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The Potential Economic Value of a Human Norovirus Vaccine for the United States

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Abstract

Vaccines against human norovirus are currently under development. We developed a simulation model to determine their potential economic value. Vaccination prevented 100–6,125 norovirus gastroenteritis cases per 10,000 vaccinees. Low vaccine cost (\$50) garnered cost-savings and a more expensive vaccine led to costs per case averted comparable to other vaccines. In the US, vaccination could avert approximately 1.0–2.2 million cases (efficacy 50%, 12 month duration), costing an additional \$400 million to \$1.0 billion, but could save \$2.1 billion (48 month duration). Human norovirus vaccination can offer economic value while averting clinical outcomes, depending on price, efficacy, and protection duration.

Keywords

Norovirus; Vaccine; Economics

1. INTRODUCTION

The increasingly recognized burden of human norovirus (NoV) gastroenteritis has motivated vaccine development, with the aim of protecting individuals from disease. NoV is the most common etiology of diarrheal disease in the community [1–3] and gastroenteritis outbreaks worldwide [4–5]. Outbreaks frequently occur [4, 6], can be costly, and cause substantial

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morbidity in vulnerable populations, especially in healthcare institutions [7–9]. The burden of sporadic disease is substantial, with an estimated 21 million cases, 71,000 hospitalizations, and 800 deaths annually in the United States (US) [2–3, 10–12]. In the US, the cost of NoV -associated hospitalizations has been estimated at approximately \$500 million, while foodborne NoV cost due to healthcare and lost productivity has been estimated at \$2 billion [13].

Despite numerous technical obstacles, several NoV vaccine candidates are under development [14–16]. One of the key challenges is that norovirus immunity is believed to be short-lived with limited cross protection, so persons of all ages are susceptible to infection and disease multiple times throughout their lifetime [4, 6]. However, the duration of protection conferred by natural or vaccine-induced protection remains unknown, but would be a key parameter for determine the health and economic values of a vaccine and, ultimately, for developing a vaccination strategy (in terms of target age groups and frequency of immunization).

A virus-like particle (VLP) based vaccine is furthest along in the development pipeline (LigoCyte, Bozeman, Montana). Phase I clinical trials of the intranasal formulation found the vaccine to be safe, well-tolerated (causing only minor nasal stuffiness), and immunogenic [17]. In human volunteers immunized intranasally with a G1.1 VLP vaccine and subsequently challenged (oral administration) with a homotypic stain, vaccination showed a 47% relative reduction in NoV -associated gastroenteritis (69% placebo vs. 37% vaccine) and 26% in the risk of NoV infection (82% placebo vs. 61% vaccine) [14]. An intramuscular liquid bivalent (GI.1/GII.4) formulation is currently undergoing Phase I/II trials with a GII.4 challenge following vaccination [18].

With candidate vaccines in the pipeline, evaluating the economic value of vaccination prior to licensure can help guide development and implementation. To this end, we constructed a Markov computer simulation model to determine the potential economic and health value of a NoV vaccine from the societal perspective. In sensitivity analyses, we varied key parameters including vaccine efficacy, cost, protection duration, and age at vaccination. Results from our study could help policy makers and vaccine manufacturers determine appropriate target populations, desired efficacy profile, investment, and vaccine price points, when it reaches the market.

2. METHODS

2.1 Model Structure

Using TreeAge Pro 2009 (Williamstown, MA) we developed a Markov computer simulation model to determine the cost-effectiveness of administering a NoV vaccine to an individual from the societal perspective, which included both direct medical costs (i.e., outpatient and hospitalization costs) and indirect costs (i.e., productivity losses due to work absenteeism and lifelong productivity losses due to mortality). A Markov model was developed, rather than a traditional decision tree, as it allows us to determine the potential impact of a vaccine over time and thus can look at the effects of vaccine protection duration, described in more detail later. Also, as natural-immunity is likely to be short lived, a Markov model allowed for individuals to develop NoV more than once over the simulation period. Furthermore, these models provide a framework in which to evaluate the sensitivity or results to parameter uncertainty. The model consisted of three mutually exclusive states: no NoV gastroenteritis, NoV gastroenteritis, and dead (Figure 1). Individuals entered the model in the “no NoV gastroenteritis” state. An individual remained in a state for the length of a cycle (one month). At the end of each cycle, the individual had probabilities of remaining in the same state or moving to another state. The probability of moving from the “no NoV” state to

the “NoV gastroenteritis” state was the risk of NoV gastroenteritis; the probability of moving from the “no NoV” state to the “dead” state was the all-cause mortality.

If an individual entered the “NoV gastroenteritis” state, he/she had probabilities of requiring ambulatory care (i.e., outpatient visit) and/or hospitalization and not surviving. Each possible outcome resulted in costs (i.e., productivity losses from missed work days either for the individual or the caregiver and/or medical costs). Those individuals who did not survive their NoV gastroenteritis infection move to the “dead” state. The “dead” state was absorptive, i.e., they could no longer move to any other state.

An individual continued to cycle in the model until he/she ended up in the “dead” state or 48 cycles (i.e., 48 months or 4 years, representing the longest protection duration explored) elapsed, whichever came first. Each individual journeyed through the model twice, once with vaccination and once without. Vaccination had a probability of causing minor side effects (e.g., fever, redness and/or swelling for an intramuscular vaccine), which incurred treatment costs. Vaccination attenuated an individual’s risk of NoV gastroenteritis by the vaccine’s efficacy for the duration of protection. Individuals accrued all costs and benefits at the time the event occurred in the model; these were summed at the end of the simulation and attributed to the age at vaccination.

2.2 Simulations and Model Outcomes

Each simulation run involved sending 1,000 individuals (age: 0 to 85) through the model 1,000 times for a total of 1,000,000 trials. For each simulation run, we calculated the cost per outcomes averted via the following formula:

$$= (\text{Cost}_{\text{Vaccination}} - \text{Cost}_{\text{No Vaccination}}) / (\text{Health Outcomes}_{\text{No Vaccination}} - \text{Health Outcomes}_{\text{Vaccination}})$$

where relevant health outcomes included NoV -associated gastroenteritis cases, outpatient visits, hospitalizations, or deaths. This formula yields the costs entailed to avert each of these outcomes. We also estimated the total cost and health burden of NoV in the US with and without vaccination (under different scenarios), by age-standardizing to the national population [19]. We provide two estimates, assuming 43% and 95% vaccination coverage, applied to every age group, based on influenza vaccination coverage rates for the 2010–2011 season [20] and DTaP (diphtheria, tetanus, and acellular pertussis) vaccination coverage levels among children [21], respectively. Paired t-tests were done in STATA 11 (College Station, TX) to determine the significance of vaccination compared to no vaccination.

2.3 Data Inputs and Sources

Table 1 shows the model inputs. Since there are limited direct data on community incidence of NoV in the US population, we used data from a large community-based study of AGE from England and Wales to estimate age-specific NoV incidence [3]. To derive the values shown in Table 1, these age-specific annual incidences were converted to monthly probabilities using a standard rate to probability conversion formula while accounting for time. The reported age-specific annual incidences were applied to the age stratified population from the US Census Bureau [19] to estimate the number of NoV cases by age group. Pooled data on self-reported healthcare utilization practices of persons with acute diarrheal disease lasting <3 days, obtained from Foodborne Diseases Active Surveillance Network (FoodNet) as described by Hall et al, [2] was used to estimate the care seeking probability among NoV cases. Recent US estimates of NoV hospitalizations [11] and deaths [10] were used to calculate age-stratified probabilities of hospitalization and mortality, using the age-stratified NoV US case estimates as the denominator.

Disease outcome estimates were multiplied by illness related costs. We used nationally-representative data sources to determine outpatient consultation and hospitalization costs, which reflect the actual costs of production, not the charge or what is billed to a patient [22–24]. For productivity loss due to illness, we assumed a 40 hour work week and included hours missed for duration of illness or hospitalization. Productivity losses due to mortality were calculated from the annual wages (discounted at 3% per year) lost for the years of life lost outlined by the Human Mortality Database [25]. A 3% annual discount rate converted all costs to 2012 \$US [26]. The vaccination program cost included the price of the vaccine itself, vaccine administration, any other health systems costs, and treatment costs associated with minor side effects; vaccination cost and efficacy was for a full series.

2.4 Sensitivity Analyses

In probabilistic sensitivity analyses (i.e., Monte Carlo simulation) all parameters were simultaneously varied throughout the distributions in Table 1. As potential NoV vaccines are in early clinical trials with many unknowns about the final product profile, in one-way sensitivity analyses vaccine efficacy (25%, 50%, and 75%), protection duration (12, 24, and 48 months), and vaccine cost (\$25, \$50, and \$75) were varied.

3. RESULTS

3.1 Clinical Outcomes

Table 2 shows clinical benefits per 10,000 vaccinations over the duration of the simulation (i.e., four years) for a 50% efficacious vaccine. The number of cases, outpatient visits, hospitalizations, and deaths averted was greatest in young children 0 to 4 years old, and tended to decrease with age and then increase again in the oldest age groups, reflecting differences in underlying risk and severity of NoV disease (Table 2). Vaccination prevented approximately 4 and 3 fewer hospitalizations per 10,000 vaccinees in children <5 and adults 65 years old, respectively, for each year of protection. Vaccination prevented few deaths (0 to 0.35 per 10,000 vaccinees) as it is a rare outcome. Vaccines with longer protection durations and higher efficacies resulted in approximately linear increases in the number of clinical outcomes averted (e.g., a vaccine protecting for 48 months offers approximately four times the clinical benefits of a vaccine protecting for 12 months). A 75% efficacious vaccine averted up to 6,125 cases per 10,000 vaccinees in 0 to 4 year olds. However, even a vaccine 25% efficacious prevented 100 (15 to 44 year olds, 12 month duration) to 2,036 (0 to 4 year olds, 48 month duration) NoV gastroenteritis cases per 10,000 vaccinees (data not shown). Vaccination was statistically significant compared to no vaccination ($p < 0.00001$) under all scenarios explored.

3.2 Economic Outcomes

Figure 2 plots the cost per NoV gastroenteritis case averted for vaccination, where negative costs imply cost-savings. Across all age groups 5 years and 65 years, a 50% efficacious vaccine costing \$25 that protects for 12 months resulted in costs per case averted between approximately \$380 and \$950 (Figure 2a). These costs essentially doubled and tripled for a vaccine costing \$50 and \$75, respectively (Figures 2c, e). In children aged 0 to 4 years, a vaccine with 50% efficacy was always cost-saving when costing \$25; and \$50 and \$75 vaccines were cost-saving when protecting for 24 months. For those aged 65 years, a 50% efficacious vaccine providing protection for 24 months was cost-savings at \$25 (–\$147, Figure 2a) and resulted in a cost per case averted of approximately \$500 (\$50 vaccine) and \$1,000 (\$75 vaccine). Figures 2b, d and f illustrate the cost per case averted for a 75% efficacious vaccine. A 75% efficacious vaccine that protected for 48 months was cost-saving in all groups at a cost of \$25, in 0 to 14 years and 65 years old at a \$50 cost, and in 0 to 4

years and 65 and over age groups at a \$75 cost. Increasing efficacy from 50% to 75% did not overcome the additional increase in vaccine cost (Figure 2a vs. 2d).

The costs per hospitalization and death averted followed a similar trend across the age groups as the cost per case averted and were lowest among those aged <5 and ≥65 years (data not shown). The cost per hospitalization averted with a \$25 vaccine ranged widely from −\$68,005 (negative value implies cost-savings; 75% efficacious, 48 month duration among those <5 years) to \$783,723 (25% efficacious, 12 month duration among 5–14 year olds). For a \$75, 75% efficacious vaccine, the cost per hospitalization averted ranged from −\$46,383 (48 month duration, 0 to 4 years) to \$798,119 (12 month duration, 45 to 64 year olds).

Table 3 reports the net cost per vaccinee (i.e., the vaccination cost minus the savings of averted outcomes) of a 50% efficacious vaccine at different vaccine costs and protection durations. For 0 to 4 year olds, vaccination was always cost-saving (upper bound of the 95% CI was <\$0) when vaccine provided 48 months protection and tended to be cost-saving (mean cost was <\$0) when vaccine provided 24 months protection. In most other age groups and cost/protection duration scenarios, the costs fell between \$0 and the vaccine cost, suggesting some additional costs would be incurred to prevent illnesses.

3.3 Impact on the United States

Without vaccination, we estimate a total of 16.7 million NoV gastroenteritis cases in the US, costing a total \$5.5 billion annually (Table 4). A 50% efficacious vaccine protecting for 12 months would result in approximately 1.0 to 2.2 million cases averted, a 5.9% to 13.0% decrease (or, a total 15.7 to 14.5 million annual cases), but would result in additional cost of \$400 million to \$1 billion (total costs of \$5.9 to \$6.5 billion) at 43% and 95% coverage, respectively. Vaccination providing 12 months protection would not reduce the total cost of NoV gastroenteritis in the US; however, cost-savings could occur if the vaccine protected for 48 months and cost \$25 with an efficacy 50% or cost \$50 with an efficacy 75%. Vaccines with these characteristics could reduce the total US costs of NoV between \$100 million and \$2.1 billion (i.e., total costs of \$5.4 to \$3.4 billion) a year.

4. DISCUSSION

Our results suggest that vaccination against NoV gastroenteritis could provide substantial health benefits and offer economic value. Under most scenarios investigated, additional net costs to society would be incurred, but for certain groups (e.g., young children) vaccination could provide cost-savings under certain conditions. Vaccination tended to provide more health and economic benefits to those under 5 and over 65 years old, as they experience the highest rates of NoV gastroenteritis and severe outcomes, respectively. Vaccine protection duration was an important driver of cost-effectiveness, with longer protection durations providing more benefit. In the shortest protection duration scenario (12 months), a \$25, \$50 and \$75 vaccine resulted in costs per case averted of approximately −\$100 to \$900, \$1,000 to \$2,000, and \$2,000 to \$3,000, respectively, in non-pediatric age groups. In children under the age of 5 years, the cost per case averted was much more favorable, even reaching cost-savings under certain vaccine cost and efficacy profiles. For a vaccine providing 48 months protection, the costs per case averted was always less than \$700. Although we have identified a range of potential costs per case averted depending on vaccine characteristics and age group vaccinated [−\$303 (\$25 vaccine in under 5 year olds) to \$3,191 (\$75 vaccine in 15 to 44 year olds)], it is not clear what costs would be considered acceptable as we have not conducted a formal analysis to determine a ‘break-even’ point or other threshold for vaccine cost. The cost per case averted for other vaccines varies widely; rotavirus vaccines are \$138 (RotaTeq [27]) and \$94 (Rotarix [28]), a \$50 influenza vaccine ranges from \$1,653

to \$3,315 [29], and a \$50 Lyme disease vaccine would cost \$4,466 per case averted [30]. At \$138 per case averted, routine rotavirus immunization was estimated, prior to introduction, to cost a total \$216 million to society [27]. In post introduction analyses, rotavirus vaccines have been estimated to reduce the number of hospitalizations by, saving approximately \$278 million in treatment costs (with approximately 32% coverage in those <5 years old) [31]. We estimate that a NoV vaccine could avert up to 48,000 hospitalizations and save up to \$2.1 billion annually in societal costs. Our results may help to map out appropriate pricing when a NoV vaccine reaches the market.

Our study highlights important data gaps in US NoV burden estimates that are important to consider in evaluating the health and economic benefits of vaccination and other prevention interventions. Perhaps most importantly, there are no age-specific NoV incidence rates for the US population. Thus, we applied community-based incidence data from the Infectious Intestinal Disease (IID) study from England and Wales to the US population; however, these data may not be representative of the US population. Our estimate of approximately 16.7 million cases in 2010 is lower than the current Centers for Disease Control and Prevention (CDC) estimate of 21 million; consequently, we may have underestimated the value of vaccination [2, 12]. Even with the underestimation of annual US cases, our model results for annual hospitalizations and deaths without vaccination are similar to the published estimates [10–11]. In addition, concerns exist that IID's estimates for adults and elderly were imprecise and biased downward due to the study's sampling strategy [3, 32–33]. Therefore, we assumed that the disease rate measured for younger adults also applied to older adults; if rates are actually lower in older adults, we may have overestimated the economic and health benefits in those groups. Finally, our results may not apply to certain sub-populations that are at heightened risk of disease or severe outcomes, such as military populations, nursing home residents, and travelers.

Other key parameters are vaccine efficacy and protection duration. Although the duration of natural immunity to NoV is often cited as being between 6 months and 2 years, these estimates come from highly unnatural challenge studies [34–35]. Vaccine trials have not yet been conducted to assess the duration of vaccine-induced immunity [14]. This is an issue of considerable uncertainty that may be fundamental to a vaccine's success, and its economic value. Moreover, we have not assessed the implications of the degree to which a vaccine provides cross protection, the diversity of circulating strains, or whether a vaccine will provide protection against an emerging variant. It is hoped that a bivalent (GI.1/GII.4) vaccine will provide broad cross protection [14], though this is likely to remain important issues. As additional data on vaccine performance from clinical trials becomes available, our model estimates can be further refined.

Our model, like all mathematical and computational models, made a number of simplifying assumptions due to available data limitations and cannot represent every possible outcome and event. It also could not capture all heterogeneities that exist in the general community. Data used in our model came from various studies of variable quality and uncertainty underlies our parameter estimates; therefore results may change as more data becomes available. Substantial unknowns regarding the profile of a NoV vaccine remain, including efficacy, protection duration, safety and cost; we have – to an extent – considered these uncertainties through a range of scenarios and sensitivity analyses.

Additionally, our model was designed to be conservative about the potential economic value of a NoV vaccine. We did not include transmission, hence, prevention of secondary cases by the reduction of disease transmission and herd immunity were not considered. To quantify productivity losses we assumed a 40 hour work week and losses for the duration of illness or hospitalization; in reality, a person may miss work beyond symptom duration or

hospitalization or have decreased productivity while recovering. We also did not include any additional costs of self treatment or home care (e.g., over the counter medications or diapers) as they are difficult to measure. Inclusion of these costs would only further enhance the economic value of NoV vaccination.

4.1 Conclusions

As NoV vaccines get closer to production, vaccine developers and manufactures will aim to maximize appropriate vaccine characteristics (i.e., cost, efficacy, protection duration) and target populations. Our results show that a vaccine candidate would need to have a minimal cost (<\$25) to be cost-saving in the community setting. However, even a \$75 vaccine with an efficacy of at least 50%, protecting for 24 months generally costs less than \$1,500 per case averted, which is comparable to other vaccines currently on the market. Protection duration was an important driver of cost-effectiveness, as a longer lasting vaccine provided more health and economic benefits given the same cost. Our analysis suggests that children under the age of 5 are the most attractive target population in terms of both cases averted (between 11% and 41% of all vaccinees with a 50% efficacious vaccine) and costs. Those 65 years and older may be the next most favorable group to vaccinate since they disproportionately suffer severe, and costly, outcomes. Future studies are needed to evaluate the potential economic consequences of NoV vaccination in other high-risk populations such as travelers, nursing home residents, and military personnel and groups important for transmission such as healthcare workers and food handlers.

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Highlights

- We modeled norovirus vaccination to determine its potential economic value.
- Prevented 100 – 6,125 norovirus gastroenteritis cases per 10,000 vaccinees.
- Costs per case averted were comparable to other vaccines.
- Vaccination can offer economic value while averting clinical outcomes.
- Benefits were greatest among young children and elderly.

^If yes, had probability of developing minor side effects

*Determined by vaccine efficacy and duration of protection if vaccinated

— — Denotes state transitions

Figure 1.
General Flow of Individuals in the Markov Model

Figure 2.

Cost per Norovirus Gastroenteritis Episode Averted by Vaccination A) for a Vaccine Efficacy of 50%, Cost \$25; B) for a Vaccine Efficacy of 50%, Cost \$50; C) for a Vaccine Efficacy of 50%, Cost \$75; D) for a Vaccine Efficacy of 75%, Cost \$25; E) for a Vaccine Efficacy of 75%, Cost \$50; F) for a Vaccine Efficacy of 75%, Cost \$75

Table 1**Model Input Parameters**

Variable	Distribution Type	Mean *	Range or Standard Deviation	Source
Outcome Probabilities				
Norovirus (Monthly)				
Ages 0 to 4 years	Triangular	0.0176	0.0132 – 0.0228	[3]
Ages 5 to 14 years	Triangular	0.0054	0.0037 – 0.0074	[3]
Ages 15 years and over	Triangular	0.0034	0.0026 – 0.0044	[3]
Given Symptoms				
Outpatient Visit				
Ages 0 to 4 years	Triangular	0.168	0.100 – 0.235	[2]
Ages 5 to 15 years	Triangular	0.168	0.111 – 0.226	[2]
Ages 16 to 25 years	Triangular	0.062	0.019 – 0.106	[2]
Ages 26 to 45 years	Triangular	0.064	0.041 – 0.087	[2]
Ages 46 to 65 years	Triangular	0.054	0.035 – 0.073	[2]
Ages 66 years and over	Triangular	0.103	0.063 – 0.143	[2]
Hospitalization				
Ages 0 to 4 years	Beta	0.00428	0.000178	[3, 11, 19]
Ages 5 to 17 years	Beta	0.00182	0.000074	[3, 11, 19]
Ages 18 to 64 years	Beta	0.00228	0.000092	[3, 11, 19]
Ages 65 years and over	Beta	0.01733	0.000709	[3, 11, 19]
Norovirus Mortality				
Ages 0 to 4 years	Beta	0.00000625	0.000000257	[3, 10, 19]
Ages 5 to 64 years	Beta	0.00000466	0.000000181	[3, 10, 19]
Ages 65 years and over	Beta	0.000435	0.000018	[3, 10, 19]
Given Vaccination				
Minor Side Effects	Beta	0.046	0.0019	[36]
All Causes Mortality (Annual)				
Ages 0 to <1 year	Beta	0.00648		[37]
Ages 1 to 4 years	Beta	0.000284		[37]
Ages 5 to 14 years	Beta	0.000141		[37]
Ages 15 to 24 years	Beta	0.000757		[37]
Ages 25 to 34 years	Beta	0.00103		[37]
Ages 35 to 44 years	Beta	0.0018		[37]
Ages 45 to 54 years	Beta	0.0042		[37]
Ages 55 to 64 years	Beta	0.00876		[37]
Ages 65 to 74 years	Beta	0.0198		[37]
Ages 75 to 84 years	Beta	0.049		[37]
Ages 85 and over	Beta	0.1221		[37]

Variable	Distribution Type	Mean *	Range or Standard Deviation	Source
Costs (\$US)				
Minor Side Effects (Ibuprofen)	Gamma	2.92	2.84	[38]
Outpatient Visit (Median)				
Ages 0 to 4 years	Gamma	76.17	3.10	[23]
Ages 5 to 17 years	Gamma	81.47	3.35	[23]
Ages 18 to 64 years	Gamma	102.51	4.19	[23]
Ages 65 to 74 years	Gamma	93.46	3.85	[24]
Ages 75 to 84 years	Gamma	92.13	3.80	[24]
Ages 85 years and over	Gamma	90.04	3.69	[24]
Hospitalization [†]				
Age 0 to <1 year	Gamma	2687.02	124.57	[22]
Ages 1 to 17 years	Gamma	2,962.38	181.39	[22]
Ages 18 to 44 years	Gamma	4,743.53	75.40	[22]
Ages 45 to 64 years	Gamma	5,406.81	95.07	[22]
Ages 65 to 84 years	Gamma	5,543.40	97.07	[22]
Ages 85 years and over	Gamma	5,402.44	124.57	[22]
Median Hourly Wage		17.26		[39]
All Cause Mortality	Triangular	7,342.67	5,672.21–9,862.07	[40]
Durations				
Hours worked/day		8		Assumption
Given Symptoms				
Missed Work Days (illness duration)				
Ages 0 to <1 year	Triangular	2	1 – 6	[41]
Ages 1 year and over	Triangular	2	1 – 3	[6]
Hospitalization (days)				
Age 0 to <1 year [†]	Gamma	2.1	0.1	[22]
Ages 1 to 17 years [†]	Gamma	1.9	0.1	[22]
Ages 18 to 44 years [†]	Gamma	3.1	0.5	[22]
Ages 45 to 64 years [†]	Gamma	4.4	0.9	[22]
Ages 65 to 84 years [†]	Gamma	5.9	1.2	[22]
Ages 85 years and over [†]	Gamma	4.7	0.6	[22]

* Mean value unless otherwise noted

Standard deviation reflects a $\pm 10\%$ range around the point estimate literature value

[†] Diagnosis of viral enteritis nos (ICD-9: 008.8)

[‡] Diagnosis of infectious Norwalk virus (ICD-9: 008.63)

Table 2

Clinical Outcomes Averted (Mean and 95% Credibility Interval) per 10,000 Vaccinations for a 50% Efficacious Human Norovirus Vaccine Over Four Years *

Age at Vaccination	Human Norovirus Cases Averted per 10,000 Vaccinations	Outpatient Visits Averted per 10,000 Vaccinations	Hospitalizations Averted per 10,000 Vaccinations	Deaths Averted per 10,000 Vaccinations
12 Month Protection Duration				
0 to 4	1,133 (480 to 1,760)	189 (−80 to 44)	4 (−40 to 50)	0.02
5 to 14	356 (10 to 710)	61 (−80 to 210)	0.5 (−10 to 20)	0.01
15 to 44	216 (−70 to 500)	14 (−60 to 80)	0.2 (−10 to 10)	0
45 to 64	221 (−60 to 530)	12 (−60 to 80)	0.7 (−10 to 10)	0.01
65 and over	214 (−80 to 500)	22 (−70 to 110)	4 (−30 to 40)	0.29
24 Month Protection Duration				
0 to 4	2,176 (1,530 to 2,810)	367 (110 to 630)	10 (−30 to 50)	0.03
5 to 14	685 (330 to 1,050)	116 (−20 to 260)	0.8 (−10 to 20)	0
15 to 44	436 (170 to 720)	28 (−50 to 110)	0.9 (−10 to 20)	0.01
45 to 64	421 (150 to 720)	24 (−40 to 90)	1 (−10 to 20)	0
65 and over	432 (150 to 720)	45 (−50 to 140)	8 (−30 to 50)	0.20
48 Month Protection Duration				
0 to 4	4,078 (3,490 to 4,660)	687 (450 to 950)	18 (−20 to 60)	0.03
5 to 14	1,288 (930 to 1,610)	219 (80 to 350)	2 (−10 to 20)	0.03
15 to 44	798 (520 to 1,080)	52 (−10 to 120)	2 (−10 to 20)	0
45 to 64	802 (530 to 1,080)	43 (−20 to 100)	2 (−10 to 20)	0.01
65 and over	779 (530 to 1,030)	82 (0 to 160)	14 (−20 to 50)	0.35

* Four years equals the duration of the simulation

The 95% credibility interval could not be calculated as death is such a rare event

NOTE: Since the model is stochastic, there are some situations in which more individuals in the vaccination arm develop norovirus gastroenteritis than in the non-vaccination arm. In these situations the number of cases averted is represented by a negative number.

Table 3

Net Cost* (\$US, Mean and 95% Credibility Interval) per Vaccinee with Different Costing Vaccines (Efficacy 50%)

Age at Vaccination	Vaccine Cost		
	\$25	\$50	\$75
12 Month Protection Duration			
0 to 4	-24 (-65 to 20)	6 (-43 to 49)	20 (-14 to 71)
5 to 14	14 (-1 to 31)	40 (23 to 57)	66 (48 to 83)
15 to 44	20 (-13 to 54)	42 (6 to 79)	69 (35 to 107)
45 to 64	17(-70 to 110)	44 (-51 to 132)	66 (-28 to 157)
65 and over	-2 (-632 to 571)	29 (-605 to 599)	48 (-555 to 616)
24 Month Protection Duration			
0 to 4	-57 (-96 to -10)	-33 (-72 to 16)	-8 (-45 to 39)
5 to 14	6 (-11 to 24)	32 (15 to 50)	54 (40 to 72)
15 to 44	12 (-21 to 47)	37 (3 to 71)	64 (29 to 101)
45 to 64	13 (-82 to 109)	36 (-60 to 136)	62 (-32 to 160)
65 and over	-6 (-637 to 590)	20 (-615 to 583)	43 (-586 to 660)
48 Month Protection Duration			
0 to 4	-108 (-148 to -62)	-86 (-121 to -38)	-55 (-99 to -12)
5 to 14	-15 (-27 to 5)	14 (-3 to 32)	39 (23 to 54)
15 to 44	4 (-32 to 37)	28 (-9 to 64)	53 (17 to 87)
45 to 64	3 (-97 to 94)	27 (-66 to 119)	52 (-40 to 145)
65 and over	-25 (-651 to 196)	8 (-573 to 504)	25 (-576 to 233)

NOTE: Negative values imply cost-savings; Bold implies vaccination is always cost saving.

* The values in the table represent average net cost per individual, including the cost of the vaccine itself. For example, if a \$25 vaccine provided no net benefit, its net cost would be \$25; if it provided \$25 in benefits, its net cost would be \$0 and if it provided \$50 in benefits, its net cost would be -\$25.

Table 4

Annual Disease Burden and Cost of Human Norovirus for the United States Population under Various Efficacy, Duration of Protection, and Cost Profiles for 43% and 95% Coverage

No Vaccination		Vaccine Efficacy		
		25%	50%	75%
12 Month Protection Duration				
Total Clinical Outcomes				
Cases	16.7M	16.2M to 15.6M	15.7M to 14.5M	15.2M to 13.4M
Outpatient Visits	1.80M	1.75M to 1.69M	1.70M to 1.57M	1.64M to 1.44M
Hospitalizations	69,000	67,000 to 66,000	65,000 to 61,000	63,000 to 56,000
Deaths	800	700 to 590	660 to 480	680 to 540
Total Cost of Norovirus (in billions)				
\$25 Vaccine	5.5	6.1 to 6.9	5.9 to 6.5	5.7 to 6.2
\$50 Vaccine	5.5	6.9 to 8.7	6.7 to 8.3	6.6 to 7.9
\$75 Vaccine	5.5	7.8 to 10.7	7.5 to 10.2	7.4 to 9.7
48 Month Protection Duration				
Total Clinical Outcomes				
Cases	16.7M	14.9M to 12.8M	13.1M to 8.81M	11.3M to 4.9M
Outpatient Visits	1.80M	1.61M to 1,380,000	1.41M to 950,000	1.22M to 53,000
Hospitalizations	69,000	62,000 to 54,000	53,000 to 35,000	47,000 to 21,000
Deaths	800	640 to 440	620 to 400	550 to 240
Total Cost of Norovirus (in billions)				
\$25 Vaccine	5.5	5.7 to 6.0	5.1 to 4.8	4.5 to 3.4
\$50 Vaccine	5.5	6.6 to 8.0	5.9 to 6.6	5.4 to 5.3
\$75 Vaccine	5.5	7.3 to 9.7	6.7 to 9.7	6.2 to 7.1

NOTE: M = million; range represents 43% and 95% vaccination coverage.