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Targeting pediatric versus elderly populations for norovirus vaccines: a model-based analysis of mass vaccination options

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ABSTRACT

Background: Noroviruses are the leading cause of acute gastroenteritis and foodborne diarrheal disease in the United States. Norovirus vaccine development has progressed in recent years, but critical questions remain regarding which age groups should be vaccinated to maximize population impact.
Methods: We developed a deterministic, age-structured compartmental model of norovirus transmission and immunity in the U.S. population. The model was fit to age-specific monthly U.S. hospitalizations between 1996 and 2007. We simulated mass immunization of both pediatric and elderly populations assuming realistic coverages of 90% and 65%, respectively. We considered two mechanism of vaccine action, resulting in lower vaccine efficacy (IVE) between 22% and 43% and higher VE (hVE) of 50%.
Results: Pediatric vaccination was predicted to avert 33% (95% CI: 27%, 40%) and 60% (95% CI: 49%, 71%) of norovirus episodes among children under five years for IVE and hVE, respectively. Vaccinating the elderly averted 17% (95% CI: 12%, 20%) and 38% (95% CI: 34%, 42%) of cases in 65+ year olds for IVE and hVE, respectively. At a population level, pediatric vaccination was predicted to avert 18–21 times more cases and twice as many deaths per vaccinee compared to elderly vaccination.
Conclusions: The potential benefits are likely greater for a pediatric program, both via direct protection of vaccinated children and indirect protection of unvaccinated individuals, including adults and the elderly. These findings argue for a clinical development plan that will deliver a vaccine with a safety and efficacy profile suitable for use in children.

1. Introduction

Noroviruses are the leading cause of acute gastroenteritis in the United States, (Patel et al., 2008; Hall et al., 2013; Ramani et al., 2014) responsible for an average 570–800 deaths, 56,000–71,000 hospitalizations, 400,000 emergency department admissions, 1.7–1.9 million outpatient admissions, and 19–21 million illnesses annually (Hall et al., 2013). Severe norovirus outcomes occur among pediatric and elderly populations, with 90% of norovirus-associated deaths in the U.S. occurring among the elderly (Hall et al., 2012). Children under five years of age experience the highest incidence (five times the general population) (Phillips et al., 2010) and have the highest rates of outpatient, emergency department, and inpatient visits (233, 38, and 9.4 per 10,000 persons per year, respectively) (Lopman et al., 2011; Gastañaduy et al., 2013). Given this substantial burden and limited options for prevention and treatment, (CDC, 2011) vaccines are considered an important means of providing protection from norovirus illness (Ramani et al., 2014).

Safety, immunogenicity, and efficacy studies on norovirus vaccines have been encouraging, with at least one bivalent intramuscular product likely to progress to Phase III field efficacy trials (Ramani et al., 2014). Current vaccine evaluations have been conducted among adults. However, as noroviruses affect all ages and are transmitted through multiple routes, an array of vaccination

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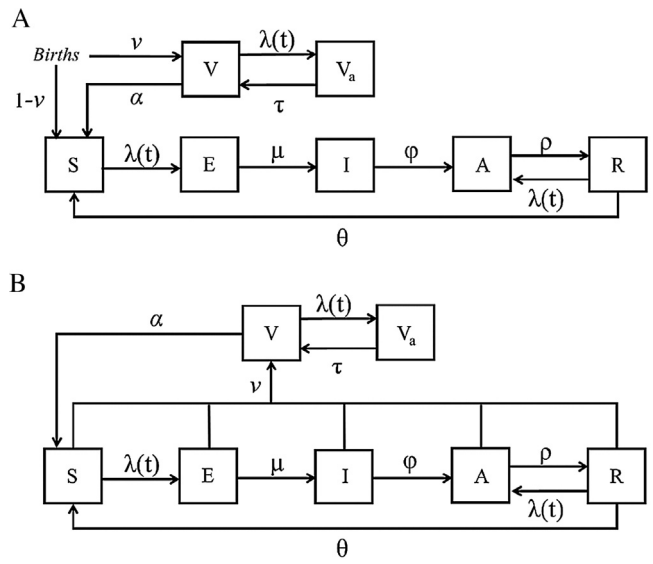

Fig. 1. Model schematic of the movement between six states of norovirus infection. In the absence of vaccination, persons are born directly into the susceptible pool (S), become exposed at the force of infection (λ(t)), and then progress through the exposed (E), symptomatic (I) and asymptomatic (A) stages at rates inversely proportional to the duration of these states (μ, φ, ρ) 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 (θ). In the presence of a pediatric vaccination (panel A), a proportion of births entering the system will receive protection from vaccines (ν) and enter the vaccinated compartment (V). In the presence of elderly vaccination (panel B), a proportion of the elderly will receive protection from vaccines (ν) and enter the vaccinated compartment (V). Only children under five and the elderly can flow into vaccinated compartments. Under both pediatric and elderly vaccine scenarios, vaccinated individuals can become asymptomatically infected at the force of infection or can become susceptible to disease through the waning of vaccine immunity (α).

strategies warrants consideration. At the current stage of vaccine development, the time is ideal for examining the population impact that various norovirus vaccination programs could have on the dynamics of disease to guide vaccine development and inform policymakers on potential impacts.

Here, we present an age-structured dynamic transmission model to project the effects of different vaccination strategies on the epidemiology and disease burden of norovirus in the U.S., including the incidence of five clinical outcomes (cases, outpatient visits, emergency department visits, inpatient visits, and deaths) for each of four age classes (0–4, 5–17, 18–64, and 65+ years). The model was used to compare vaccination strategies targeting pediatric versus elderly populations, both in terms of impact on disease burden and relative efficiency under various assumptions about vaccine efficacy.

2. Methods

We adapted a previously-published, deterministic, age-structured compartmental model that simulates norovirus transmission and estimates disease incidence in the U.S. (Simmons et al., 2013). The model follows a Susceptible-Exposed-Infected-Recovered (SEIR-like) framework (Fig. 1, S1 Text). We consider four age classes: 0–4, 5–17, 18–64, and 65+ years old, and applied realistic, age-specific population sizes, aging and death rates, and a heterogeneous contact structure (Table 1, S1 Text, Table S1). Lacking detailed mixing data specific to the U.S., we used average contact patterns from representative samples of eight European countries in the POLYMOD study (Mossong et al., 2008).

We estimated age-specific susceptibilities (q_i) to allow the four age classes (i; 0–4, 5–17, 18–64, and 65+ year olds) to exhibit heterogeneous probabilities of infection given exposure to an infectious contact. We also considered models with different numbers of estimated age-specific susceptibilities (q_i) and where transmission was dependent on susceptible or infectious individuals (S1 Text, Table S2); the results of this paper focus on the best-fit model, where the probabilities of infection on contact for 5–17 and 18–64 year olds were equal ($q_2 = q_3$).

We assume maternal immunity is short-lived and negligible (Gray et al., 1993). Therefore, absent vaccination, children are born into the susceptible class (S). Susceptible individuals are subjected to a force of infection ($\lambda_i(t)$), and progress through pre-symptomatic (E), symptomatic (I) and post-symptomatic (A) stages at rates inversely proportional to the duration of incubation (μ), symptomatic illness (φ), and asymptomatic shedding (ρ), respectively, before entering the recovered compartment (R). In this framework, individuals acquire natural immunity that protects against disease, but not against infection, until immunity wanes (Phillips et al., 2010; Lindesmith et al., 2003). From the recovered compartment, persons can become asymptomatically infected (A) or susceptible to disease as natural immunity wanes (θ). To simulate seasonality, we applied a seasonal forcing parameter (β_1) that governs the peak-to-mean amplitude in transmissibility. To estimate clinical outcomes, we multiplied the projected disease incidence by age-specific probabilities (given norovirus illness) of outpatient (OP) admission, emergency department (ED) admission, hospitalization (IP), and death due to norovirus. These probabilities were determined from U.S. population estimates and described in more detail in previous work (Bartsch et al., 2012).

Model simulation, fitting, and analysis were conducted in R version 3.1.1. (R Core Team, 2016). Specific R packages used for these analyses are detailed in the supplement. We fit the model to age-specific monthly counts of norovirus-associated hospitalizations by maximum likelihood to estimate the susceptibility ($q_{1...4}$) and seasonality (β_1,ω) parameters (Lopman et al., 2011). We assumed the monthly numbers of hospitalizations in each age group were Poisson distributed with mean equal to the model-predicted age-specific incidence multiplied by the probability of hospitalization (White et al., 2007). Age-specific R_0 values were calculated following procedures detailed in the supplement (S1 Text) and (Simmons et al., 2013).

2.1. Vaccine scenarios

We assumed vaccine response was "take-type:" either protection against disease was complete or vaccinated individuals remained fully susceptible (Smith et al., 1984). We assumed vaccines confer protection in the same manner as we conceptualize natural immunity: providing protection against disease, but not infection. Thus, vaccinated individuals can become asymptomatically infected or susceptible to disease as vaccine-induced immunity wanes (τ) (Fig. 1).

After model fitting, we simulated routine, age-targeted vaccination of infants around the time of birth with vaccine coverage of 90% (i.e. Pediatric immunization) and individuals turning age 65 and every five years thereafter with vaccine coverage of 65% (i.e. Elderly immunization). Vaccine coverage for these scenarios was based on recent age-specific uptake of measles and influenza vaccines (Annunziata et al., 2012; CDC, 2012; Lu et al., 2013). No vaccine efficacy (VE) estimates from field trails exist for norovirus vaccines, so we considered two different values, based on different interpretations of vaccine-challenge studies. These studies suggest monovalent or bivalent norovirus vaccination followed by a homotypic challenge reduces disease by approximately 50% among vaccinated individuals (Bernstein et al., 2015; Atmar et al., 2011