-63	-49	78%	-0.53	-0.42	79%
Age 2-4	0.163	***	(0.015)	-0.083	-0.066	79%	-1.4	-1.1	80%	-56	-45	80%	-62	-50	80%	-0.49	-0.39	80%
Age 5-9	0.053	***	(0.008)	-0.070	-0.049	70%	-0.3	-0.2	71%	-18	-13	70%	-23	-16	70%	-0.13	-0.09	70%
Age 10-14	0.052	***	(0.007)	-0.068	-0.047	70%	-0.3	-0.2	70%	-18	-12	70%	-23	-16	70%	-0.12	-0.09	70%
Age 15-17	0.035	***	(0.007)	-0.048	-0.026	55%	-0.2	-0.1	54%	-13	-7	55%	-16	-9	55%	-0.08	-0.05	55%
Age 18-24	-0.015	*	(0.008)	-0.025	-0.012	48%	-0.8	-0.3	40%	-20	-9	43%	-65	-27	41%	-0.20	-0.08	41%
Age 25-29	0.014	*	(0.008)	-0.032	-0.019	59%	-1.1	-0.7	57%	-27	-15	58%	-90	-51	57%	-0.25	-0.14	57%
Age 30-34	0.029	***	(0.007)	-0.036	-0.023	65%	-1.3	-0.9	64%	-31	-20	65%	-105	-68	65%	-0.27	-0.17	65%
Age 35-39	0.016	**	(0.006)	-0.034	-0.021	63%	-1.2	-0.7	61%	-28	-17	62%	-95	-58	61%	-0.22	-0.13	61%
Age 40-44	0.009		(0.006)	-0.030	-0.018	60%	-1.1	-0.6	57%	-25	-15	58%	-84	-48	58%	-0.17	-0.10	58%
Age 45-49	-0.010		(0.007)	-0.022	-0.012	53%	-0.7	-0.3	46%	-18	-9	49%	-58	-27	47%	-0.11	-0.05	47%
Age 50-54	-0.018	**	(0.008)	-0.019	-0.010	51%	-8.5	-3.6	43%	-74	-33	45%	-344	-149	43%	-0.96	-0.41	43%
Age 55-59	-0.021	**	(0.008)	-0.016	-0.008	49%	-6.7	-2.5	37%	-58	-24	40%	-270	-102	38%	-0.65	-0.25	38%
Age 60-64	-0.021	*	(0.011)	-0.016	-0.007	48%	-6.2	-2.0	32%	-55	-20	37%	-251	-84	33%	-0.51	-0.17	33%
Age 65-69	-0.024	**	(0.010)	-0.010	-0.003	34%	-20.3	7.6	-	-61	12	-	-304	103	-	-1.37	0.48	-
Age 70-74	-0.040	***	(0.009)	-0.007	-0.001	19%	-7.3	18.6	-	-28	39	-	-115	262	-	-0.41	0.96	-
Age 75+	-0.030	**	(0.012)	-0.011	-0.006	50%	-15.7	4.1	-	-52	0	-	-240	49	-	-0.51	0.09	-

Figure 1

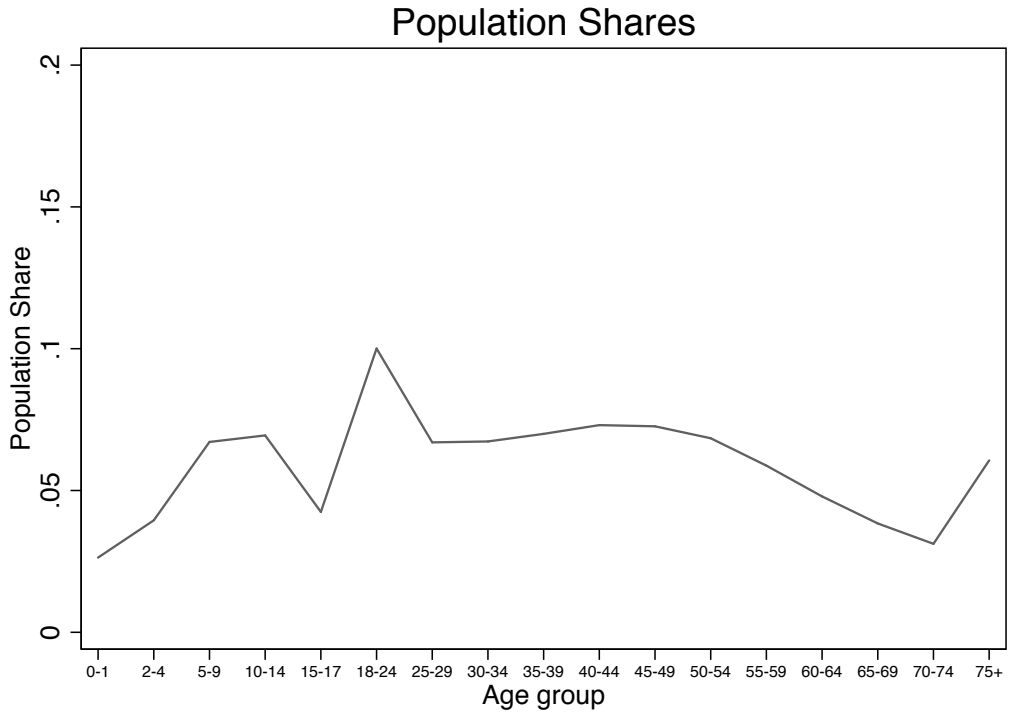


Figure 2

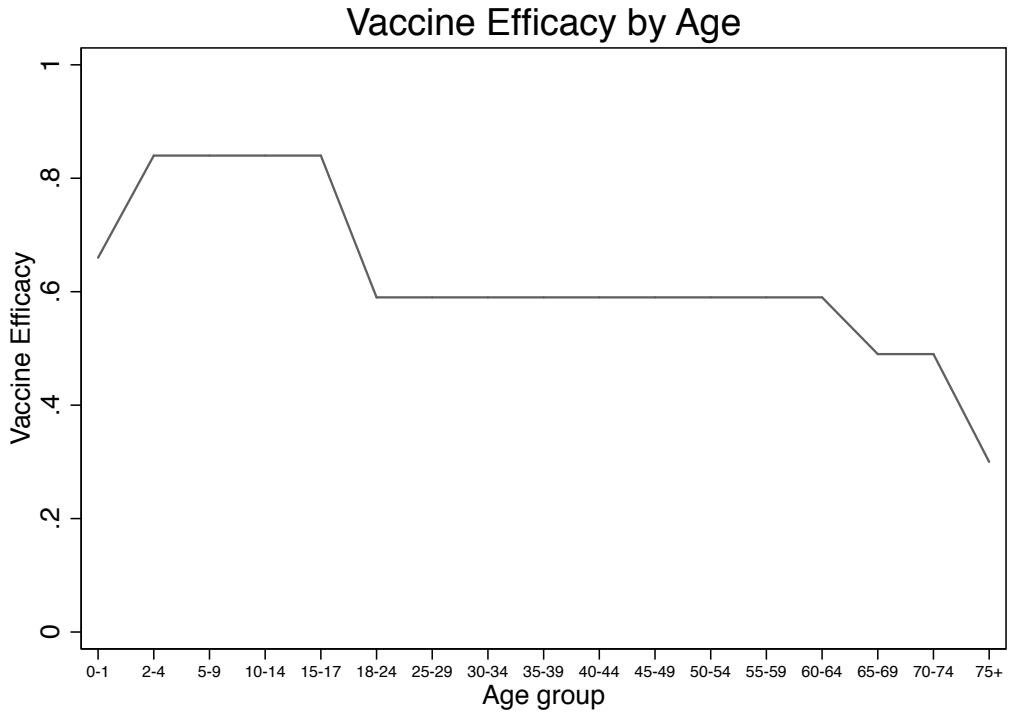


Figure 3

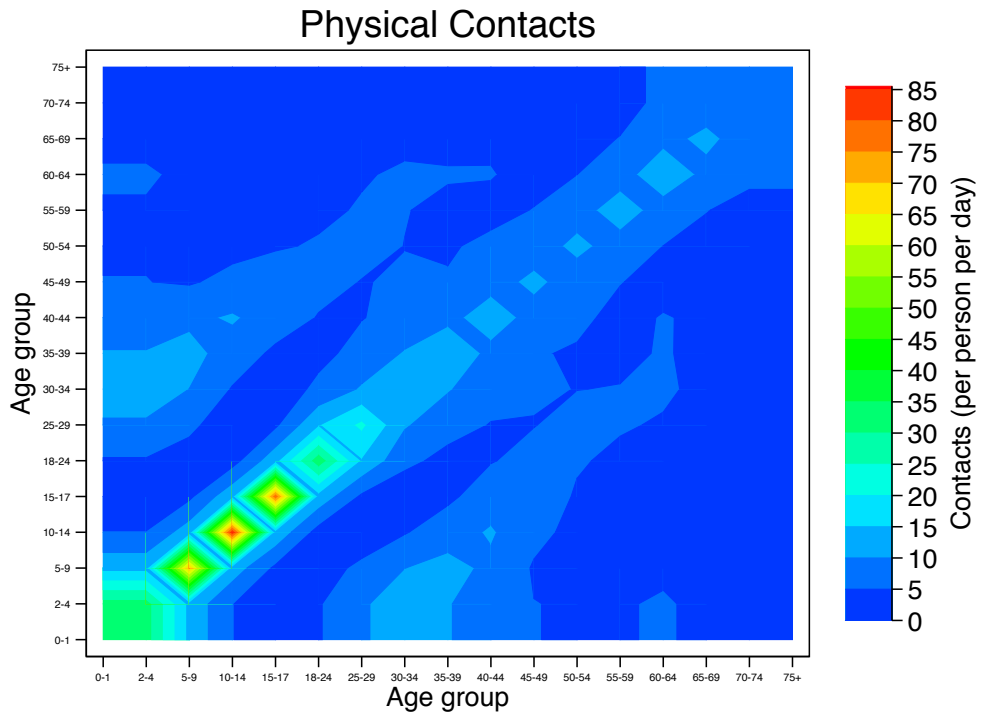


Figure 4

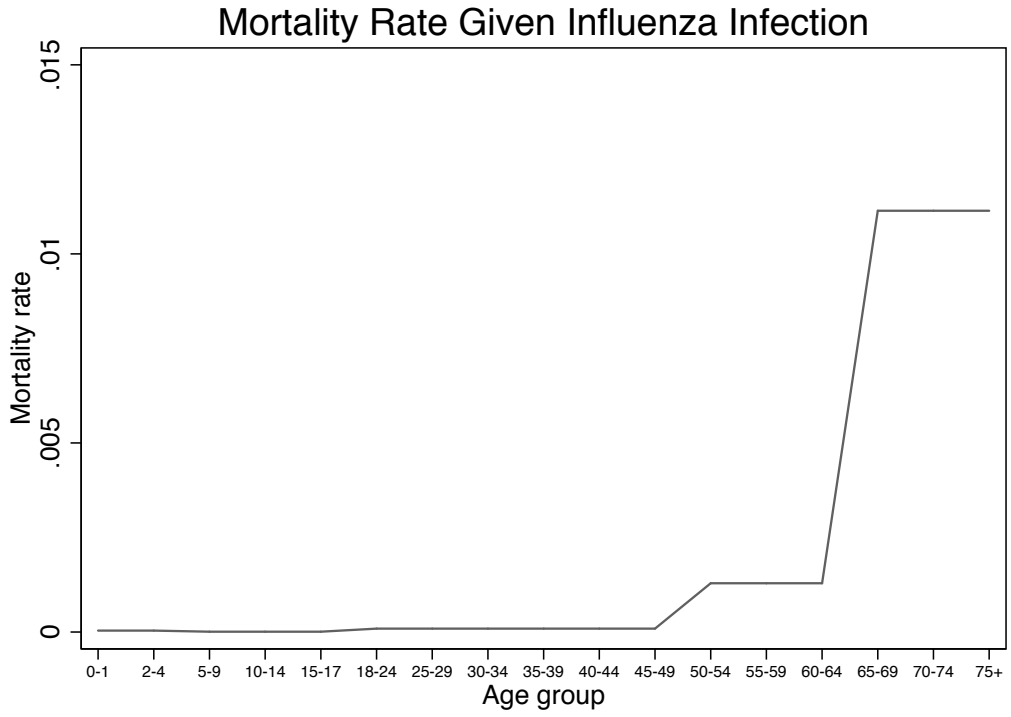
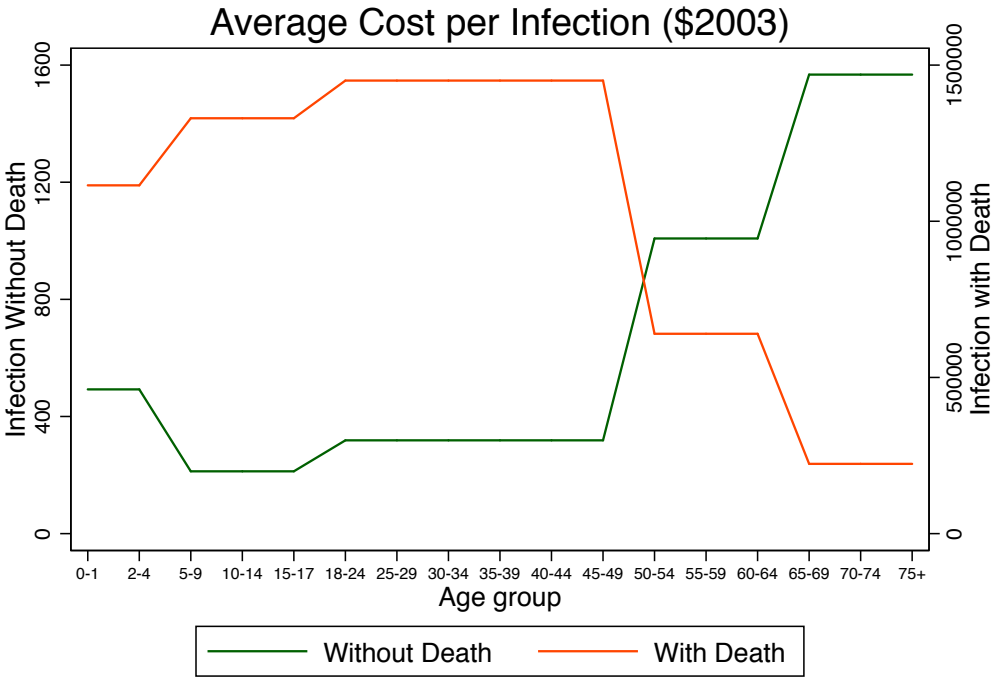
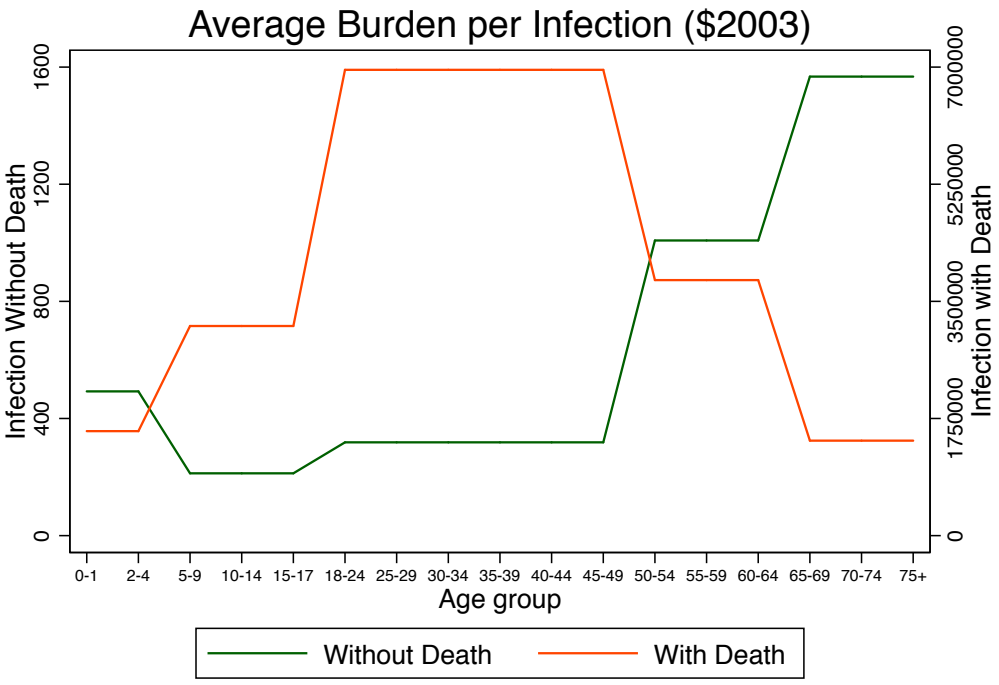


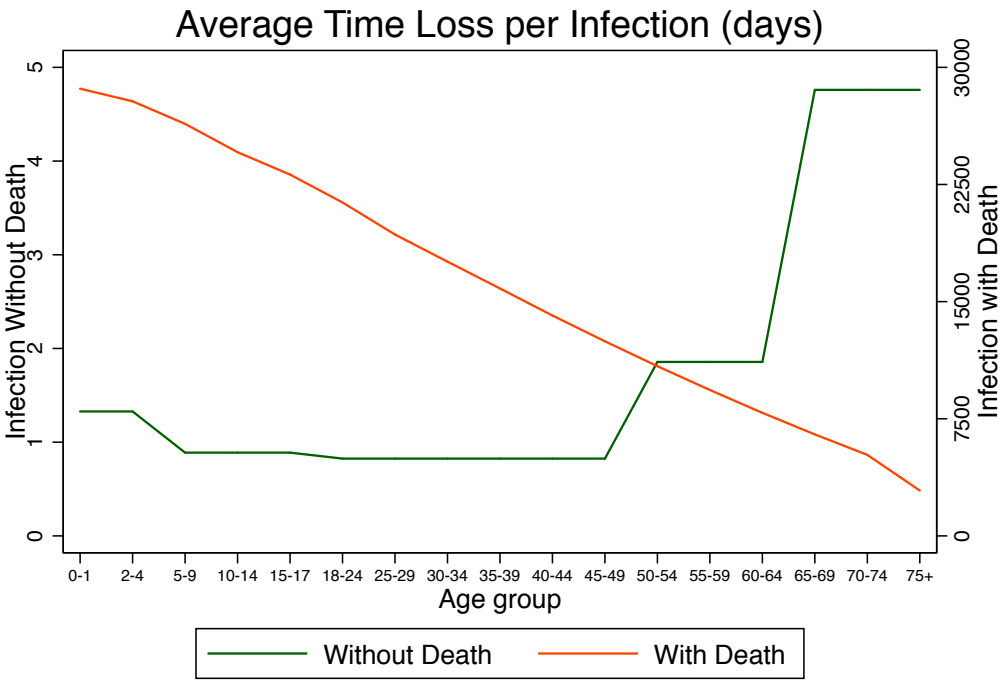
Figure 5 – Average Loss: Cost, Burden, Time



Note: Average cost includes direct medical costs and productivity losses

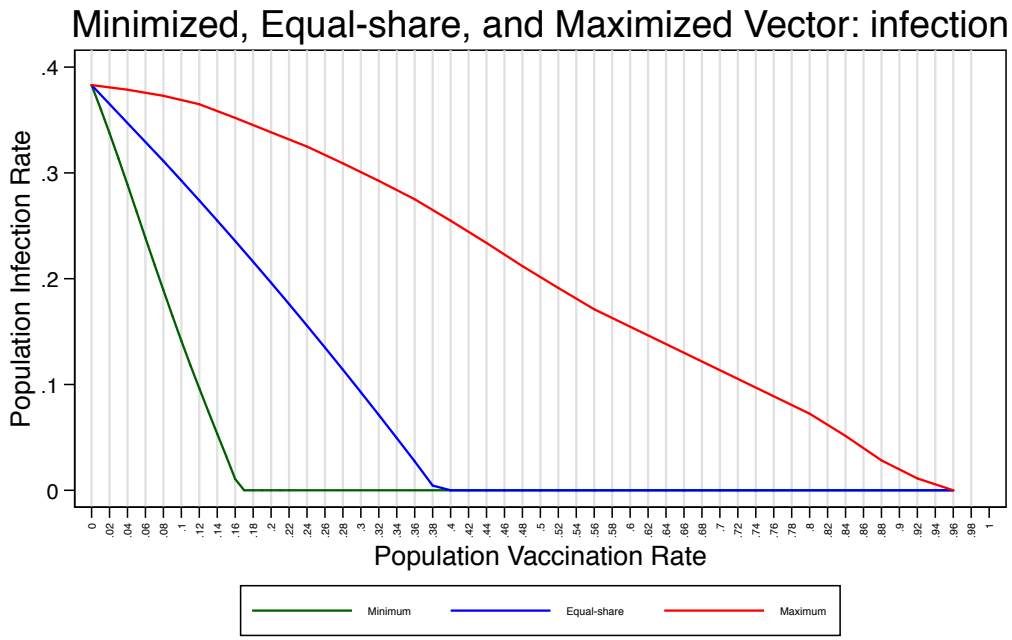


Note: Average burden includes direct medical costs and value-of-a-statistical-life losses



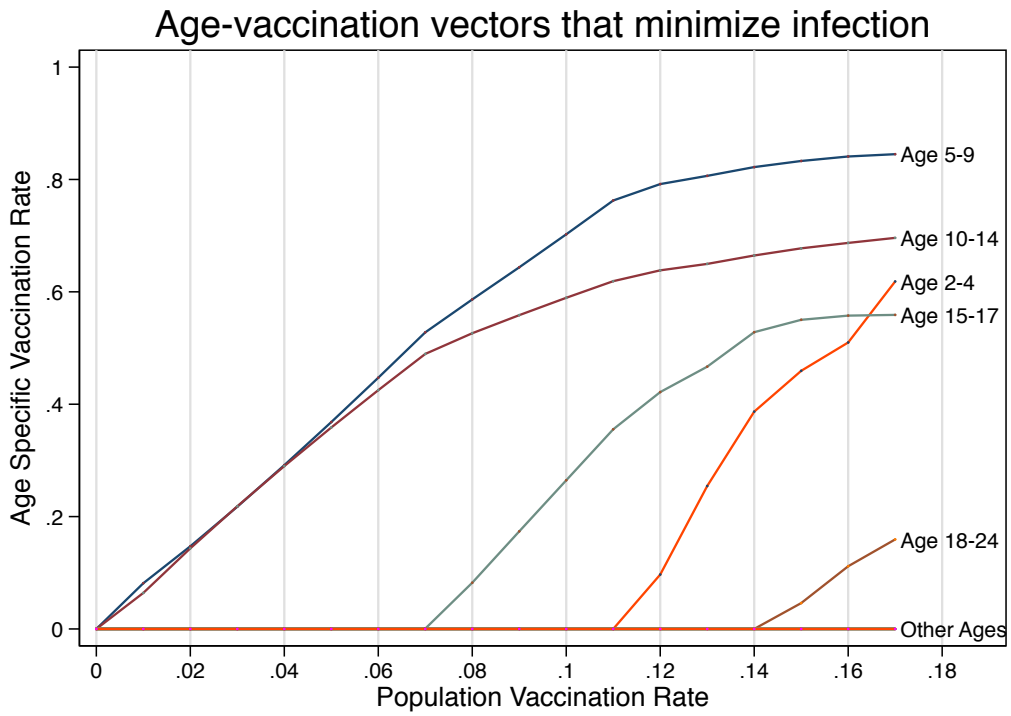
Note: Average time loss includes days lost to illness and potential life-years lost (rescaled in days)

Figure 6



Note: In the minimum age-distribution vector, the distribution of vaccination is chosen to minimize infection.
In the Equal-share age-distribution vector, vaccination rates are equivalent for each age group
In the maximum age-distribution vector, the distribution of vaccination is chosen to maximize infectio

Figure 7 Panel a



Note: At a vaccination rate of 18 percent, the spread of disease falls to zero. At this point the age-distribution vector that minimize infection is no longer unique but is instead satisfied by a set of vectors. The marginal effect of vaccination to any age group at this point falls close to zero.

Figure 7 panel b

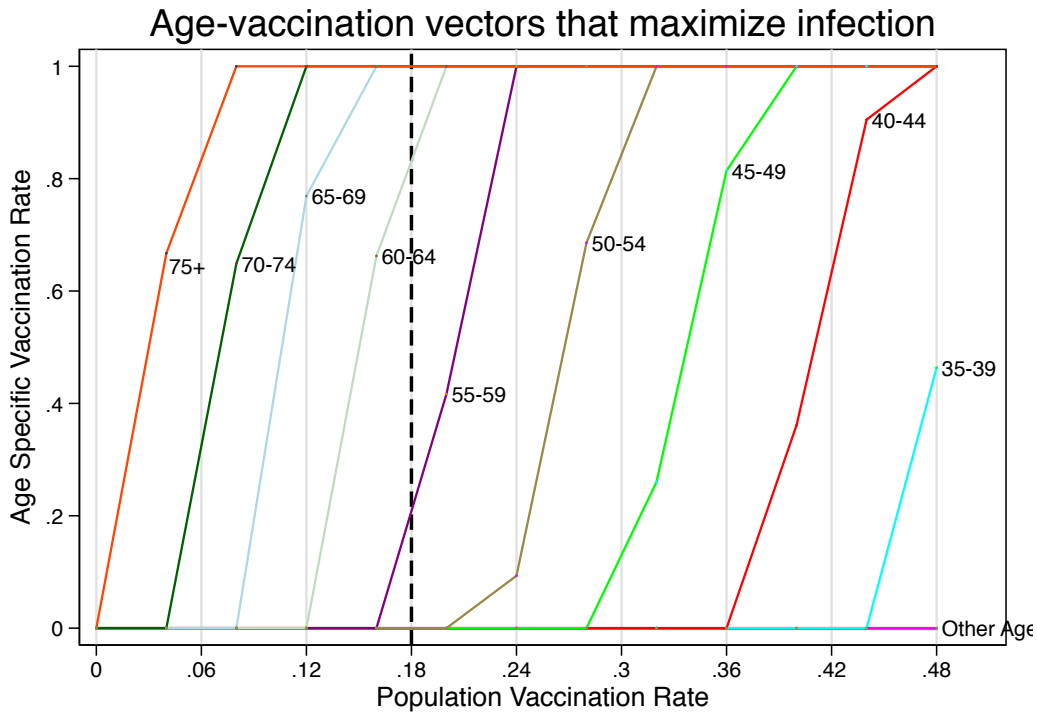
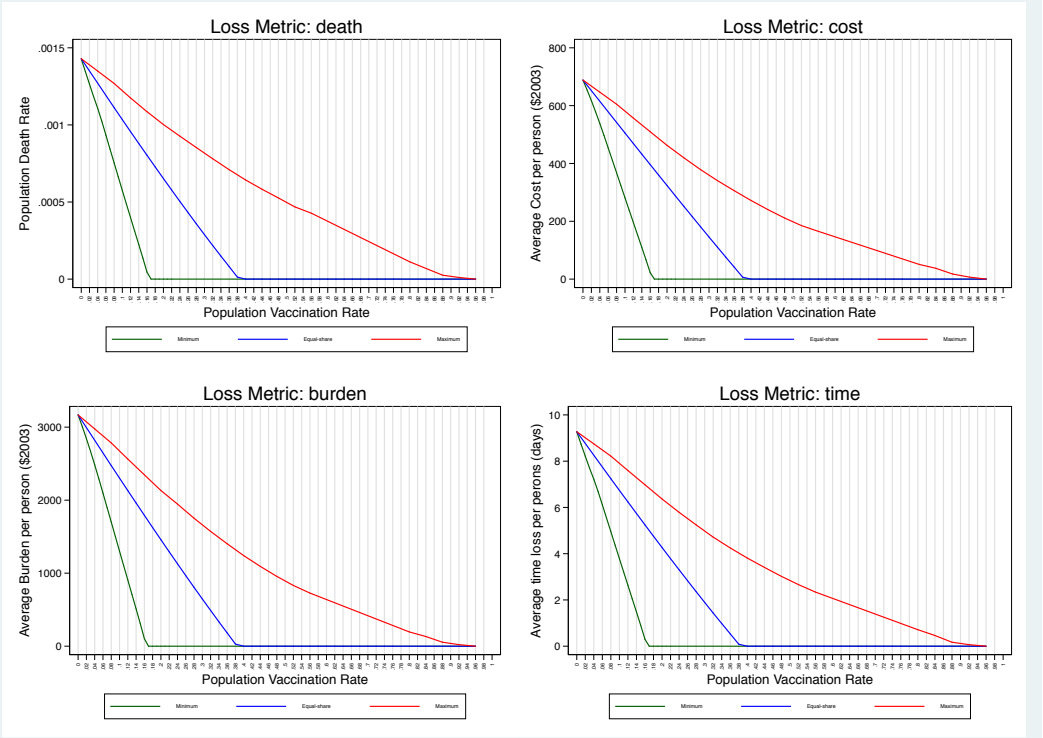
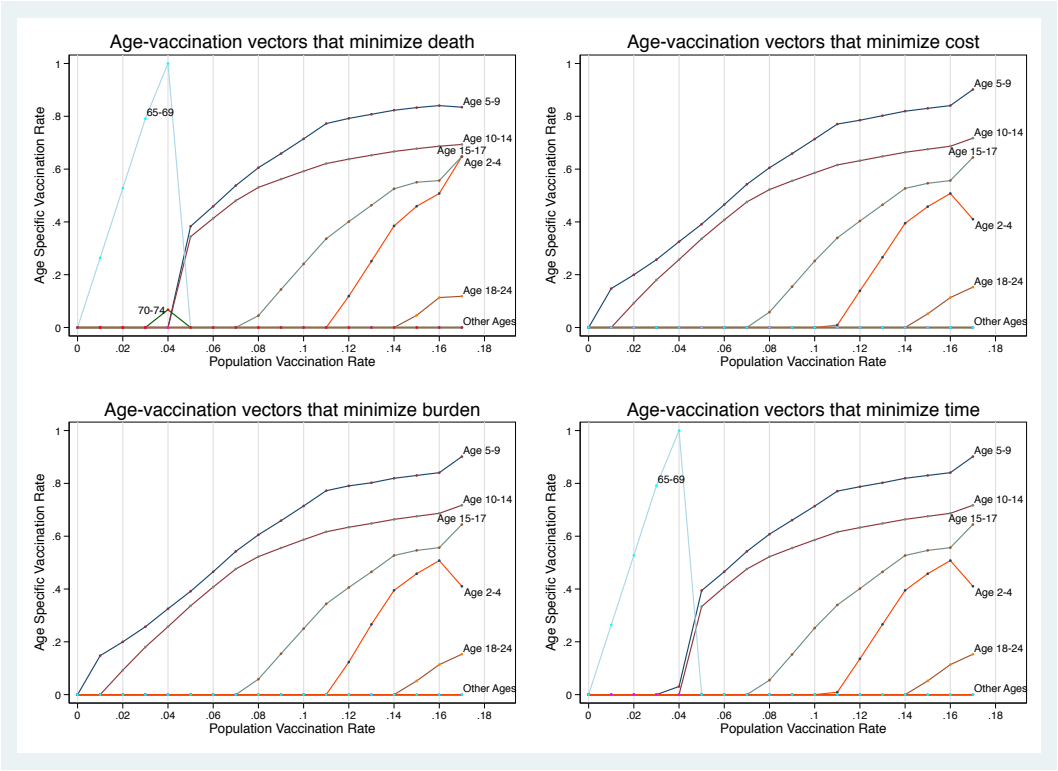


Figure 8



Note: In the minimum age-distribution vector, the distribution of vaccination is chosen to minimize the indicated loss metric. In the equal share age- distribution vector, vaccination rates are equivalent for each age group. In the maximum age- distribution vector, the distribution of vaccination is chosen to maximize indicated loss metric. In the case of death, the model delivers the death rate explicitly. In the case of cost, the loss includes direct medical costs and the value of lost productivity (due to illness/death). In the case of burden, the loss includes medical costs and the value of lost life (due to illness/death). In the case of time loss, the loss includes time lost due to illness or due to death. For the cost, burden, and time metrics, total losses are specified separately by age and severity of infection, where severity is categorized as: not medically attended, outpatient care, inpatient care, and death. The severity specific losses are then applied to the infections and deaths for each age group and summed over the population for each chosen age-vaccination vector.

Figure 9



Note: At a vaccination rate of 18 percent, the spread of disease falls to zero. At this point the age-distribution vector that minimize infection is no longer unique but is instead satisfied by a set of vectors. The marginal effect of vaccination to any age group at this point falls close to zero.

Figure 10

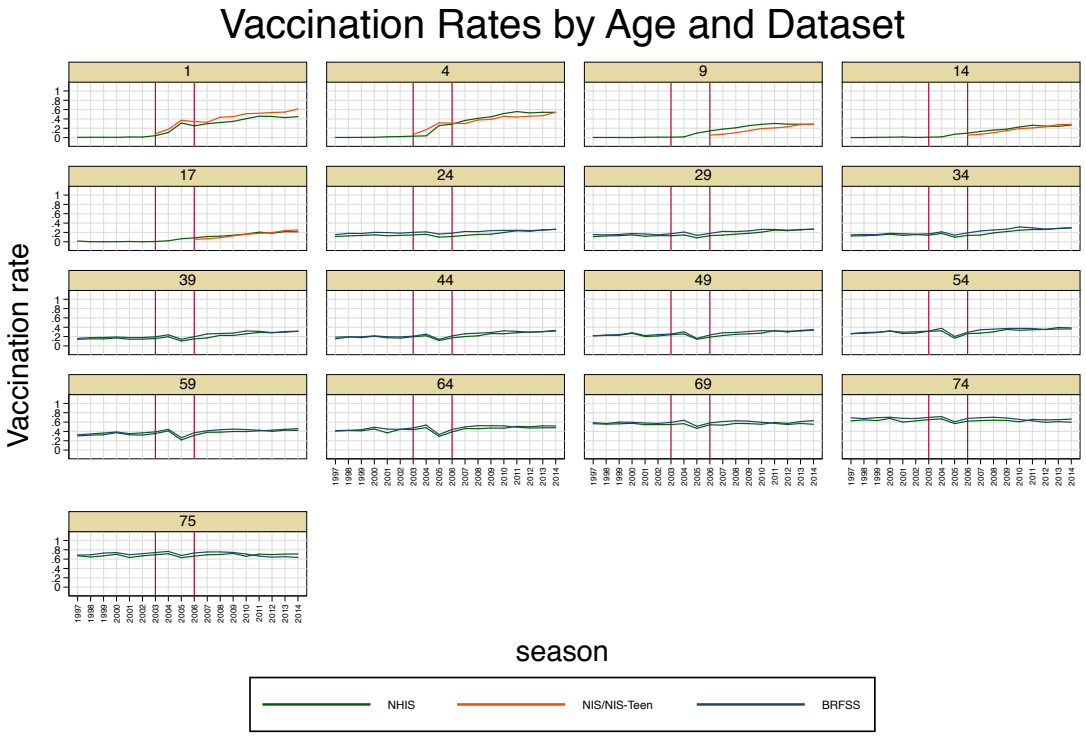
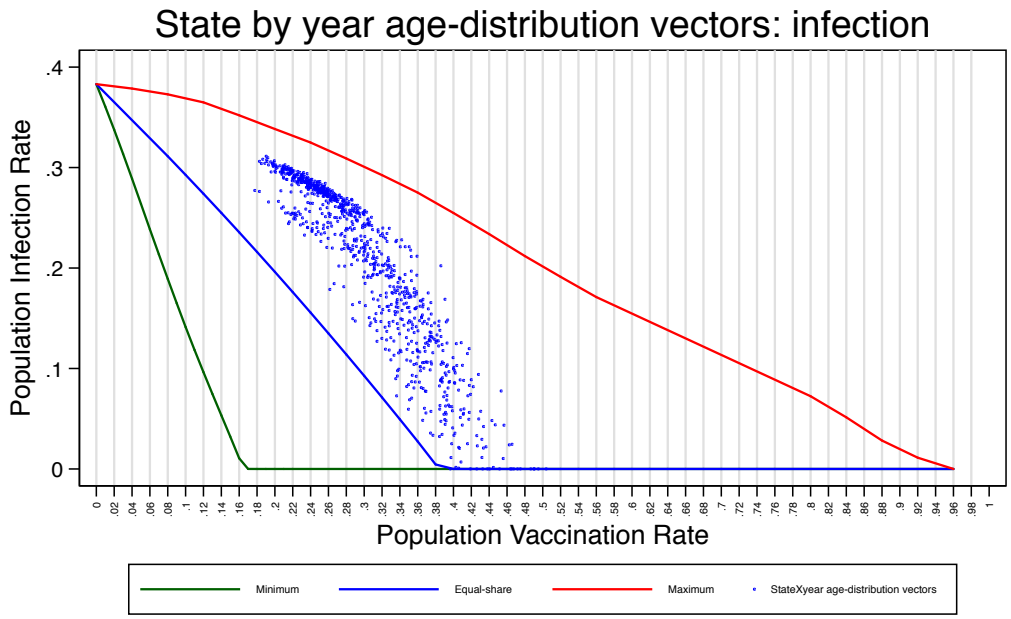
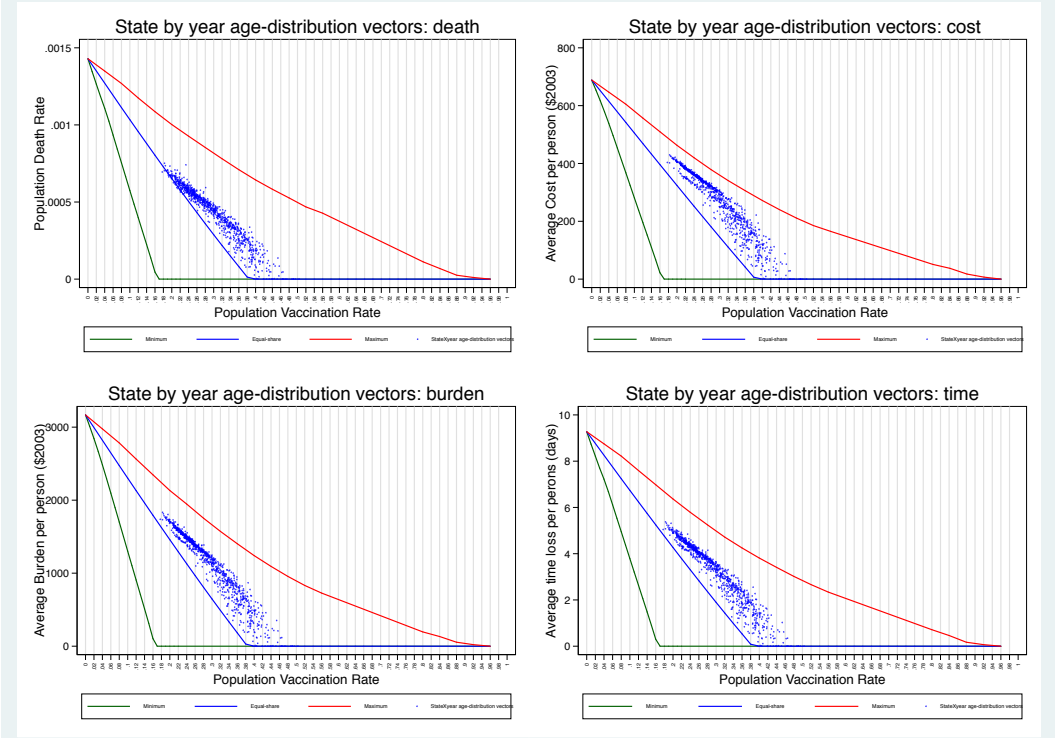

Vaccination Rates by Age and Dataset
1
4
9
14
17
24
29
34
39
44
49
54
59
64
69
74
75
Vaccination rate
season
NHIS
NIS/NIS-Teen
BRFSS
Graphs by Age Group

Figure 11



Note: In the minimum age-distribution vector, the distribution of vaccination is chosen to minimize infection.
In the Equal-share age-distribution vector, vaccination rates are equivalent for each age group
In the stateXyear age-distribution vector, vaccination rates are set to the rates within in each state from 19
In the maximum age-distribution vector, the distribution of vaccination is chosen to maximize infecti

Figure 12



Note: In the minimum age-distribution vector, the distribution of vaccination is chosen to minimize the indicated loss metric. In the equal share age-distribution vector, vaccination rates are equivalent for each age group. In the maximum age-distribution vector, the distribution of vaccination is chosen to maximize indicated loss metric. The state-by-year data represent age-distribution vectors for all states over the years 1997-2014. In the case of death, the model delivers the death rate explicitly. In the case of cost, the loss includes direct medical costs and the value of lost productivity (due to illness/death). In the case of burden, the loss includes medical costs and the value of lost life (due to illness/death). In the case of time loss, the loss includes time lost due to illness or due to death. For the cost, burden, and time metrics, total losses are specified separately by age and severity of infection, where severity is categorized as: not medically attended, outpatient care, inpatient care, and death. The severity specific losses are then applied to the infections and deaths for each age group and summed over the population for each chosen age-vaccination vector.

Figure 13

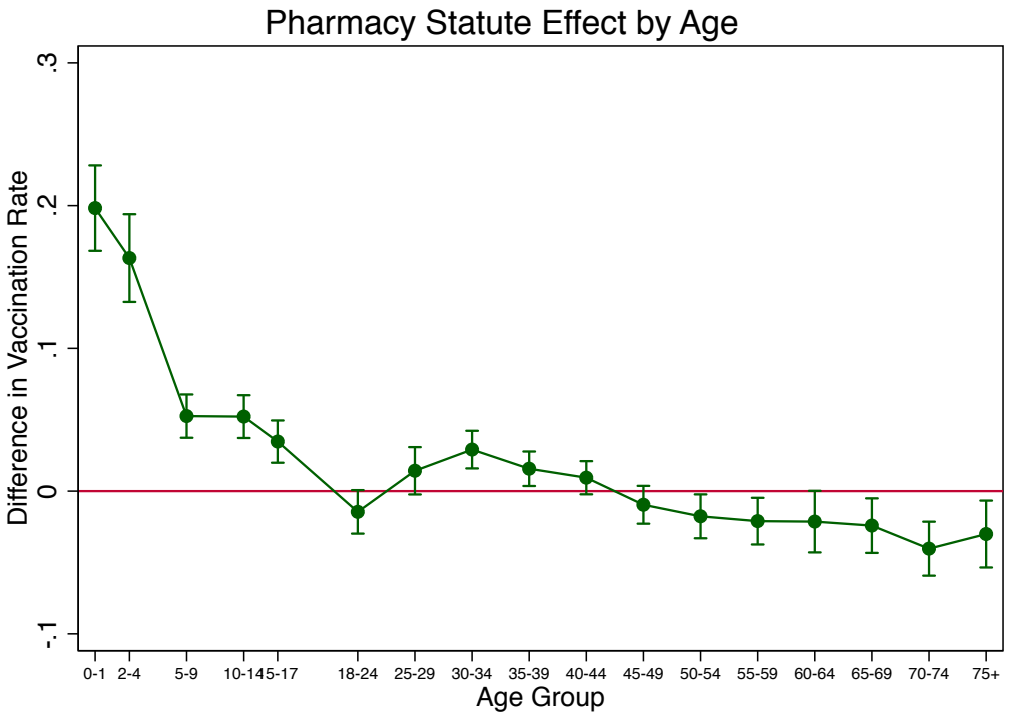

Pharmacy Statute Effect by Age
Difference in Vaccination Rate
-.1
0
.1
.2
.3
0-1
2-4
5-9
10-14
15-17
18-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75+
Age Group

Figure 15

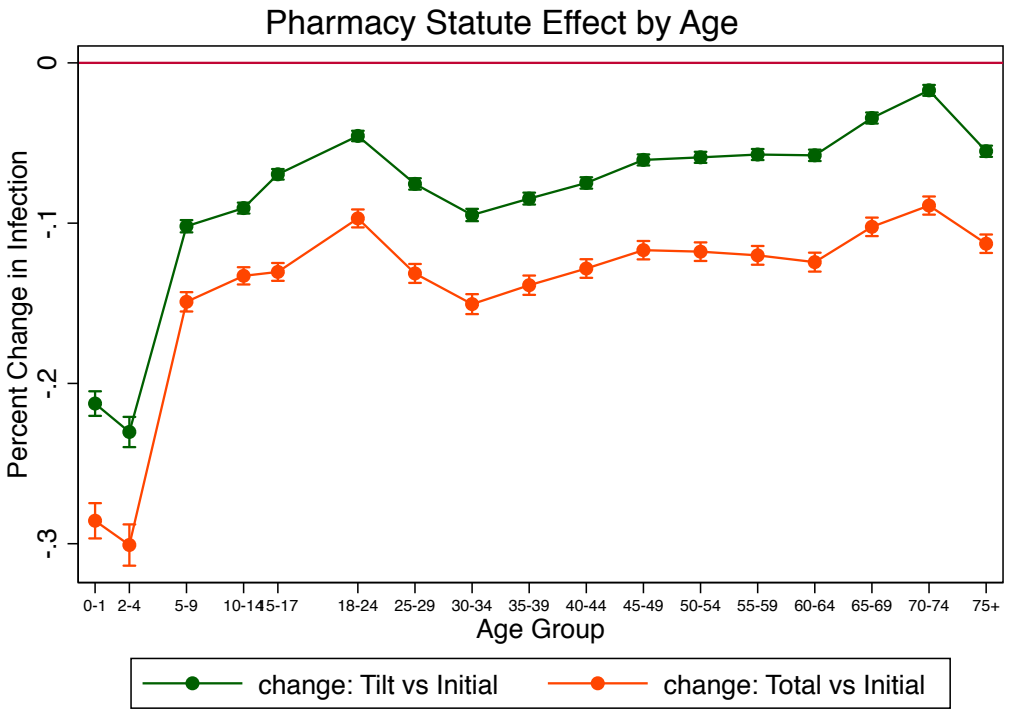
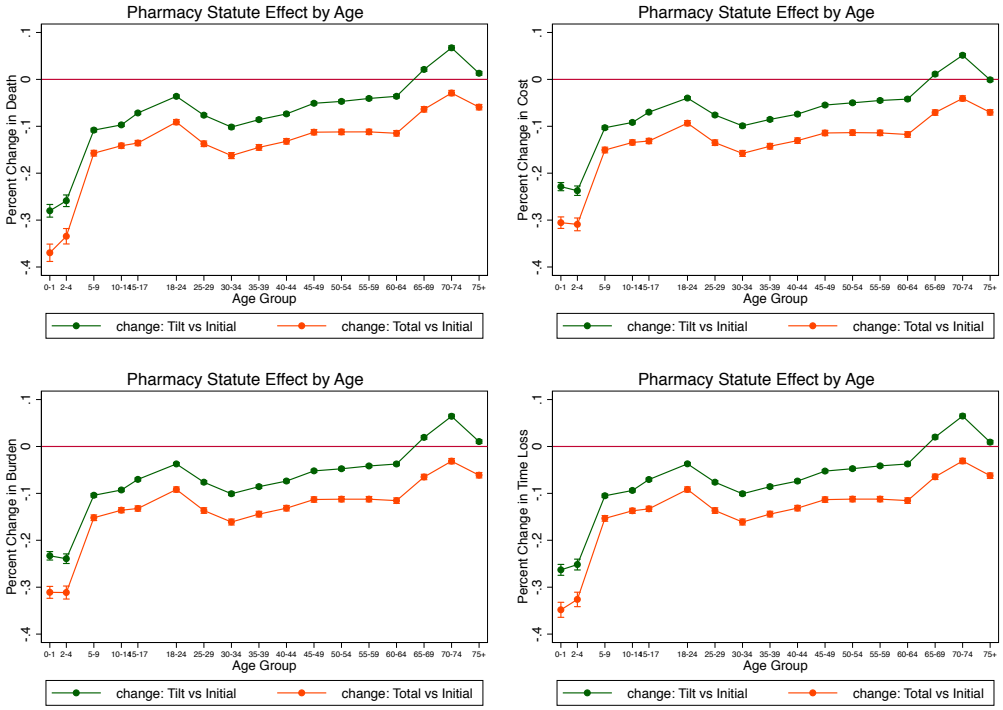

Pharmacy Statute Effect by Age
Percent Change in Infection
0
-.1
-.2
-.3
0-1
2-4
5-9
10-14
15-17
18-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75+
Age Group
change: Tilt vs Initial
change: Total vs Initial

Figure 16


Pharmacy Statute Effect by Age
Percent Change in Death
Age Group
change: Tilt vs Initial
change: Total vs Initial
Pharmacy Statute Effect by Age
Percent Change in Cost
Age Group
change: Tilt vs Initial
change: Total vs Initial
Pharmacy Statute Effect by Age
Percent Change in Burden
Age Group
change: Tilt vs Initial
change: Total vs Initial
Pharmacy Statute Effect by Age
Percent Change in Time Loss
Age Group
change: Tilt vs Initial
change: Total vs Initial