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Journal Title: Epidemics
Volume: Volume 17
Publisher: Elsevier: Creative Commons Licenses | 2016-12-01, Pages 42-49
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1016/j.epidem.2016.10.006
Permanent URL: https://pid.emory.edu/ark:/25593/s447f

Final published version: http://dx.doi.org/10.1016/j.epidem.2016.10.006

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Accessed December 21, 2018 2:55 PM EST
Targeting pediatric versus elderly populations for norovirus vaccines: a model-based analysis of mass vaccination options

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\textbf{A R T I C L E   I N F O}

\textbf{Article history:}
Received 8 June 2016
Received in revised form 23 October 2016
Accepted 23 October 2016
Available online 24 October 2016

\textbf{Keywords:}
Vaccination
Norovirus
Transmission
Mathematical modeling
Herd immunity

\textbf{A B S T R A C T}

\textit{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.

\textit{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 mechanisms of vaccine action, resulting in lower vaccine efficacy (IVE) between 22\% and 43\% and higher VE (hVE) of 50\%.

\textit{Results:} Pediatric vaccination was predicted to avert 33\% (95\% CI: 27\%, 40\%) of cases in 65+ year olds 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.

\textit{Conclusion:} 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.

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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...
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 pol-
cymakers 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 pedi-
atriic 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
different 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 infec-
tious contact. We also considered models with different numbers
of estimated age-specific susceptibilities (\( q_i \)) and where transmis-
sion 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 asymptomatic (A) stages at rates inversely
proportional to the duration of these states (\( \mu, \phi, \rho \)) 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 (\( \theta \)). In the presence of a pediatric vaccina-
tion (panel A), a proportion of births entering the system will receive protection from
vaccines (\( \nu \)) and enter the vaccinated compartment (V). In the presence of elderly
vaccination (panel B), a proportion of the elderly will receive protection from vac-
cines (\( \nu \)) 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 (\( \alpha \)).

We assumed vaccine response was “take-type;” either protec-
tion 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 conceptu-
alyze 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 (\( \tau \)).

After model fitting, we simulated routine, age-targeted vacci-
nation 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 sug-
gest 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).

---

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 (\( \lambda_i(t) \)), and then progress through the
exposed (E), symptomatic (I) and asymptomatic (A) stages at rates inversely
proportional to the duration of these states (\( \mu, \phi, \rho \)) 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
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vaccination (panel B), a proportion of the elderly will receive protection from vac-
cines (\( \nu \)) 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 (\( \alpha \)).
Table 1
Parameter input values, ranges tested in uncertainty analyses, and sources.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Input value</th>
<th>Range (+/− standard deviation)</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of incubation period</td>
<td>µ</td>
<td>32.8 h</td>
<td>(30.9–34.6)</td>
<td>Uniform</td>
<td>(Devasia et al., 2014)</td>
</tr>
<tr>
<td>Duration of symptomatic infectiousness</td>
<td>ϕ</td>
<td>48 h</td>
<td>(38.5–50.7)</td>
<td>Uniform</td>
<td>(Devasia et al., 2014)</td>
</tr>
<tr>
<td>Duration of asymptomatic infectiousness</td>
<td>ρ</td>
<td>10 days</td>
<td>(1–20)</td>
<td>Uniform</td>
<td>(Atmar et al., 2008)</td>
</tr>
<tr>
<td>Duration of natural immunity during incubation and asymptomatic period</td>
<td>θ</td>
<td>5.1 years</td>
<td>(4.0–6.7)</td>
<td>Uniform</td>
<td>(Simmons et al., 2013)</td>
</tr>
<tr>
<td>Duration of vaccine asymptomatic infectiousness</td>
<td>τ</td>
<td>10 days</td>
<td>(1–20)</td>
<td>Uniform</td>
<td>Assumed equal to duration of natural infection</td>
</tr>
<tr>
<td>Duration of vaccine immunity</td>
<td>α</td>
<td>5.1 years</td>
<td>(4.0–6.7)</td>
<td>Uniform</td>
<td>Assumed equal to duration of natural immunity</td>
</tr>
</tbody>
</table>

OP admission probability
- 0–4 years                                             | 0.168  | (0.100–0.235) | Uniform | (Bartsch et al., 2012) |
- 5–17 years                                            | 0.168  | (0.111–0.226) | Uniform | (Bartsch et al., 2012) |
- 18–64 years                                           | 0.06   | (0.019–0.160) | Uniform | (Bartsch et al., 2012) |
- 65+ years                                             | 0.103  | (0.063–0.143) | Uniform | (Bartsch et al., 2012) |

IP admission probability
- 0–4 years                                             | 0.00428 | +/− 0.000178 | Normal | (Bartsch et al., 2012) |
- 5–17 years                                            | 0.00182 | +/− 0.000074 | Normal | (Bartsch et al., 2012) |
- 18–64 years                                           | 0.00228 | +/− 0.000092 | Normal | (Bartsch et al., 2012) |
- 65+ years                                             | 0.01733 | +/− 0.000079 | Normal | (Bartsch et al., 2012) |

Death probability
- 0–4 years                                             | 0.00000625 | +/− 2.57 × 10^{-7} | Normal | (Bartsch et al., 2012) |
- 5–17 years                                            | 0.00000466 | +/− 1.81 × 10^{-7} | Normal | (Bartsch et al., 2012) |
- 18–64 years                                           | 0.00000466 | +/− 1.81 × 10^{-7} | Normal | (Bartsch et al., 2012) |
- 65+ years                                             | 0.000435  | +/− 0.000018  | Normal | (Bartsch et al., 2012) |

ED visit probability
- 0–4 years                                             | 0.0179  | (0.0112–0.0246) | Uniform | (Bartsch et al., 2012) |
- 5–17 years                                            | 0.0199  | (0.0114–0.0280) | Uniform | (Bartsch et al., 2012) |
- 18–64 years                                           | 0.026   | (0.0153–0.0368) | Uniform | (Bartsch et al., 2012) |
- 65+ years                                             | 0.0325  | (0.0199–0.0452) | Uniform | (Bartsch et al., 2012) |

Fitted Parameters
- Susceptibility of 0–4 year olds                       | q1     | 0.208       | (0.141, 0.402)                  | Estimated   |
- Susceptibility of 5–17 and 18–64 year olds            | q1,2   | 0.032       | (0.023, 0.057)                  | Estimated   |
- Susceptibility of 65+ year olds                       | q1     | 0.020       | (0.014, 0.035)                  | Estimated   |
- Seasonal amplitude                                    | βs     | 0.034       | (0.008, 0.089)                  | Estimated   |
- Seasonal offset                                       | h      | 2.147       | (1.961, 2.266)                  | Estimated   |

* Range in the fitted value based on 1000 random samples of the fixed parameters.

Atmar et al., 2011). In low-efficacy vaccine scenarios (i.e., Pediatric and Elderly), we assume only those immunologically susceptible to norovirus at the time of vaccine administration gain additional protection from disease. About 44% and 55% of 0–4 year olds are susceptible and recovered, respectively, prior to vaccination, resulting in a VE around 22% for 0–4 year olds. In the elderly population, 85% are susceptible and 14% are recovered prior to vaccination, thus VE is approximately 43% for the elderly. Under a more optimistic high VE (hVE) scenario, we assume vaccination confers a 50% reduction in disease incidence over one year among vaccinated individuals.

For these four vaccine scenarios—and for a scenario without vaccination—we estimated age-specific incidence of disease and clinical outcomes. Analyses of long-term impacts of vaccination were conducted after the system had reached equilibrium, approximately 40 years after vaccine introduction. We simulated a well-established vaccination program with coverage similar to other vaccines. More detailed analysis are required to model the scale-up of vaccine coverage in the first few years after implementation and the associated epidemiological impacts. We calculated population direct and indirect effects of vaccination by comparing vaccine to no-vaccine simulations. We also assessed the efficiency of vaccine simulations, defined as the number of clinical outcomes averted per vaccinee (S1 Text).

2.2. Parameters and simulations

Parameter values (and ranges) for natural history, and clinical outcome probabilities were set to values identified in observational/challenge studies, and previous modeling studies (Table 1). We used Latin hypercube sampling to generate 1100 random samples of parameter sets and then re-fit the transmission probabilities and seasonality parameters in the absence of vaccination, for each parameter set. We then ranked the 1100 sampled and fitted parameter sets by their negative log likelihood (NLL) value. The 100 parameter sets with the highest NLL values were discarded, and we ran each vaccine scenario with the remaining 1000 parameter sets. For summary statistics, we report medians and 2.5/97.5 percentiles of the annual clinical outcomes averted. These annual data are four year averages. In order to quantify the sensitivity of model projections to uncertainty in each parameter’s value, we calculated partial rank correlation coefficients (PRCC) for natural history and vaccine parameters. PRCC values were calculated between model parameters and the percentage of cases averted in the total population and the age group targeted for vaccination in a given vaccination scenario.
3. Results

3.1. Model fitting

The best fit model based on the minimum Akaike information criterion (Table S2) included three age-specific probabilities of infection on contact. The observed and predicted average annual norovirus hospitalizations were 71,461 and 71,906, respectively (Fig. 2). A seasonal forcing of 3.4% (95% CI: 1.1%, 8.1%) of peak-to-mean amplitude provided the best fit to observed seasonal variation in monthly hospitalizations (Table 1, Fig. S2, Table S2). In the best-fit model, 0–4 year olds contributed the most to transmission, with an age-specific basic reproduction number \( R_0 \) of 4.3 compared to 1.4, 1.2, and 0.4 from 5–17, 18–64, and 65+ years, respectively (S1 Text).

3.2. Vaccine impact

The Pediatric programs rapidly reduced disease incidence in 0–4 year olds. Disease incidence exhibited inter-annual variability for the first several years before reaching lower equilibria (Fig. 3A). In the first five years of the IVE Pediatric program, incidence among 0–4 year olds was reduced by 24%, 41%, 22%, 37%, and 30%. In the first five years of the hVE Pediatric program, incidence among 0–4 year olds was reduced by 42%, 78%, 59%, 46%, and 68%.

Elderly vaccination led to gradual reductions in disease incidence, achieving a new equilibrium of lower incidence in approximately 15 years (Fig. 3B). In the first five years of the IVE Elderly program, incidence among the elderly was reduced by 3%, 6%, 9%, 11%, and 12%. In the first five years of the hVE Elderly program, incidence among the elderly was reduced by 5%, 13%, 19%, 23%, and 26%.

The IVE Pediatric program at equilibrium was predicted to avert 33% (95% CI: 1.7%, 43%) of all clinical outcomes in 0–4 year olds annually (Table 2, Figs. 4A, 5A). Approximately 71% of the averted outcomes were achieved through direct effects and 29% through indirect effects (Fig. 4A). In older age classes, 14–16% of cases were averted primarily through indirect effects (Figs. 4A, 5A, Table 2).

The hVE Pediatric program at equilibrium was predicted to avert 60% (95% CI: 49%, 71%) of all clinical outcomes in 0–4 year olds annually (75% through direct and 25% indirect protection; Table S3, Figs. 4C, 5C). In older age classes, 29–33% of cases were averted primarily through indirect protection (Table S3, Figs. 4C, 5C).

A IVE Elderly program at equilibrium would avert approximately 17% (95% CI: 12%, 20%) of all clinical outcomes almost exclusively through direct effects in the elderly (Table 3, Figs. 4B, 5B). Minimal impacts were conferred on other age groups as less than 1% of outcomes in 0–64 year olds were averted through indirect effects (Table 3, Figs. 4B, 5B).

The hVE Elderly program at equilibrium was predicted to avert 38% (95% CI: 34%, 42%) of all clinical outcomes in the elderly almost exclusively through direct effects (Table S4, Figs. 4D, 5D). Minimal impacts were conferred on younger age groups, with approximately 1% or less of outcomes averted through indirect effects (Table S4, Figs. 4D, 5D).

Pediatric programs were more efficient than Elderly programs. Per 100,000 vaccinees assuming IVE, the Pediatric program averted...
Table 2
Outcomes averted (95% CI) annually with a pediatric vaccine program with vaccine coverage of 90% and vaccine efficacy of 22% (lVE Pediatric).

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cases Averted (100,000 doses)</th>
<th>Outpatients Averted (100,000 doses)</th>
<th>ED Visits Averted (100,000 doses)</th>
<th>Hospitalizations Averted (100,000 doses)</th>
<th>Deaths Averted (100,000 doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4 years</td>
<td>1,430,000</td>
<td>237,000</td>
<td>25,700</td>
<td>6200</td>
<td>9 (7, 11)</td>
</tr>
<tr>
<td>5–17 years</td>
<td>419,000</td>
<td>69,000</td>
<td>8100</td>
<td>800</td>
<td>2 (1, 3)</td>
</tr>
<tr>
<td>18–64 years</td>
<td>1,157,000</td>
<td>70,000</td>
<td>30,000</td>
<td>2600</td>
<td>5 (3, 9)</td>
</tr>
<tr>
<td>65+ years</td>
<td>266,000</td>
<td>27,000</td>
<td>8500</td>
<td>4600</td>
<td>115 (75, 180)</td>
</tr>
<tr>
<td>Total (#)</td>
<td>3,282,000</td>
<td>407,000</td>
<td>72,400</td>
<td>14,200</td>
<td>132 (87, 202)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>19%</td>
<td>22%</td>
<td>18%</td>
<td>20%</td>
<td>16% (11%, 25%)</td>
</tr>
</tbody>
</table>

Table 3
Outcomes averted (95% CI) with routine elderly immunization with vaccine coverage of 65% and vaccine efficacy of 43% (lVE Elderly).

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cases Averted (100,000 doses)</th>
<th>Outpatients Averted (100,000 doses)</th>
<th>ED Visits Averted (100,000 doses)</th>
<th>Hospitalizations Averted (100,000 doses)</th>
<th>Deaths Averted (100,000 doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4 years</td>
<td>8500</td>
<td>1400</td>
<td>150</td>
<td>36</td>
<td>0.05 (0.03, 0.09)</td>
</tr>
<tr>
<td>5–17 years</td>
<td>9200</td>
<td>1500</td>
<td>180</td>
<td>17</td>
<td>0.04 (0.03, 0.07)</td>
</tr>
<tr>
<td>18–64 years</td>
<td>42,300</td>
<td>2500</td>
<td>1100</td>
<td>100</td>
<td>0.20 (0.12, 0.31)</td>
</tr>
<tr>
<td>65+ years</td>
<td>276,900</td>
<td>28,100</td>
<td>8800</td>
<td>4800</td>
<td>120 (88, 151)</td>
</tr>
<tr>
<td>Total (#)</td>
<td>336,900</td>
<td>33,800</td>
<td>10,200</td>
<td>4900</td>
<td>120 (88, 151)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>1.9%</td>
<td>1.8%</td>
<td>2.5%</td>
<td>6.9%</td>
<td>15% (5.1%, 8.5%)</td>
</tr>
<tr>
<td></td>
<td>(1.4%, 2.5%)</td>
<td>(1.1%, 2.9%)</td>
<td>(1.6%, 3.7%)</td>
<td>(5.1%, 8.5%)</td>
<td>(11%, 18%)</td>
</tr>
</tbody>
</table>

Table 4
Clinical outcomes averted per 100,000 vaccinees (95% CI) over 1 year.

<table>
<thead>
<tr>
<th>Vaccine strategy</th>
<th>Cases averted per 100,000 doses</th>
<th>Outpatient visits averted per 100,000 doses</th>
<th>ED visits averted per 100,000 doses</th>
<th>Hospitalizations averted per 100,000 doses</th>
<th>Deaths averted per 100,000 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVE Pediatric</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 years</td>
<td>39,500</td>
<td>6600</td>
<td>710</td>
<td>170</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Total</td>
<td>90,600</td>
<td>(63,400, 130,300)</td>
<td>(710, 16,900)</td>
<td>(170, 200)</td>
<td>(0.0)</td>
</tr>
<tr>
<td>IVE Elderly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65+ years</td>
<td>3500</td>
<td>360</td>
<td>110</td>
<td>61</td>
<td>2 (1, 2)</td>
</tr>
<tr>
<td>Total</td>
<td>4300</td>
<td>(3000, 5600)</td>
<td>(80, 200)</td>
<td>(50, 80)</td>
<td>(1, 2)</td>
</tr>
<tr>
<td>hVE Pediatric</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 years</td>
<td>72,400</td>
<td>11,900</td>
<td>1280</td>
<td>3100</td>
<td>0 (0, 1)</td>
</tr>
<tr>
<td>Total</td>
<td>178,000</td>
<td>(119,400, 256,200)</td>
<td>(13,000, 33,400)</td>
<td>(3100, 1070)</td>
<td>(0, 11)</td>
</tr>
<tr>
<td>hVE Elderly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65+ years</td>
<td>8100</td>
<td>840</td>
<td>270</td>
<td>141</td>
<td>4 (3, 4)</td>
</tr>
<tr>
<td>Total</td>
<td>9900</td>
<td>(8400, 12,000)</td>
<td>(600, 1400)</td>
<td>(141, 160)</td>
<td>(3, 4)</td>
</tr>
</tbody>
</table>

21 times more cases; 26 times more OP visits; 15 times more ED visits; 6 times more IP admissions; and twice as many deaths (Table 4) as Elderly programs. For lVE, the Pediatric programs averted 18 times more cases; 21 times more OP visits; 13 times more ED visits; 5 times more IP admissions; and twice as many deaths (Table 4) as Elderly programs. For every one case averted through direct effects, 3 and 5 cases in the total population were averted through indirect effects with lVE and hVE Pediatric programs, respectively. For every one case averted through direct effects with lVE programs.
4. Discussion

Results from this transmission modeling study suggest the overall population impact of norovirus vaccination can vary substantially depending on the age group targeted. Pediatric programs offered the greatest reductions in all clinical outcomes, with a 33% to 60% decrease in cases aged 0–4 year olds, and 14% to 33% reductions in older age groups achieved primarily through indirect protection. Pediatric programs were 18–21 times more efficient at preventing cases and 5–6 and two times more efficient at preventing IP admissions, and deaths, respectively, when compared to Elderly programs. Elderly programs averted between 17% and 38% of cases in the elderly, and provided protection almost exclusively through direct effects. This is a result of the minimal contribution that the elderly make to disease transmission. In fact, Pediatric programs were predicted to confer similar benefits to the elderly as Elderly programs. Taken together, these results indicate targeting pediatric populations for vaccination leads to greater direct and indirect benefits for the total population than vaccine programs that target the elderly. Children under five have higher disease, OP, and ED admission rates; thus vaccines can directly prevent these outcomes. The indirect benefits of Pediatric programs are a result of reductions in disease transmission, owing to the importance of young children in transmission. This finding is consistent with observational studies that identified contact with a young child with norovirus gastroenteritis as a risk factor for diarrhea for older children and adults (Phillips et al., 2010; de Wit et al., 2001). Large indirect benefits have been observed with the introduction of pediatric rotavirus and pneumococcal vaccines in the U.S., with unvaccinated populations protected through reductions in the overall force of infection (Tate et al., 2011; Lexau et al., 2005).

A second important finding was the identification of key parameters that influence the impact of vaccination programs. For both Pediatric and Elderly vaccination programs, the duration of vaccine-induced immunity, and age-specific transmission parameters ($q_{2,2}$ and $q_{4}$ for Pediatric and Elderly programs, respectively) strongly determined the outcome of the analysis. These are parameters for which we have limited empirical data because transmission is largely unobservable (Sukhrie et al., 2012), and no vaccine studies have included long-term follow-up for clinical outcomes (Treonar et al., 2014). In order to better predict the impacts of norovirus vaccines in future work, this analysis highlights the high value of collecting information on transmission from obser-
vational studies and conducting clinical trials that can estimate the duration of protection for both children under five and the elderly.

The predicted impacts of IVE scenarios were modest due to technical reasons related to our model construction. First, we assume vaccination only provides additional protection for those who are susceptible to disease (in the S class) at the time of immunization. Individuals who have acquired natural immunity will receive no added protection. This assumption strongly limits the impact of vaccination for adults as many will have acquired immunity, whereas we assume all children are susceptible at the time of infant immunization. A second explanation is that we assume exponential waning of both natural and vaccine immunity; thus while the average duration of protection is 5.1 years, most individuals have a shorter-duration immunity while a few have longer-term protection. Compartmental models can be modified to assume other distributions for waning immunity; however no data are available to inform the functional form of waning immunity to norovirus. The IVE scenarios which were based on a 50% vaccine efficacy (Bernstein et al., 2015; Atmar et al., 2011) resulted in more optimistic impacts. The values and concepts of vaccine action that are most appropriate can be informed by future clinical trial data.

There are several limitations to this study. First, there is uncertainty in the robustness of the epidemiological data used to fit the model. We used U.S. hospitalization data, which are model estimates, and community incidence rates were informed by a U.K. study. In that study, incidence in older age groups was low and may have been biased downwards (Phillips et al., 2010). Fitting to such low incidence limited the potential impact of elderly immunization in our model and limited the role of the time people in transmission. Second, there is considerable uncertainty in model parameters due to our limited understanding of natural history of norovirus disease and transmission, particularly the relative roles of pre- and post-symptomatic transmission. Third, our model construction assumes a single strain of norovirus; thus infection from, or vaccination against, one strain of norovirus provides protection against all other infections. This is a major simplification, as noroviruses are highly genetically diverse and natural immunity provides only limited cross-protection within genogroups (Wyatt et al., 1974). However, this simplification may be partially accounted for by the duration of immunity parameter, particularly in the low vaccine efficacy scenario. In addition, novel genogroup 2 type 4 (GII.4) strains emerge every two to four years, that may evade host population immunity. Current data are insufficient to establish the degree of cross-protection to norovirus, or to parameterize a multi-strain model as has been accomplished for influenza (Arinaminpathy et al., 2012). For a more complete understanding of norovirus transmission and vaccination, these are important areas for further empirical studies and, subsequently, model development. Additionally, we did not consider a model that incorporated a class of individuals that are genetically resistant to norovirus infection. As more data become available on the effect of vaccination among genetically resistant individuals, future modeling studies should consider such a class. Another important limitation is that we assumed that VE was the same for all clinical outcomes and disease severity. This may not be the case. For rotavirus, VE is greater for severe outcomes (Tate et al., 2011). Finally, while we developed a model to predict the impact of infant and elderly vaccination, there have been no studies of VE in pediatric populations and only one immunogenicity study in the elderly (Treanor et al., 2014). Human safety, immunogenicity and efficacy studies have all involved experimental challenge of adults (typically 18–49 years old) (Bernstein et al., 2015; Atmar et al., 2011; El-Kamary et al., 2010). While these results are promising, clinical trials will be pivotal in determining VE among infants and the elderly. Though our study made several simplifying assumptions—as all models do—the dynamic transmission framework presented here offers a more comprehensive understanding of total population benefits of vaccination than previous studies that included only direct effects (Bartsch et al., 2012).

In summary, our results quantitatively demonstrate that the potential public health value of a norovirus vaccine is likely greatest with pediatric immunization. This finding argues for a clinical development plan for a vaccine with a safety and efficacy profile suitable for use in children. To improve models for future analyses, better data are needed on the duration of natural and vaccine immunity, the extent of cross-protection and process of norovirus infection. Future modeling studies should incorporate norovirus strain diversity to examine the implications of multiple, evolving strains for vaccination. As more data become available on the extent of cross-protection and the duration of vaccine immunity, this modeling framework can be adapted to more precisely estimate population-level impacts of norovirus vaccination. Models should also be adapted to developing world settings where the force of infection is higher (Shioda et al., 2015) and disease burden is greater (Ahmed et al., 2014).

### 5. Funding

This work was supported by a NoroCORE Graduate Fellowship funded by the United States Department of Agriculture - National Institute of Food and Agriculture Food Virology Collaborative [to MKS]; a fellowship from the Oak Ridge Institute for Science and Education [to MKS]; the National Institutes of Health/National Institute of Allergy and Infectious Diseases [K01AI091864 to JVR]; the National Science Foundation Water Sustainability and Cli-
mate Program [1360330 to JVR]; and the National Institutes of Health/Fogarty International Center [R01TW010286 to JVR]. The funding sources for this study had no role in the study design, data collection, analysis, interpretation, or writing the report.

Conflicts of interest

None.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, or the US Department of Health and Human Services.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.epidem.2016.10.006.

References


