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Modelling Vaccine Strategies for Norovirus Gastroenteritis

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M.Sc., The Pennsylvania State University, 2013

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A thesis submitted to the Faculty of the
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Abstract

Modelling Vaccine Strategies for Norovirus Gastroenteritis

By Molly Steele

Background: Noroviruses are the leading cause of acute gastroenteritis and foodborne diarrheal disease in the United States. Norovirus vaccine development has progressed rapidly in recent years, but critical questions, including which age groups should be vaccinated to maximize population impact, remain to be addressed.

Methods: A deterministic, age-structured compartmental model was developed that tracks norovirus transmission and immunity in the U.S. population. Three age specific transmission parameters (q_{1-3}) were estimated using maximum likelihood and fitting the model to age-specific monthly US hospitalizations between 1996 and 2007. Four vaccine strategies were simulated under the assumption that immunization provides the same duration of protection as natural infection: routine immunization around the time of birth and individuals turning 65 years old, followed by re-vaccination every five years. In initial simulations, vaccine efficacy is assumed to be 50% and vaccine coverage for 0-4 year-olds is assumed to be 90% while vaccine coverage for the 65 year and older age group is assumed to be 65%.

Results: Model outputs achieved good fit to the U.S. hospitalization data, and results indicated that the youngest age group, 0-4 year olds, have the highest susceptibility to norovirus with approximately 3.38 infections resulting from an infection from any age group. The older age groups are less susceptible to infection, as 1.86 and 0.33 infections occur in 5-64 year olds and 65 year and older, respectively, from an infection from any age group. Routine immunization of infants with 90% coverage at equilibrium was predicted to avert 6,318 (a 33% reduction) hospitalizations in 0-4 year olds and 8,974 (15%) hospitalizations in all other age groups annually. Routine immunization of 65 year-olds was estimated to avert 4,480 (16%) hospitalizations in the 65+ age group and 147 (0.4%) hospitalizations in all other age groups annually. In considering total population effects, vaccinating 0-4 and 65+ years was estimated to avert 395 and 72 hospitalizations, respectively, per 100,000 doses administered, with much greater indirect benefits accrued from the infant immunization program.

Conclusion: The modelling analysis demonstrated that population-level impacts of norovirus vaccination may be maximized by vaccinating young children, due to their importance in transmission.

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CHAPTER 1: INTRODUCTION

Impact of Norovirus

Acute gastroenteritis has the second highest burden of all infectious diseases, causing an annual estimated loss of 89.5 million disability-adjusted life years (DALY) and 1.45 million deaths globally.[1,2] Noroviruses are among the leading causes of both endemic enteric disease and outbreaks of gastroenteritis worldwide.[3–5] It has been estimated that 18% of sporadic gastroenteritis cases worldwide are caused by noroviruses.[6] Norovirus illnesses are particularly prevalent—generally accounting for more than 20% of sporadic gastroenteritis cases—in low-mortality developed countries such as the United States.

In recent years, noroviruses have been recognized as the leading causative agent of acute gastroenteritis and foodborne diarrheal disease in the United States.[4,7–9] On average, Noroviruses are responsible for 570–800 deaths, 56,000–71,000 hospitalizations, 400,000 emergency department visits, 1.7–1.9 million outpatient visits, and 19–21 million total illnesses annually in the United States.[7] An estimated 5,000 quality-adjusted life years (QALY) attributable to norovirus illness are lost annually in the United States as well.[10] Though norovirus illness impacts all ages, the severity of disease outcomes differs between age groups.[11] Lopman et al. estimated hospitalization rates, finding the highest rates among children under the age of 5 (9.4 hospitalizations per 10,000 people per year) and in the elderly 65 years of age and older (8.1 hospitalizations per 10,000 people per year).[12] Hall et al. estimated that 90% of the annual norovirus-associated deaths in the United States occurred in the elderly (65 years and older), resulting in a death rate of 0.20 deaths per 10,000 persons per year.[13]

In addition to the health burden, foodborne norovirus illness causes a substantial economic burden; approximately $2 billion in annual costs are associated with foodborne norovirus illness.[10,14] This economic burden accounts for both direct costs of illness (e.g., costs of physician visits, outpatient treatment, and hospitalizations) and indirect costs of illness (e.g., productivity and days of work lost due to illness). The substantial burden of norovirus illness is a result of the unique epidemiology and genetic diversity of the virus as well as difficulties associated with infection control.

Classification

Noroviruses are single stranded RNA viruses that are divided into six genegroups, GI-GVI. Viruses in genegroups I, II and IV are infectious to humans.[11] Gengroup II, genotype 4 (GII.4) strains of norovirus are estimated to cause 70-80% all norovirus outbreaks[15] and 70% of sporadic norovirus illnesses in children 18 years old or younger.[16] The emergence of new variants of this strain often coincide with global epidemics of norovirus illness.[11,17] The emergence of new variants is typically driven by population immunity; as larger proportions of the population are immune to a given variant, the virus mutates and evolves new variants to evade host immunity.[18,19] Between 2001 and 2007, eight GII.4 variants were identified worldwide, four of which caused pandemics.[20]

Epidemiology

Norovirus exhibits a seasonal pattern where there are marked increases of disease during the winter months.[7,21–24] A meta-analysis of known norovirus outbreaks from 1993 – 2011 found that 63-73% of all norovirus illnesses occur from October to March.[7]

Noroviruses are highly infectious, with infectious doses as low as 18 viral particles [25], and are primarily spread through the fecal-oral route as well as vomitus droplets.[26] The most common routes of transmission are person-to-person transmission, environmental and foodborne transmission.[26] Upon exposure to the noroviruses, individuals will enter a short incubation period that on average lasts 32.8 hours (95% CI: 30.9-34.6).[27] Symptoms of norovirus last on average 44.2 hours (95% CI: 38.9-50.7) [27] and are characterized by the sudden onset of vomiting, watery, non-bloody diarrhea and abdominal cramps.[11] Individuals will shed virus in their stool, both prior to symptomatic illness and after symptoms resolve. Peak viral shedding occurs 2-5 days after infection.[28] The viral shedding period is highly variable between individuals and has been documented to begin as short as 18 hours after exposure and as long as eight weeks post exposure.[28] However, the median reported duration of viral shedding is four weeks.[28] Though little is known about how infectious individuals are during this asymptomatic shedding period, studies have shown that while asymptomatic individuals appear to cause subsequent infections, they were less likely to cause infections as symptomatically infected individuals.[29,30] After exposure to noroviruses, individuals will acquire natural immunity. Clinical studies have shown that the duration of immunity is short term, typically six months to two years.[31–34] In contrast, mathematical modelling studies suggest the duration of immunity to norovirus is long term, around four to six years.[35]

Treatment of norovirus illness is primarily focused on supplementing fluid loss with oral rehydration or, in more severe cases of illness, intravenous fluids.[11] The current accepted methods for norovirus prevention and intervention are: the promotion of hand hygiene, exclusion and isolation of those infected with norovirus, and environmental

disinfection with chlorine bleach. Hand hygiene is currently the most important method for norovirus prevention.[36] Proper hand washing with soap and water for at least 20 seconds reduces the amount of virus by 0.7 – 1.2$\log_{10}$.[37] There is mixed evidence of the efficacy of alcohol-based sanitizers against norovirus, therefore it is recommended that alcohol based sanitizers be used in addition to proper hand washing.[37–43] As noroviruses can persist on environmental surfaces, contaminated surfaces should be cleaned with a 1,000-5,000ppm concentration of chlorine bleach as noroviruses resistant to many common household chemical cleaners.[44–47]

Due to the virus' low infectious dose, stability in the environment and resistance to common chemical cleaners, norovirus infection may be impossible to prevent and challenging to control using traditional infection control and food safety approaches.[48] For this reason, there has been significant interest in determining the role vaccines might play in limiting norovirus transmission.

Vaccine Development

Vaccine development for noroviruses has been challenging as there currently is no standard *in vitro* culturing system.[49–53] Thus instead of developing live vaccines, development has focused on the use of virus like particles (VLPs). When recombinant norovirus VP1 capsid proteins are expressed, these capsid proteins will self-assemble VLPs.[54] These norovirus VLPs produce immunogenic responses in humans that are comparable to what the virus itself causes.[55–57] Phase I/II safety, immunogenicity, and efficacy (challenge) studies on norovirus vaccines have been encouraging, with at least one product moving into Phase III field efficacy trials [8,48]. The product moving into phase

III clinical trials is a bivalent, intramuscular VLP vaccine. These vaccines are immunogenic, producing strain specific IgG and IgA antibodies, with no severe adverse side effects [8,58–63].

Current vaccine development studies have focused on producing vaccines for use in adults. However, since noroviruses affect all ages and cause disease through multiple transmission routes, there is an array of possible vaccine strategies ranging from untargeted mass vaccination (like the current influenza vaccine guidance) to age targeted (e.g. young children or elderly) or targeting of groups important in transmission (e.g. food handlers). It is imperative to consider the potential impact that vaccination programs could have on the dynamics of norovirus infection and disease at a population level, so that policy makers can advise the most effective vaccination strategies. Vaccine development has progressed rapidly in recent years, but the influence of vaccine use on the transmission of norovirus has not been examined quantitatively. Mathematical models can be used to quantitatively assessments of the impact of vaccines on the transmission of norovirus.

Epidemiological Models

Mathematical models have been used extensively to explore the dynamics of many infectious diseases in a range of contexts and with a diversity of analytical goals. For example, with regards to the ongoing Ebola outbreak in West Africa, mathematical models have been used to estimate the transmission dynamics of the virus [64,65], to predict the probability of international spread of the virus [66,67], and to evaluate the potential impact of different intervention strategies[68,69]. Many of the mathematical models used to explore the dynamics of infectious diseases, such as some of the models used to study the

Ebola outbreak in West Africa, are SIR based compartmental models. The classic SIR model is a compartmental mathematical model represented by a set of differential equations, where S represents susceptible hosts, I represents infected hosts and R represents recovered hosts,[70] and the flow of individuals from one compartment to another is determined by a set of rate parameters.[70]

Many studies of have used versions of SIR models to explore the dynamics of norovirus infections.[35,39,71,72] Several have used these models to explore transmission dynamics of norovirus outbreaks,[39,71] while others have used compartmental models to explore the dynamics of sporadic norovirus illness at the population level.[35,72] However, very few studies have sought to quantitatively assess the potential impact of vaccines on norovirus illness. A study done by Bartsch et al. used a Markov model to assess the impact of norovirus vaccines and associated economic benefits of vaccination.[73] The Markov model used in this study did not consider the dynamics of disease transmission, and therefore did not account for the impacts of vaccination in terms of herd immunity and reductions in transmission.[73] The potential impacts of vaccination calculated by Bartsch et al. may therefore be a substantial underestimate.[73]

Here, an age-structured transmission model is used to explore the potential effect of vaccination strategies on the dynamics of norovirus, including on the incidence of norovirus illness as well as hospitalization rates for each of four age classes in the population: young children (0-4 years), older children (5-17 years), adults (18-64 years) and the elderly (65+ years). The model is used to: 1) compare and contrast the population-level impacts of vaccine strategies that target young children for vaccination versus those

that target the elderly for vaccination; and 2) examine the efficiency of different vaccine strategies with varying levels of vaccine efficacy and duration of vaccine immunity.

CHAPTER 2: MATERIALS AND METHODS

Compartmental Model

The model used for this project is adapted from a previously published, deterministic, age-structured compartmental model that tracks norovirus spread at a population level.[35] The model uses a Susceptible-Exposed-Infected-Recovered (SEIR) framework, and is fit to norovirus incidence and hospitalization data. The model has seven state variables that characterize the immunity/susceptibility profiles of the population: susceptible to infection (S), exposed but not symptomatic (E), infected with symptoms (I), infected but asymptomatic (A), immune to disease but not protected against infection (R), vaccine-acquired immunity to disease and infection (V), and vaccinated with asymptomatic infection (Va) (Figure 1).

The model assumes that maternal immunity is negligible, as the youngest age class in this model includes children up to 4 years old, and maternal antibodies to norovirus have been documented to wane within the first 6 months of life.[74] Therefore everyone born into the system is susceptible to infection. After the infection period, individuals acquire natural immunity that protects against disease, but not against infection, until immunity wanes.[34,75,76] In the absence of vaccination, persons are born directly into the susceptible pool (S), are exposed and subjected to the force of infection (λ), and progress through the exposed (E), symptomatic (I) and asymptomatic (A) stages at rates inversely proportional to the duration of incubation ($1/\mu_s$), the duration of symptomatic illness ($1/\mu_{a)}$ and the duration of asymptomatic shedding ($1/\rho$) before entering the recovered compartment (R). From the recovered compartment, persons can become asymptomatically infected at a rate equal to the force of infection (λ), or can become

susceptible to disease through the waning of natural immunity (1/θ). In the presence of vaccination, a certain proportion of susceptible individuals (v) will be protected and move into the vaccinated compartment (V). Vaccinated individuals can become asymptomatically infected at a rate equal to the force of infection, or can become susceptible to disease through the waning of vaccine immunity (1/α).

The model outputs estimates age-specific incidence of norovirus illness. Age specific clinical outcome probabilities, calculated by Bartsch et al., were multiplied by the age specific incidence of disease to obtain estimated outpatient visits, emergency department (ED) visits, hospitalizations, and deaths.[73] The ordinary differential equations that support the model structure described above are as follows:

State	**Equation**
Young children (0-4 years)	
Susceptible	$\frac{dS_i}{dt} = B(1-v) + 1/\theta R_i + 1/\alpha V_i - (\lambda_i(t) + a_i + D_i)S_i$
Exposed	$\frac{dE_i}{dt} = \lambda(t)S_i - (1/\mu_s + a_i + D_i)E_i$
Infected Symptomatic	$\frac{dI_i}{dt} = 1/\mu_s E_i - (1/\mu_a + a_i + D_i)I_i$
Infected Asymptomatic	$\frac{dA_i}{dt} = 1/\mu_a I_i + \lambda_i(t)R_i - (1/\rho + a_i + D_i)A_i$
Recovered	$\frac{dR_i}{dt} = 1/\rho A_i - (\lambda_i(t) + 1/\theta + a_i + D_i)R_i$
Vaccinated	$\frac{dV_i}{dt} = Bv - (1/\alpha + a_i + D_i)V_i$
Older Children, Adults (5-64 years)	
Susceptible	$\frac{dS_i}{dt} = a_{i-1}S_{i-1} + 1/\theta R_i - (\lambda_i(t) + a_i + D_i)S_i$
Exposed	$\frac{dE_i}{dt} = a_{i-1}E_{i-1} + \lambda(t)S_i - (1/\mu_s + a_i + D_i)E_i$

Infected Symptomatic	$\frac{dI_i}{dt} = a_{i-1}I_{i-1} + 1/\mu_s E_i - (1/\mu_a + a_i + D_i)I_i$
Infected Asymptomatic	$\frac{dA_i}{dt} = a_{i-1}A_{i-1} + 1/\mu_a I_i + \lambda_i(t)R_i - (1/\rho + a_i + D_i)A_i$
Recovered	$\frac{dR_i}{dt} = a_{i-1}R_{i-1} + 1/\rho A_i - (\lambda_i(t) + 1/\theta + a_i + D_i)R_i$
Elderly (65+ years)	
Susceptible	$\frac{dS_i}{dt} = a_{i-1}S_{i-1} + 1/\theta R_i + 1/\alpha V_i - (\lambda_i(t) + v + D_i)S_i$
Exposed	$\frac{dE_i}{dt} = a_{i-1}E_{i-1} + \lambda(t)S_i - (1/\mu_s + D_i)E_i$
Infected Symptomatic	$\frac{dI_i}{dt} = a_{i-1}I_{i-1} + 1/\mu_s E_i - (1/\mu_a + D_i)I_i$
Infected Asymptomatic	$\frac{dA_i}{dt} = a_{i-1}A_{i-1} + 1/\mu_a I_i + \lambda_i(t)R_i - (1/\rho + D_i)A_i$
Recovered	$\frac{dR_i}{dt} = a_{i-1}R_{i-1} + 1/\rho A_i - (\lambda_i(t) + 1/\theta + D_i)R_i$
Vaccinated	$\frac{dV_i}{dt} = a_{i-1}S_{i-1}v + S_i v - (1/\alpha + D_i)V_i$

Where

i = age group, young children (0-4), older children (5-17), adults (18-64), and elderly (65+)

S_i = Susceptible to infection

E_i = Exposed to infection

I_i = Infected with symptoms

A_i = Infected, asymptomatic

R_i = Recovered, immune to disease but not infection

V_i = Vaccinated, immune to disease and infection

B = births entering the system

a_i = proportion of individuals aging out the group

D_i = deaths from age group *i* exiting the system

θ = the duration of natural immunity

α = the duration of vaccine immunity

v = proportion of individuals protected by vaccination

$\lambda(t)$ = the force of infection

μ_s = the duration of incubation

μ_a = the duration of symptomatic infection

ρ = the duration of asymptomatic shedding

The force of infection was modeled as:

$$\lambda_i(t) = b_i q_i \sum_{j=1}^{4} c_{ij}\, s(t) \frac{\left(\varepsilon E_j + I_j + \varepsilon A_j\right)}{N_j}$$

where b_i is the total number of contacts an individual of age group *i* makes in a day, q_i represents the age-specific susceptibility to norovirus infection, c_{ij} is the contact rate of age group *i* with age group *j*, and ε represents how infectious exposed and asymptomatic individuals are relative to symptomatically infected individuals. As norovirus exhibits a strong seasonal pattern in the United States, the model incorporates the effect of seasonality ($s(t)$):

$$s(t) = 1 + \beta_1 \times \cos(2\pi t + \omega)$$

where β_1 is the amplitude of the seasonal fluctuation and ω is the seasonal offset parameter.

Other model structures were considered (Table 4) that implement a different number and representation of the age-specific susceptibility parameters (q_i). As written in the model structure described above, q_i represents the susceptibility of age group i to infection from all other age groups. Alternatively, q_i may also be written to represent the infectivity of age group i to all other age groups (see alternative models 2 and 3 in Table 4). The model structure described above was selected as it provided the best fit to observed data when compared against alternative model structures (see Table 4).

Model Parameters

Many model parameters were fixed to values determined in previous studies (Table 1). The values and ranges for the durations of incubation and symptoms were derived from a meta-analysis of norovirus outbreak data.[27] Data from challenge studies have shown that the duration of asymptomatic infection is highly variable and little is known about how infectious individuals are during this asymptomatic shedding period.[28] The value for the duration of asymptomatic infection in the model is derived from data from a challenge study [28], however this parameter was assigned wide range to reflect the high amount of uncertainty. The duration of immunity was obtained from a previous modelling study that estimated duration of immunity to be more long term than what challenge studies have previously estimated.[35] The age specific probabilities of for clinical outcomes given cases of norovirus were calculated previously by dividing the number of individuals that had the clinical outcome by the number of norovirus cases that occurred in a specific age group.[73]

The model assumes that exposed and asymptomatic individuals contribute to transmission, and they are assumed to be 5% (ε=0.05) as infectious as individuals with symptomatic infections. This assumption is based on data of the secondary transmission rates of norovirus in hospital settings [29,30], and the value for this parameter was derived from a previous modelling study.[35] The duration of vaccine acquired immunity and duration of asymptomatic infection in vaccinated individuals is assumed to be the same the durations of natural immunity and natural asymptomatic infection. The age-specific contact rates (c_{ij}) and total number of daily contacts (b_i) were obtained from the POLYMOD dataset (Appendix A).[77]

Model Fitting

As the processes embodied by the seasonality (β1 and ω) and transmission parameters (q_1, q_2 and q_3) cannot be directly observed, model fitting was used to estimate these parameters. Model fitting was conducted using the statistical program R version 3.1.1, and the nloptr and deSolve packages [78–80]. Maximum likelihood estimation was used to fit the model to data collected on the monthly number of hospitalizations due to norovirus in the United States between 1996 and 2007 [12]. The monthly number of hospitalizations was assumed to be Poisson distributed.[81] 95% confidence intervals were obtained for each of the estimated parameters. The number of infections in age group *i* resulting from an infection in any age group was calculated as follows:

$$q_i * b_i * \mu_a$$

where q_i represents the age specific susceptibility to norovirus infection, b_i the total number of contacts that age group *i* makes, and μ_a the duration of symptomatic infection.

Vaccine Scenarios

Vaccines in this model are assumed to confer protection similar to that of natural immunity, therefore vaccines provide protection against disease, but not against infection (Figure 1). Additionally, vaccines are assumed to be "take-type;" either protection to disease is fully conferred or protection is not conferred and the vaccinated individual is fully susceptible to disease. The proportion of individuals protected by vaccines (v) was calculated as follows:

$$v = p * \gamma$$

where p is the proportion of individuals covered by the vaccine and γ represents the efficacy of the vaccine.

After model fitting, we explored four age-targeting vaccine scenarios. The two base case scenarios were: routine immunization of infants around the time of birth with vaccine coverage of 90% and vaccine efficacy of 50% (scenario A); and routine immunization of individuals turning age 65 and every five years after with vaccine coverage of 65% and vaccine efficacy of 50% (scenario B). We also explore two alternative vaccine scenarios: routine immunization of infants around the time of birth with vaccine coverage of 90% and vaccine efficacy of 90% (scenario C) and routine immunization of individuals turning age 65 and every five years after with vaccine coverage of 65% and vaccine efficacy of 90% (scenario D). Infants and the elderly were chosen for vaccination target populations as these two age groups are more susceptible to severe outcomes of disease.[11–13] Vaccine coverage values for these scenarios are based on data of the current age-specific uptake of vaccines, such as measles and influenza vaccines.[82–84] Vaccine efficacy values for the base case scenarios, scenarios A and B, are based on the limited data available on the

efficacy of current norovirus vaccines under development.[57,58] For scenarios C and D, a more optimistic value for efficacy was chosen to assess the potential impact of a highly efficacious vaccine.

Analyses pertaining to the impact of each vaccine scenario were conducted 10 years after the introduction of vaccines to ensure the system reached achieved a stable equilibrium. For each of the four vaccine scenarios—and for a scenario without vaccination—we estimated the age specific incidence of disease. To assess the potential impact of vaccination we calculated the number of clinical outcomes averted (cases, outpatient visits, ED visits, hospitalizations and deaths) as well as the direct and indirect effects of vaccination for each vaccine scenario. The number of clinical outcomes averted was calculated by subtracting the number of clinical outcomes that occurred under a given vaccine scenario from the number of clinical outcomes that occurred under the scenario without vaccination. Indirect effects of vaccination were calculated by dividing the number of clinical outcomes averted under a given vaccine scenario by the number of clinical outcomes that occurred without vaccination. The direct effects of vaccination were calculated using the following formula described by Pitzer et. al., 2012:

$$DE_{y,k} = \frac{\sum_{w=1}^{52y} \sum_i v_{i,w}\, x_{i,w_{pv}} VE_k}{\sum_{w=1}^{52y} \sum_i x_{i,w_{pv}}}$$

where $w = 1$ represents the week when vaccines are introduced; $52y$ represents the number of weeks for y years of vaccination; $v_{i,w}$ is the proportion of vaccinated individuals in age group *i* at week *w*; $x_{i,w_{pv}}$ is the number of norovirus cases in age group *i* during an average pre-vaccination week w_{pv}; and VE_k is the vaccine efficacy for scenario k.[85]

Parameter Uncertainty Analysis

To explore the effect of uncertainty in the values for the fixed and estimated parameters on the predicted outcome of the model, an uncertainty analysis was conducted on key parameters, using the statistical program R version 3.1.1, and the lhs and deSolve packages.[80,86] Table 1 identifies the parameters included in the uncertainty analysis and the range of values that were tested. Latin hypercube sampling was used to create a random sample of parameter values given the range and distributions specified for each parameter. Each model scenario (four vaccine scenarios and no vaccine scenario) was run 1,000 times with the randomly sampled parameter sets. The number of clinical outcomes averted annually was calculated, as described above, for all 1,000 model runs. The median values for clinical outcomes are reported along with 95% confidence intervals.

CHAPTER 3: RESULTS

Model Fitting

Alternative model structures produced different estimates for the age-specific transmission probabilities. Particularly, the two alternative models that represented q_i as the infectivity of age group *i* to all other age groups, had high transmission probabilities for 0-4 year olds (q1 ≈ 0.3) and all older age group probabilities were essentially equal to 0 (see alternative models 2 and 3 in Table 4). Being as it is highly unlikely that only 0-4 year olds contribute to the transmission of norovirus,[35] the alternative model structures were rejected as implausible. Of the two models that represent q_i as the susceptibility of age group *i* to all other age groups, the model that used 3 transmission probabilities (q1, q2, q3) exhibited a better fit to the observed data than the model that used 2 transmission probabilities (q1, q2) (see alternative models 1 and 4 in Table 4). Thus the model with three transmission probabilities, represented as the susceptibility of age group *i* to all other age groups, was selected for further analysis.

The model produced a qualitatively good fit to the US monthly hospitalization data for each of the four age groups (Figure 2B). Relative to the 3 alternative models explored, the model chosen for analysis provided the best fit to the data with the smallest negative log likelihood (NLL=239847.7; Table 4). The observed average annual number of hospitalizations due to norovirus was approximately 69,696 while the model predicted 70,457 hospitalizations annually (Figure 2A). Estimates and 95% confidence intervals for the values for the seasonality (β1 and ω) and transmission probabilities (q_1, q_2 and q_3) are reported in Table 3. A mild seasonal forcing function, representing approximately a 3% increase in the proportion of infectious contacts, produced a fairly good fit to the observed

seasonal fluctuations in the US monthly hospitalization data (β_1=0.0337; 95% CI: 0.0335, 0.0340) (Figure 2B, Table 3). The estimated age specific transmission probability for 0-4 year olds (q1=0.20839; 95% CI: 0.20717, 0.20951) was approximately 7 times larger than the 5-64 year old transmission probability (q2=0.03173; 95% CI: 0.03168, 0.03180) and approximately 11 times larger than the 65 years old and older transmission probability (q3=0.01960; 95% CI: 0.01951, 0.01969). The youngest age group, 0-4 year olds, are predicted to have the highest susceptibility to norovirus with approximately 3.38 infections resulting from an infection from any age group. The older age groups are less susceptible to infection, as 1.86 and 0.33 infections occur in 5-64 year olds and 65 year and older, respectively, from an infection from any age group.

Vaccine Scenarios

Infant Immunization Strategies

For both infant immunization programs (scenarios A and C), after the introduction of the vaccine program, there was a rapid reduction in the incidence of disease in the youngest age class (0-4 year olds). For the first several years of these vaccine programs the incidence of disease in 0-4 year olds exhibited modest inter-annual variability, then reached a new stable equilibrium of lower incidence of disease (Figure 3A).

Vaccine scenario A at equilibrium was predicted to avert 1,478,182 cases, 237,099 outpatient visits, 26,079 ED visits, 6,318 hospitalizations and 9.23 deaths in the 0-4 year old age class over a one year time period. This represents about a 33% reduction in all five clinical outcomes in this age class (Table 5). In the total population, vaccine scenario A was predicted to avert 3,510,447 (21%) cases, 428,167 (23%) outpatient visits, 76,262

(19%) ED visits, 15,292 (21%) hospitalizations and 147 (19%) deaths over a one year time period (Table 5). This vaccine scenario was predicted to provide modest direct and indirect protection to the targeted age group, with 23% of cases in 0-4 year olds averted through direct effects and 10% of cases in 0-4 year olds through indirect effects. Indirect benefits were conferred to the other age groups in the population through vaccine scenario A as 14-16% of cases in 5 years and older age classes were averted through indirect effects (Figure 5A, Table 5).

There was a considerable amount of uncertainty in the number of clinical outcomes averted in scenario A as exhibited by the wide confidence intervals associated with the estimates presented in Table 5. For example, the 95% confidence interval for the number of cases averted in the 0-4 year old age group under this vaccine scenario ranged from -1,004,468 cases averted (meaning there were more cases when vaccines were implemented relative to when there were no vaccines) to 3,742,005 cases averted over a one year time period (Figure 6A, Table 5).

Increasing the efficacy of vaccines in scenario C resulted in higher numbers of clinical outcomes averted both within the vaccinated age group, 0-4 year olds, and in the total population (Appendix B). Briefly, this vaccine scenario was predicted to avert approximately 59% of cases in 0-4 year olds with both direct and indirect effects, and 27-31% of cases were averted in 5 years and older age classes through indirect effects (Figure 5C). The amount of uncertainty in the number of clinical outcomes averted in this infant vaccine strategy remained high (Figure 6C, Appendix B).

Both infant immunization strategies led to increases in the proportion of susceptible individuals in the older age classes. Notably, the average percent of the elderly population

that was susceptible to norovirus increased from approximately 85% to approximately 87% under vaccine scenario A (Figure 4A). Under vaccine scenario C, the average percent of the elderly population that was susceptible to norovirus increased from approximately 85% to approximately 89% after the introduction of vaccines (Figure 4C).

There was a weak, positive correlation between the percent of cases averted over a 1 year time period and the duration of vaccine immunity in both of the infant vaccination strategies. For scenario A the correlation coefficient, $\rho = 0.09$, is statistically significant (p-value=0.007). The correlation is slightly stronger for scenario C ($\rho = 0.19$, p-value<0.001), but still indicates a weak relationship between the duration of vaccine induced immunity and the percent of cases averted (Figures 7A and 7C).

Elderly Immunization Strategies

For both elderly immunization programs (scenarios B and D), after the introduction of the vaccine program, there was a slow and gradual reduction in the daily incidence of disease in the elderly (65 year old and older). These vaccine programs are predicted to take many years, approximately 9 years, to reach a new stable equilibrium of lower incidence of disease (Figure 3B). Both elderly immunization strategies resulted in negligible changes to the percent of susceptible individuals in the younger age classes (Figures 4B and 4D).

Vaccine scenario B at equilibrium was predicted to avert 259,648 cases, 24,819 outpatient visits, 7,923 ED visits, 4,683 hospitalizations and 113 deaths in the 65 years old and older age class over a one year time period. This represents approximately a 16% reduction in all five clinical outcomes in this age class (Table 5). In the total population, vaccine scenario B was predicted to avert 330,149 (1.91%) cases, 31,643 (1.71%)

outpatient visits, 9,420 (2.46%) ED visits, 4,683 (2.46%) hospitalizations and 113 (15%) deaths over a one year time period (Table 6). This vaccine scenario, over a one year time period, was predicted to avert 16% of cases in 65 years and older primarily through direct effects; the indirect effects in this age class were negligible. Minimal indirect benefits were conferred to the other age groups in the population as less than 1% of cases in 0-64 year olds were averted through indirect effects (Figure 5B). There was minimal uncertainty in the number of clinical outcomes averted in scenario B. The 95% confidence interval for the number of cases averted in the elderly age group under this vaccine scenario ranged from 24,272 to 589,350 cases averted over a one year time period (Table 6, Figure 6B).

Increasing the efficacy of vaccines in vaccine scenario D produced modest increases in the number of clinical outcomes averted within the elderly age group, and resulted in minimal changes to the number of clinical outcomes averted in the rest of the population (Appendix C). This vaccine scenario was predicted to avert approximately 26% of cases elderly primarily through direct effects, and less than 1% of cases were averted in the younger age classes through indirect effects (Figure 5D). There was a minimal amount of uncertainty in the number of clinical outcomes averted in scenario D (Figure 6D, Appendix C).

The duration of vaccine immunity had a strong, positive correlation to the percent of cases averted over a 1 year time period in the two elderly vaccine strategies. In vaccine scenario B, the percent of cases averted in the elderly age class more than doubles as the duration of vaccine immunity increases from 1,400 days to 2,400 days ($\rho = 0.70$, p-value<0.001) (Figure 7B). In vaccine scenario D, the percent of cases averted in the elderly

age class nearly triples as the duration of vaccine immunity increases from 1,400 days to 2,400 days ($\rho = 0.69$, p-value<0.001) (Figure 7D).

Efficiency of Vaccine Strategies

Both of the infant immunization strategies were highly efficient with respect to clinical outcomes averted per dose of vaccine. One year of vaccine scenario A was predicted to avert 91,410 cases, 11,328 outpatient visits, 2,036 ED visits, 395 hospitalizations and 4 deaths in the population with every 100,000 doses of vaccines administered (Table 7). The efficiency of infant immunization increased with increasing vaccine efficacy; vaccine scenario C was predicted to avert 170,712 cases, 20,720 outpatient visits, 3,842 ED visits, 732 hospitalizations and 7 deaths in the population, with every 100,000 doses of vaccines administered (Table 7).

The elderly vaccination strategies were predicted to have low efficiency with regards to clinical outcomes averted per dose of vaccine. Vaccine scenario B was predicted to avert 5,120 cases, 516 outpatient visits, 158 ED visits, 75 hospitalizations and 2 deaths in the population with every 100,000 doses of vaccines administered (Table 7). When the efficacy of vaccines were increased in scenario D the efficiency of the program improved slightly. One year of this vaccine scenario D was predicted to avert 9,286 cases, 937 outpatient visits, 287 ED visits, 136 hospitalizations and 3 deaths in the population with every 100,000 doses of vaccines administered (Table 7).

CHAPTER 4: DISCUSSION

This study is among the first to quantitatively assess the potential impact of norovirus vaccines in the United States using a dynamic transmission model. The results of this study suggest that the overall potential impact of norovirus vaccines on the clinical outcomes of disease can vary substantially by targeting different age groups for vaccination. Of the four vaccine scenarios tested, the two infant immunization strategies, scenarios A and C, were predicted to have the highest reductions in the clinical outcomes of disease, with indirect benefits for the entire population (scenario A: % cases averted in population = 21%; scenario C: % cases averted in population = 39%). The two elderly vaccination strategies (scenarios B and D) were predicted to provide protection to the elderly through direct effects of the vaccine, while providing minimal indirect protection to the rest of the population (scenario B: % cases averted in population = 2%; scenario D: % cases averted in population = 3%).

Interestingly, the infant immunization strategies are predicted to confer protection to the elderly age group that is similar to the protection that an elderly vaccine would confer. Scenarios A and C were predicted to avert 18% and 35%, respectively, cases of norovirus illness in the elderly while scenarios B and D were predicted to avert 16% and 25%, respectively, cases of norovirus illness in the elderly. The infant immunization strategies were also predicted to be more efficient than the elderly immunization strategies, as the infant immunization strategies consistently averted more clinical outcomes in the total population per dose of vaccine administered.

Taken together, these results indicate that targeting young children for vaccination results in greater direct and indirect benefits to the total population than vaccine programs

that target the elderly. The infant immunization strategies provide indirect benefits to the population because vaccinating young children reduces transmission to the older age groups. The elderly contribute very little to transmission, therefore vaccination of the elderly will result in minimal reductions in transmission and subsequently will provide minimal indirect benefits. Similar trends of large indirect benefits when vaccinating young children have been seen with other vaccination programs. Observational studies have shown that the introduction of rotavirus vaccines in the US has not only reduced the incidence of rotavirus among vaccinated individuals, but has also resulted in substantial declines of rotavirus gastroenteritis in unvaccinated populations.[84,87] Similarly, the introduction of pediatric pneumococcal vaccines in the US lead to reductions of invasive pneumococcal disease in unvaccinated adults.[88] These indirect effects of vaccinating young children in both rotavirus and pneumococcal vaccine programs were attributed to reductions in overall disease transmission.[87,88]

The finding of the importance of young children in the transmission of norovirus has been also been observed in previous studies.[5,35,75] Observational studies that determined the community incidence of norovirus have indicated that a high risk of infection for older children and adults results from contact with young children who are symptomatically infected with norovirus.[5,75] A mathematical modelling study conducted by Simmons et. al. predicted that young children (0-4 year olds) contribute more to transmission than older age groups. The models developed by Simmons et. al. were fit to community incidence data collected in the United Kingdom.[35] The model in the present study was fit to data collected on the monthly number of hospitalizations in the US.

Therefore the prediction of the importance of young children in the transmission of norovirus is consistent for data pertaining to both the US and the UK.

A second important finding from this study is that the influence of the duration of vaccine induced immunity on the predicted impact of vaccines differs between the vaccine scenarios. The duration of vaccine immunity had a strong, positive correlation to the percent of cases averted in the two elderly vaccine strategies, such that increases in the duration of vaccine induced immunity would significantly increase the percent of cases averted (scenario B: $\rho = 0.70$, p-value<0.001; scenario D: $\rho = 0.69$, p-value<0.001). This correlation between percent of cases averted over a 1 year time period and the duration of vaccine immunity was not as strong for the two infant strategies, however there were slight increases in the percent of cases averted as the duration of vaccine induced immunity increases (scenario A: $\rho = 0.09$, p-value=0.007; scenario C: $\rho = 0.19$, p-value<0.001). The weaker correlation observed for the infant immunization strategies suggests that the duration of vaccine immunity alone does not explain the variation in the percent of cases averted well. This further suggests that other model parameters, such as the more influential parameters involved in disease transmission, may provide an additive effect to the impact of these vaccine scenarios. In contrast, the impacts of the elderly vaccine scenarios have very strong, positive relationships with the duration of vaccine immunity. Therefore vaccine programs that target the elderly for vaccination would greatly benefit from vaccines that have longer durations of protection.

The amount of uncertainty surrounding the model predictions of the clinical outcomes averted is much higher for the infant immunization strategies relative to the elderly immunization strategies. This indicates that the impacts of the infant vaccination

strategies are highly sensitive to uncertainties in the parameter values that were tested, particularly the parameters that govern disease transmission (i.e. transmission probabilities, natural history parameters). As the infant immunization strategies are predicted to reduce transmission, resulting in indirect benefits to the population, the uncertainty surrounding the parameters involved in transmission are reflected in the predicted impact of the vaccine strategy. In contrast, the elderly immunization strategies are predicted to have minimal influence on disease transmission, and subsequently provide minimal indirect benefits to the population, therefore the predicted impact of these vaccine strategies are less sensitive to the uncertainty surrounding the parameters that govern transmission.

There are several limitations to this study that need to be considered. First, the model in this study assumes a single-strain of norovirus, therefore infection from, or vaccination against, one strain of norovirus will provide protection against all other infections. This assumption is a simplification that is not necessarily true, as noroviruses are highly genetically diverse and natural immunity provides limited cross-protection.[89] Influenza vaccination programs have demonstrated reductions in the effectiveness of vaccines due to the genetic diversity of the virus. For example, for the 2014-2015 influenza season the vaccine formulation did not contain the predominant circulating strains, thus the estimated vaccine efficacy was much lower than previous influenza seasons.[90] Additionally, novel GII.4 strains emerge every few years and evade host acquired immunity. Both the limited cross-protective immunity of vaccines, and the emergence of novel GII.4 strains of norovirus could reduce both the direct and indirect impacts of vaccines, therefore the estimates of the impacts of vaccines from this study may be overestimated.

A second limitation of this study is the large amount of uncertainty in model parameters. This uncertainty is due to the limited understanding of natural history of norovirus illness, particularly the durations of asymptomatic infectious period and natural immunity. Data from challenge studies have shown that the duration of asymptomatic shedding is highly variable between individuals; it has been documented to begin as short as 18 hours after exposure and as long as eight weeks post exposure.[28] In addition to the duration of asymptomatic shedding being highly variable, little is known about how infectious individuals are and at what times during this asymptomatic shedding period individuals are most infectious.[28,91] Therefore this study accounts for that uncertainty with a wide range for the duration of asymptomatic infectious period. For the duration of natural immunity, clinical studies have shown that the duration is short term (six months to two years).[31–34] However, mathematical modelling studies suggest the duration of immunity to norovirus is long term, around four to six years.[35] Additionally, the way in which waning immunity occurs is not well understood. The model assumes that natural immunity wanes exponentially, thus the majority of individuals have a duration of immunity that is shorter than the assigned duration of 5.3 years. While the traditional SEIR model framework assumes exponential waning,[70] compartmental models can be modified to assume a gamma distribution for the waning of immunity, which allows a slower waning process than an exponential distribution.[92]

Another limitation of this study is that while the model is designed to reflect norovirus transmission in the US, it relies on contact data from European countries. The contact data used for the model was an average of eight countries represented in the POLYMOD study (Appendix A).[77] While the averaged contact data most likely

represents, on average, the contact structure of a developed country, this averaged data may not accurately reflect the contact structure within the US. To achieve better estimates of the impact of norovirus vaccines in the US, there is a need for studies to collect data on the contact structure in the US, similar to what was done for the POLYMOD study.[77]

Finally, while the model predicts the impacts of infant and elderly vaccinations, there have been no studies of the efficacy of this vaccine in pediatric populations and only one study has explored the immunogenicity of vaccines in the elderly. The vast majority of current vaccine development studies have focused on the safety, immunogenicity and efficacy of vaccines in adults (ages typically ranged from 18-49 years old).[55–58,93] One study, however explored the immunogenicity of vaccines in adults (18-49 years old) as well as the elderly (two age groups: 50-64 and 65-83 years old), and found that vaccines were well tolerated and produced robust immune responses in all age groups.[59] While these results are promising, it remains to be seen if this vaccine will be effective in young children.

Though this study has made simplifying assumptions, this dynamic transmission model was able to capture the impact of vaccination on the disease transmission process. The model therefore provides a better understanding of both the indirect and direct benefits of vaccination, whereas previous studies predicting the potential impact of vaccination only captured the direct effects of vaccination.[73] This study also highlights the vast differences in the population-level impacts of vaccines that target young children versus vaccines that target the elderly. The results of this study have important implications for vaccine development and policy. This modelling analysis demonstrated that population-level impacts of norovirus vaccination may be maximized by vaccinating young children,

due to their importance in transmission. Currently, vaccine development studies have focused on determining the safety, immunogenicity and efficacy of norovirus vaccines in adults.[56,58–60] Given the findings of this study, vaccine development studies could benefit from exploring the safety, immunogenicity and efficacy of norovirus vaccines in young children.

To improve our understanding of the potential impact of norovirus vaccines, better data on the duration of immunity and extent of cross-protection provided by norovirus vaccines are needed. Additionally, future modelling studies may want to consider incorporating norovirus strain diversity to examine the potential limitations of vaccination when multiple, evolving strains of norovirus exist. Given the emergence of novel strains of GII.4 noroviruses every few years, several in the scientific community have suggested the potential need to re-formulate norovirus vaccines every few years, similar to influenza vaccine development.[54,57,94] One recent study suggests however that norovirus vaccines may not need to be re-formulated.[63] As more data becomes available on vaccine efficacy, the extent of cross-protection against multiple strains, and the duration of immunity provided by norovirus vaccines, modelling studies can be adapted to reflect more precise estimates of the impact of vaccination at a population-level.

As the model presented in this study focuses on the population-level impacts of vaccination, future modelling studies may want to examine the impact of vaccination in outbreak settings. The results of this study indicate that an infant immunization strategy may increase the percent of susceptible individuals in the older, unvaccinated age groups (Figure 4), which may lead to more outbreaks occurring in these populations. Of particular concern are the groups of people in long-term care facilities, where the majority of

norovirus outbreaks occur.[95] Therefore future modelling studies could examine whether vaccination of long-term care residents could mitigate, or even prevent outbreaks of norovirus in these settings.

Future studies should also evaluate the cost effectiveness of these age targeted vaccine strategies. Previous economic analyses of the impact of norovirus vaccines have predicted that cheap vaccines ($25 - $50 per dose), with a duration of protection of 48 months and vaccine efficacy ≥ 50% could reduce the total cost of norovirus (including direct and indirect costs of illness) in the US between $100 million and $2.1 billion.[73] This previous economic analysis however, was based on the estimated direct effect of vaccines therefore those cost effectiveness estimates were likely underestimated.[73] In the present study, both direct and indirect effects of vaccination are considered, therefore an economic analysis of the impact of vaccination predicted by this model could provide a more accurate assessment of the potential economic benefit of age targeted norovirus vaccine programs.

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FIGURES

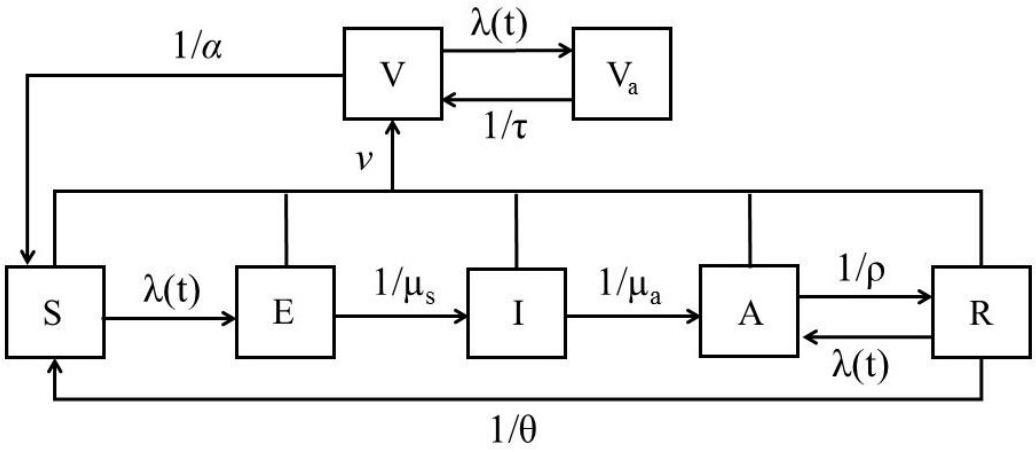

Figure 1: Model schematic of the movement between six states of norovirus infection. In the absence of vaccination, persons are born directly into the susceptible pool (S), become exposed at the force of infection (λ), and then progress through the exposed (E), symptomatic (I) and asymptomatic (A) stages at rates inversely proportional to the duration of these states ($1/\mu_s$, $1/\mu_a$, $1/\rho$) before entering the recovered compartment (R). From the recovered compartment, persons can become asymptomatically infected at the force of infection or can become susceptible to disease through the waning of natural immunity ($1/\theta$). In the presence of a vaccination, susceptible individuals move into the vaccinated compartment (V) at the rate of vaccination (ν). Vaccinated individuals can become asymptomatically infected at the force of infection or can become susceptible to disease through the waning of vaccine immunity ($1/\alpha$).

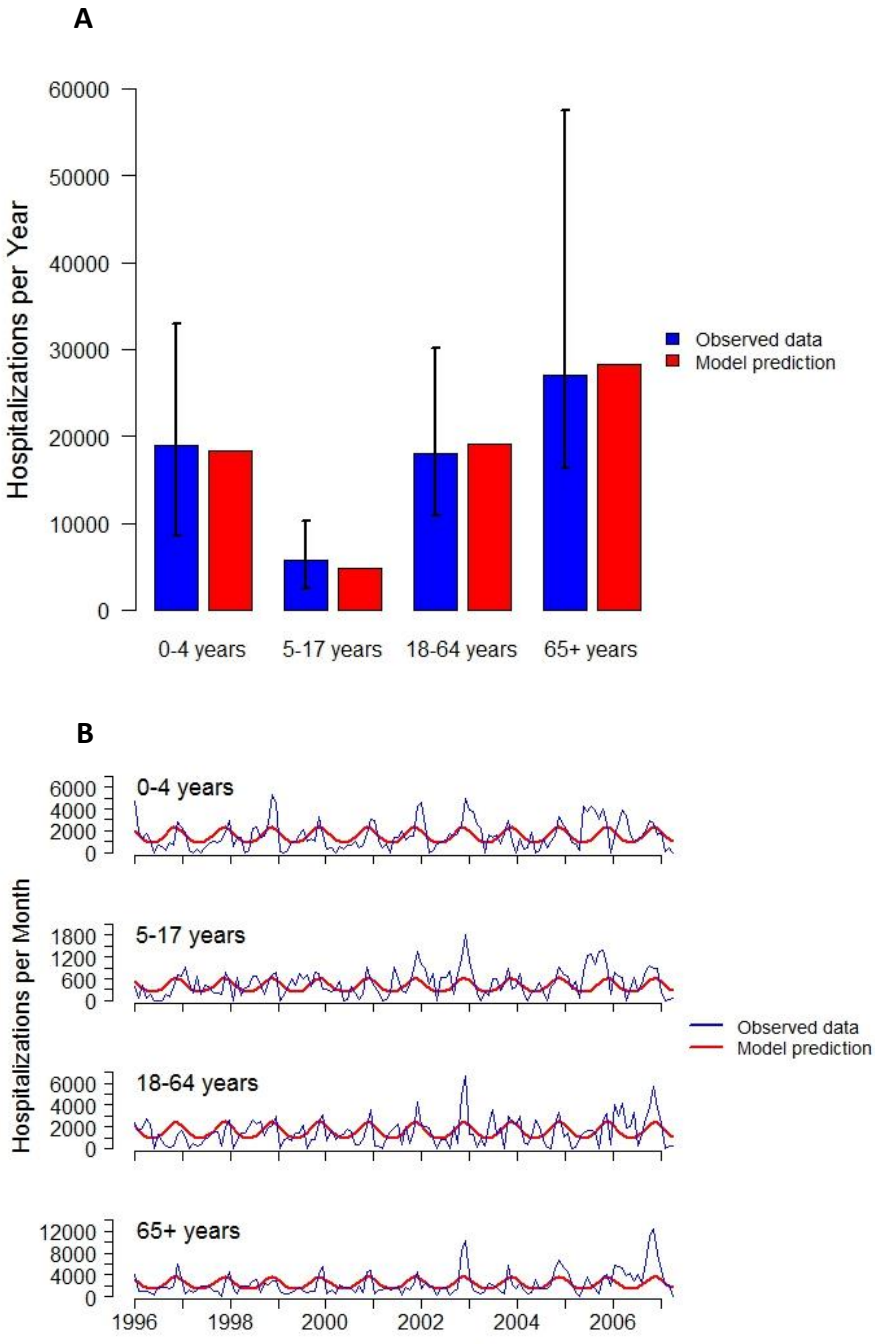

Figure 2: A Age-specific observed number of hospitalizations per year compared to predicted annual number of hospitalizations. **B** Model prediction of number of hospitalizations due to norovirus for four age groups fit to data collected between 1996 and 2007. The blue line represents the observed data while the red line represents model predictions.

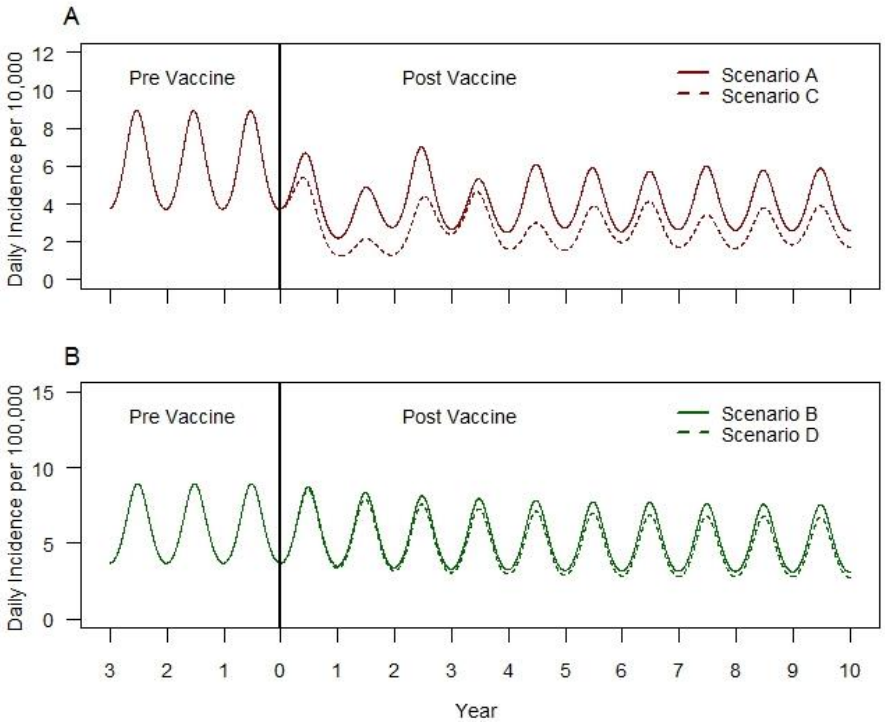

Figure 3: Predicted reductions in the incidence of disease within the age-group targeted for vaccination over time. The top panel shows the impact of the two infant immunization strategies on incidence of disease in 0-4 year olds. The solid line represents a vaccine program with 90% coverage and 50% efficacy (scenario A) while the dashed line represents the vaccine program with 90% coverage and 90% efficacy (scenario C). The bottom panel shows the impact of the two elderly immunization strategies on incidence of disease in 65 year olds and older. The solid line represents the vaccine program with 65% coverage and 50% efficacy (scenario B) while the dashed line represents the vaccine program with 65% coverage and 90% efficacy (scenario D).

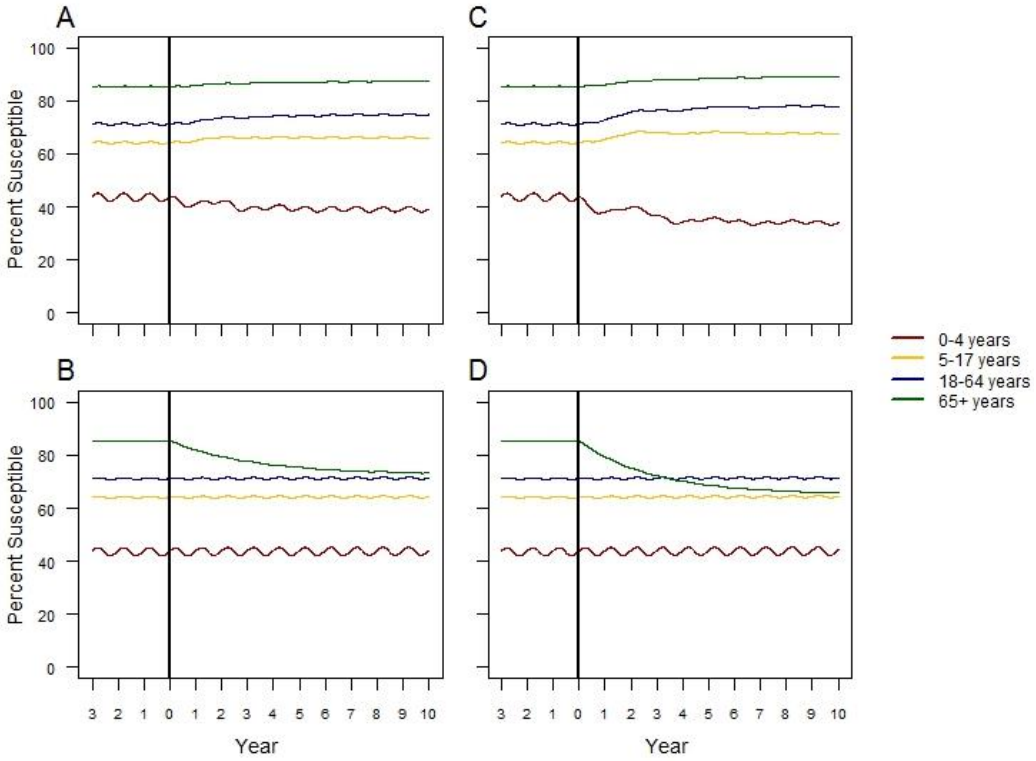

Figure 4: Predicted changes over time in the proportion of susceptible individuals within each age-group for each vaccine strategy. **A:** Changes in the susceptibility profiles under an infant immunization program with 90% coverage and 50% efficacy (scenario A). **B:** Changes in the susceptibility profiles under an elderly immunization program with 65% coverage and 50% efficacy (scenario B). **C:** Changes in the susceptibility profiles under an infant immunization with 90% coverage and 90% efficacy (scenario C). **D:** Changes in the susceptibility profiles under an elderly immunization program with 65% coverage and 90% efficacy (scenario D).

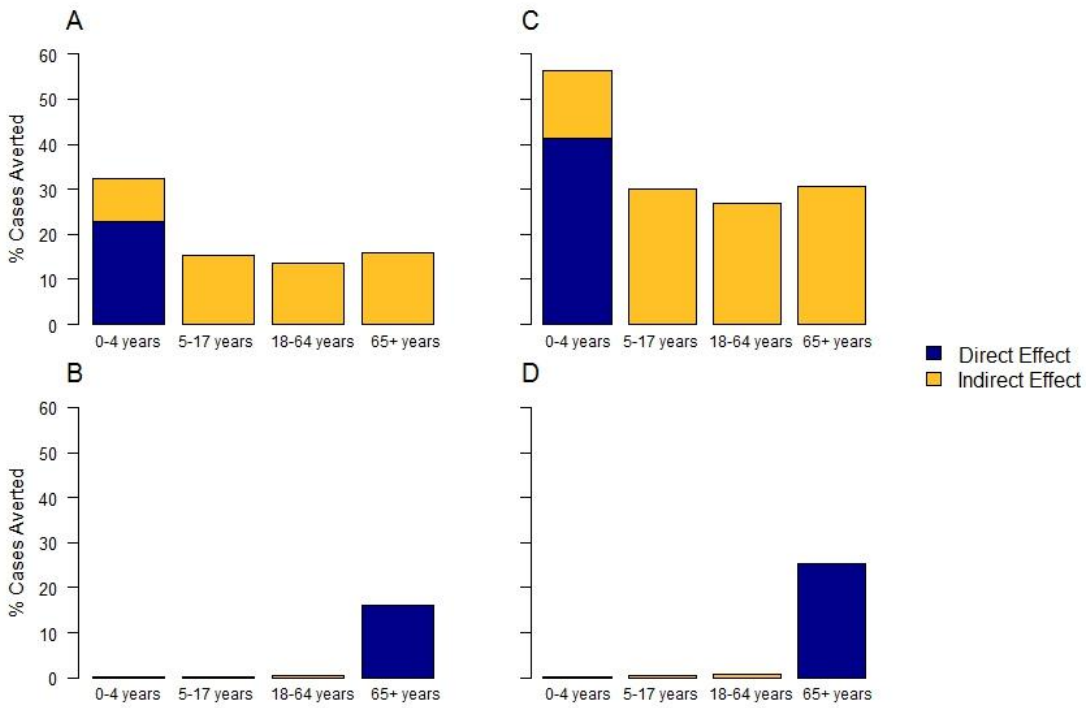

Figure 5: Comparison of the direct (blue) and indirect effects (yellow) of vaccines for each vaccine scenario. **A:** infant vaccine with 90% coverage and 50% efficacy. **B:** elderly vaccine with 65% coverage and 50% efficacy. **C:** infant vaccine with 90% coverage and 90% efficacy. **D:** elderly vaccine with 65% coverage and 90% efficacy.

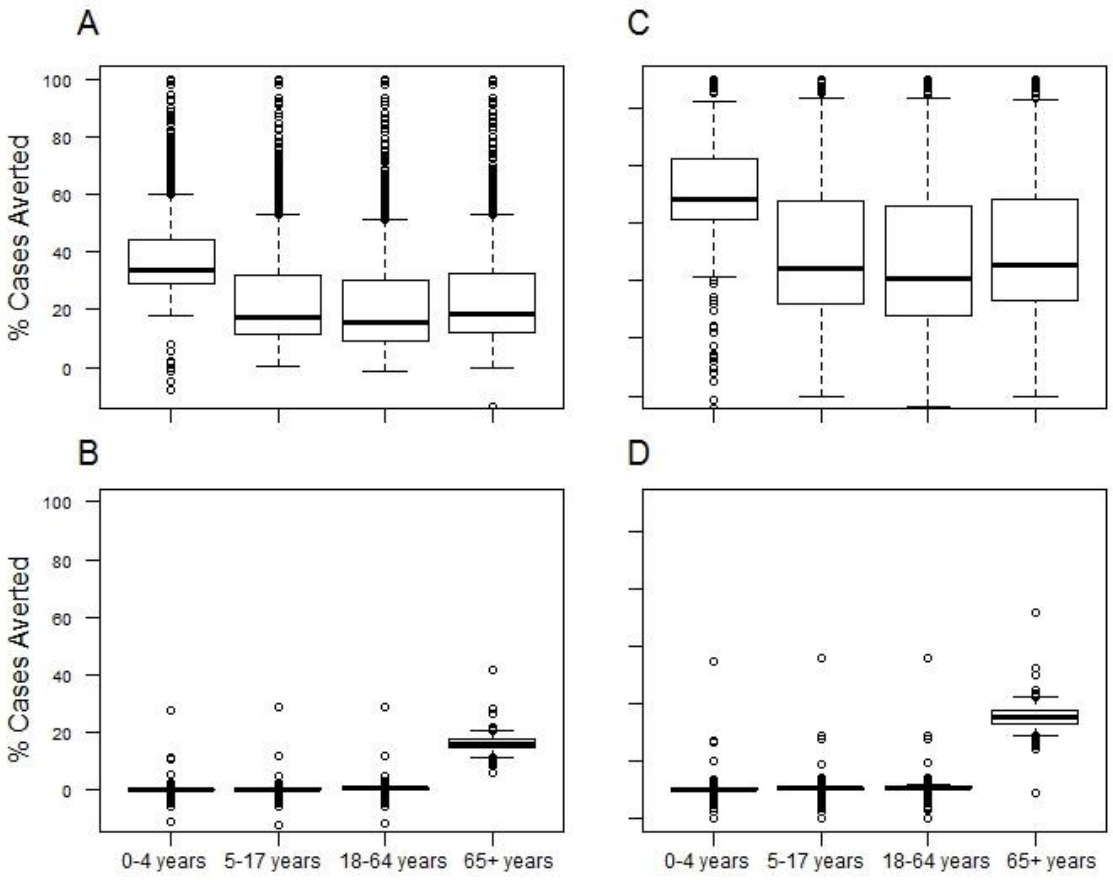

Figure 6: Boxplots representing the range of uncertainty in the percent of cases averted over a one year time period, given uncertainty in parameter input values. **A:** infant vaccine with 90% coverage and 50% efficacy. **B:** elderly vaccine with 65% coverage and 50% efficacy. **C:** infant vaccine with 90% coverage and 90% efficacy. **D:** elderly vaccine with 65% coverage and 90% efficacy.

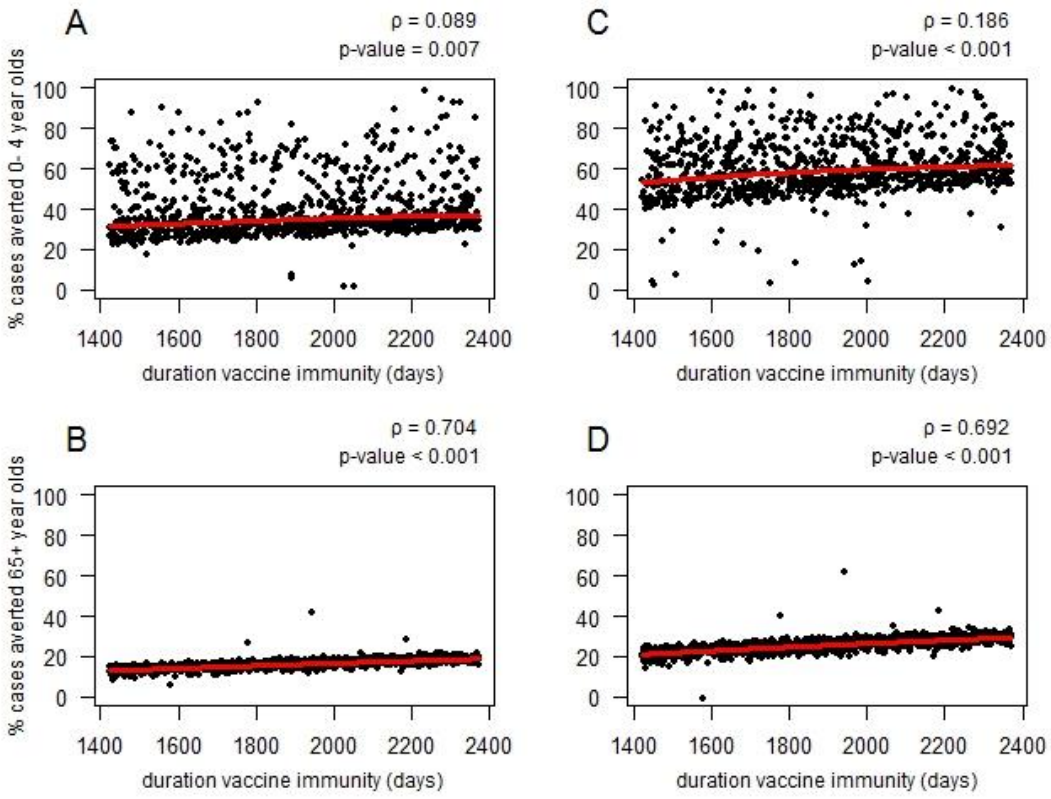

Figure 7: Scatterplots, with LOWESS regression lines, of the correlation of % cases averted in targeted age group and the duration of vaccine immunity (α) for each of the four vaccine scenarios. Each panel also presents the correlation coefficient (ρ) and associated p-value. **A:** infant vaccine with 90% coverage and 50% efficacy. **B:** elderly vaccine with 65% coverage and 50% efficacy. **C:** infant vaccine with 90% coverage and 90% efficacy. **D:** elderly vaccine with 65% coverage and 90% efficacy.

TABLES

Table 1. Parameter input values, ranges tested in uncertainty analyses, and sources values and ranges are derived from

Parameter	Input value	Range	Distribution	Source
Transmission/Susceptibility				
q1	0.208	+/- 10%	Uniform	Estimated
q2	0.032	+/- 10%	Uniform	Estimated
q3	0.020	+/- 10%	Uniform	Estimated
Duration of incubation period	32.8 hours	(30.9 – 34.6)	Uniform	Devasia et al 2014 [27]
Duration of symptomatic infection	48 hours	(38.9 – 50.7)	Uniform	Devasia et al 2014 [27]
Duration of asymptomatic infection	10 days	(1-20)	Uniform	Atmar et. al 2008 [28]
Duration of natural immunity	5.1 years	(3.9–6.5)	Uniform	Simmons et. al 2013 [35]
Relative infectiousness during incubation and asymptomatic period	0.05	+/- 10%	Uniform	Model Assumption
Duration of asymptomatic infection among vaccinated	10 days	(1-20)	Uniform	Model Assumption
Duration of vaccine immunity	5.1 years	(3.9–6.5)	Uniform	Model Assumption
Outpatient visit rate				
0-4 years	0.168	(0.100–0.235)	Uniform	Bartsch et al 2012 [73]
5-17 years	0.168	(0.111–0.226)	Uniform	Bartsch et al 2012 [73]
18-64 years	0.06	(0.019–0.106)	Uniform	Bartsch et al 2012 [73]
65+ years	0.103	(0.063–0.143)	Uniform	Bartsch et al 2012 [73]
Hospitalization rate				
0-4 years	0.00428	+/- 0.000178	Normal	Bartsch et al 2012 [73]
5-17 years	0.00182	+/- 0.000074	Normal	Bartsch et al 2012 [73]
18-64 years	0.00228	+/- 0.000092	Normal	Bartsch et al 2012 [73]
65+ years	0.01733	+/- 0.000709	Normal	Bartsch et al 2012 [73]
Death rate				
0-4 years	0.00000625	+/- 2.57×10^{-7}	Normal	Bartsch et al 2012 [73]
5-17 years	0.00000466	+/- 1.81×10^{-7}	Normal	Bartsch et al 2012 [73]
18-64 years	0.00000466	+/- 1.81×10^{-7}	Normal	Bartsch et al 2012 [73]
65+ years	0.000435	+/- 0.000018	Normal	Bartsch et al 2012 [73]
Emergency Department visit rate				
0-4 years	0.0179	(0.0112-0.0246)	Uniform	Bartsch et al 2012 [73]
5-17 years	0.0199	(0.0114-0.0280)	Uniform	Bartsch et al 2012 [73]
18-64 years	0.026	(0.0153-0.0368)	Uniform	Bartsch et al 2012 [73]
65+ years	0.0325	(0.0199-0.0452)	Uniform	Bartsch et al 2012 [73]

Table 2: Vaccine Scenarios

Scenario	Age Targeted	Time of Vaccination	Vaccine Coverage	Vaccine Efficacy
A	Infants	Soon after birth	90%	50%
B	Elderly	Age 65, 70, 75, 80 and 85	65%	50%
C	Infants	Soon after birth	90%	90%
D	Elderly	Age 65, 70, 75, 80 and 85	65%	90%

Table 3: Maximum likelihood estimation of fitted parameters

Parameter	Value	95% Confidence Interval
Susceptibility of 0-4 year olds (q1)	0.208	(0.207, 0.210)
Susceptibility of 5-64 year olds (q2)	0.032	(0.032, 0.032)
Susceptibility of 65+ year olds (q3)	0.020	(0.019, 0.020)
Seasonal amplitude (β1)	0.034	(0.034, 0.034)
Seasonal offset (ω)	2.147	(2.140, 2.154)

Table 4: Alternative models exploring different numbers and interpretations of age specific transmission probabilities (q_i).

Model No.	Model Description	Force of infection	No. estimated parameters	Estimated values	Negative Log(L)	AIC
1	The force of infection is dependent on age specific susceptibility parameters (q1 for 0-4 years and q2 for 5+ years). These q parameters determine what proportion of infectious contacts from the community an individual is susceptible to	$\lambda_i(t) = b_i q_i \sum_{j=1}^{4} c_{ij}\, s(t) \frac{(\varepsilon E_j + I_j + \varepsilon A_j)}{N_j}$	4	β1=0.060 ω =2.169 q1=0.262 q2=0.032	289835.0	579679.9
2	The force of infection is dependent on age specific infectivity parameters (q1 for 0-4 years and q2 for 5+ years). These q parameters determine what proportion of infectious contacts from the community are successful	$\lambda_i(t) = b_i \sum_{j=1}^{4} q_j c_{ij}\, s(t) \frac{(\varepsilon E_j + I_j + \varepsilon A_j)}{N_j}$	4	β1= 0.049 ω = 2.361 q1= 0.287 q2= 1.706×10^{-8}	298886.9	597781.9
3	The force of infection is dependent on age specific infectivity parameters (q1 for 0-4 years and q2 for 5+ years). These q parameters determine what proportion of infectious contacts from the community are successful	$\lambda_i(t) = b_i \sum_{j=1}^{4} q_j c_{ij}\, s(t) \frac{(\varepsilon E_j + I_j + \varepsilon A_j)}{N_j}$	5	β1=0.046 ω =2.246 q1=0.282 q2=8.694×10^{-4} q3=2.888×10^{-9}	299138.1	598286.3
4	The force of infection is dependent on age specific susceptibility parameters (q1 for 0-4 years q2 for 5-64 years and q3 for 65+). These q parameters determine what proportion of infectious contacts from the community an individual is susceptible to	$\lambda_i(t) = b_i q_i \sum_{j=1}^{4} c_{ij}\, s(t) \frac{(\varepsilon E_j + I_j + \varepsilon A_j)}{N_j}$	5	β1 =0.033 ω = 2.146 q1= 0.208 q2= 0.032 q3= 0.020	239847.7	479705.6

Table 5: Clinical outcomes averted annually with routine infant immunization with vaccine coverage of 90% and vaccine efficacy of 50% (scenario A).

Age Group	Cases Averted	Outpatients Averted	ED Visits Averted	Hospitalizations Averted	Mortalities Averted	% of Outcome Averted
0-4 years	1,478,182 (-1,004,468, 3,742,005)	237,099 (-171,300, 658,944)	26,079 (-18,061, 69,399)	6,318 (-4,262, 15,927)	9.23 (-6.33, 23.53)	33% (-139%, 95%)
5-17 years	455,551 (-795,667, 1,840,280)	75,018 (-121,841, 302,708)	8,824 (-12,898, 36,119)	839 (-1,439, 3,477)	2.12 (-3.69, 8.53)	17% (-181%, 94%)
18-64 years	1,314,046 (-2,556,335, 5,694,668)	75,459 (-121,596, 374,434)	33,170 (-52,875, 147,656)	2,972 (-5,731, 13,095)	6.09 (-11.68, 26.76)	16% (-188% , 93%)
65+ years	300,670 (-420,659, 1,006,738)	30,221 (-41,081, 97,492)	9,577 (-13,706, 32,950)	5,207 (-7,147, 17,095)	130 (-177, 433)	18% (-181%, 93%)
Total (#)	3,510,447 (-4,686,008, 12,208,002)	428,167 (-438,593, 1,432,168)	79,262 (-96,197, 284,111)	15,292 (-18,407, 50,206)	147 (-200, 493)	
Total (%)	21% (-170%, 94%)	23% (-160%, 94%)	19% (-172%, 94%)	21% (-168%, 94%)	19% (-179%, 93%)	

Table 6: Clinical outcomes averted annually with routine elderly immunization with vaccine coverage of 65% and vaccine efficacy of 50% (scenario B).

Age Group	Cases Averted	Outpatients Averted	ED Visits Averted	Hospitalizations Averted	Mortalities Averted	% Outcome Averted
0-4 years	8,232 (-20,698, 36,301)	1,294 (-3,345, 6,322)	141 (-347, 708)	35 (-90, 159)	0.051 -0.126, 0.229)	0.18% (-2.19%, 1.15%)
5-17 years	9,285 (-9,177, 25,964)	1,493 (-1,309, 4,495)	174 (-169, 520)	17 (-16, 47)	0.043 (-0.043, 0.119)	0.35% (-1.91%, 1.39%)
18-64 years	41,814 (-25,208, 95,936)	2,338 (-1,235, 7,352)	1,037 (-604, 2,667)	95 (-56, 220)	0.194 (-0.116, 0.452)	0.49% (-1.79%, 1.51%)
65+ years	259,648 (24,272, 589,350)	24,819 (2,305, 67,360)	7,923 (692, 21,225)	4,480 (411, 10,461)	113 (11, 257)	16.09% (11.35%, 20.37%)
Total (#)	330,149 (-13,886, 691,548)	31,643 (-1,855, 76,338)	9,420 (17, 23,255)	4,683 (363, 10,638)	113 (11, 258)	
Total (%)	1.91% (-0.58%, 2.76%)	1.71% (-0.73%, 3.13%)	2.46% (0.06%, 4.05%)	6.46% (3.76%, 8.31%)	14.46% (10.35%, 17.96%)	

Table 7: Clinical outcomes averted per 100,000 doses of vaccine over 1 year.

Vaccine strategy	Cases averted per 100,000 doses	Outpatient visits averted per 100,000 doses	ED visits averted per 100,000 doses	Hospitalizations averted per 100,000 doses	Deaths averted per 100,000 doses
scenario A[1]					
0-4 years	39,400	6,619	706	169	0
Total	91,410	11,328	2,036	395	4
scenario B[2]					
65+ years	4,182	431	136	72	2
Total	5,120	516	158	75	2
scenario C[3]					
0-4 years	68,313	11,477	1,223	292	0
Total	170,712	20,720	3,842	732	7
scenario D[4]					
65+ years	7,590	782	247	132	3
Total	9,286	937	287	136	3

1. Infant immunization with 90% coverage and 50% efficacy
2. Elderly immunization with 65% coverage and 50% efficacy
3. Infant immunization with 90% coverage and 90% efficacy
4. Elderly immunization with 65% coverage and 90% efficacy

APPENDECES

Appendix A: Several steps were taken to obtain the proportion of contacts made by age group *i* with age group *j* (c_{ij}). Raw numbers of the age-specific daily number of contacts from eight European countries (Belgium, Germany, Finland, Great Britain, Italy, Luxembourg, The Netherlands and Poland) were collected from the POLYMOD study.[77] Next, these contact data were summed into the four defined age groups of this study (0-4 years, 5-17 years, 18-64 years, and 65+ years). To obtain rates of contact (R_{ij}), the counts of contacts (C_{ij}) were divided by the number of participants in each contact group (N_{ij}):

$$R_{ij} = C_{ij}/N_{ij}$$

As the raw data for contacts made between age groups *i* and *j* are unlikely to be symmetric (meaning each contact between an individual in age group *i* an individual in age group *j* is recorded by both the individual in age group *i* and the individual in age group *j*) due to reporting errors, the contact rates were corrected for differences in reporting by different age groups with the following equation described by Eames et. al.[96]:

$$B_{ij} = (N_i * R_{ij} + N_j * R_{ij})/2N_i$$

Where N_i is the number of individuals in age group *i*, N_j is the number of individuals in age group *j*, and R_{ij} is the contact rate of age group age group *i* with age group *j*. $2N_i$ assumes that contacts of individuals within the sample (N_i) made contacts with individuals outside of the sampled population. Finally, the following equation was used to obtain the proportion of contacts made by age group *i* with age group *j* (c_{ij}):

$$c_{ij} = B_{ij}/a_i$$

Where B_{ij} represents the corrected contact rates (see equation above) and a_i represents the total number of contacts an individual in age group i makes in one day. The table below shows the proportion of contacts made by age group i with age group j (c_{ij}):

	0-4 years	**5-17 years**	**18-64 years**	**65+ years**
0-4 years	0.275823	0.179901	0.505645	0.0386302
5-17 years	0.0342415	0.633432	0.312933	0.019394
18-64 years	0.0463218	0.150616	0.753492	0.04957
65 + years	0.0439444	0.115911	0.61554	0.224605

The total number of contacts each age group makes in one day are as follows:

0-4 years (a_1) = 8.11894

5-17 years (a_2) = 15.5198

18-64 years (a_3) = 13.9435

65+ years (a_4) = 8.5331

Appendix B: Clinical outcomes averted annually with routine infant immunization with vaccine coverage of 90% and vaccine efficacy of 90% (scenario C)

Age Group	Cases Averted	Outpatients Averted	ED Visits Averted	Hospitalizations Averted	Mortalities Averted	% Outcome Averted
0-4 years	2,534,347 (-153,863, 4,726,383)	396,429 (-28,365, 840,550)	43,518 (-3,272, 87,578)	10,747 (-659, 20,280)	15.87 (-.89, 28.97)	58.53% (-15.99%, 100%)
5-17 years	861,697 (-381,587, 2,255,710)	139,167 (-58,768, 374,378)	16,407 (-6,758, 43,751)	1,561 (-670, 4,083)	3.98 (-1.75, 10.42)	34.31% (-75.01%, 100%)
18-64 years	2,472,357 (-1,277,369, 6,646,758)	138,917 (-60,452, 488,438)	62,332 (-25,330, 181,620)	5,626 (-2,980, 15,645)	11.54 (-5.96, 31.98)	30.77% (-84.34%, 100%)
65+ years	550,896 (-218,664, 1,284,051)	55,071 (-25,521, 143,494)	17,562 (-6,092, 46,233)	9,512 (-3,814, 22,304)	239 (-95, 551)	35.36% (-74.69%, 100%)
Total (#)	6,380,993 (-1,978,841, 14,806,931)	764,255 (-169,664, 1,757,368)	144,398 (-44,564, 334,184)	27,559 (-7,602, 61,345)	272 (-105, 626)	
Total (%)	38.61% (-62.95%, 100%)	42.66% (-60.56%, 100%)	37.13% (-73.27%, 100%)	39.7% (-46.73%, 100%)	35.72% (-61.47%, 100%)	

Appendix C: Clinical outcomes averted annually with routine elderly immunization with vaccine coverage of 65% and vaccine efficacy of 90% (scenario D)

Age Group	Cases Averted	Outpatients Averted	ED Visits Averted	Hospitalizations Averted	Mortalities Averted	% Outcomes Averted
0-4 years	12,958 (-33,412, 57,030)	2,063 (-5,418, 10,149)	224 (-568, 1,122)	55 (-145, 249)	0.081 (-0.204, 0.364)	0.29% (-3.56%, 1.79%)
5-17 years	14,764 (-14,618, 41,666)	2,377 (-2,112, 7,151)	274 (-272, 823)	27 (-27, 75)	0.068 (-0.068, 0.192)	0.55% (-3.05%, 2.19%)
18-64 years	66,222 (-40,468, 151,391)	3,717 (-2,051, 11,513)	1,638 (-1,065, 4,225)	150 (-91, 347)	0.31 (-0.186, 0.718)	0.78% (-2.81%, 2.38%)
65+ years	412,696 (38,707, 932,244)	39,609 (3,700, 106,999)	12,642 (1,100, 33,461)	7,138 (657, 16,430)	181 (17, 409)	25.54% (18.64%, 31.63%)
Total (#)	525,484 (-21,241, 1,090,331)	50,175 (-3,337, 120,643)	15,152 (44, 36,932)	7,469 (586, 16,739)	182 (17, 409)	
Total (%)	3.03% (-0.9%, 4.31%)	2.72% (-1.14%, 4.91%)	3.9% (0.13%, 6.34%)	10.33% (6.1%, 13.02%)	22.97% (16.97%, 27.94%)	