Cost-effectiveness of pediatric norovirus vaccination in daycare settings

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Abstract

Objective: Noroviruses are the leading cause of acute gastroenteritis in the United States and outbreaks frequently occur in daycare settings. Results of norovirus vaccine trials have been promising, however there are open questions as to whether vaccination of daycare children would be cost-effective. We investigated the incremental cost-effectiveness of a hypothetical norovirus vaccination for children in daycare settings compared to no vaccination.

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Methods: We conducted a model-based cost-effectiveness analysis using a disease transmission model of children attending daycare. Vaccination with a 90% coverage rate in addition to the observed standard of care (exclusion of symptomatic children from daycare) was compared to the observed standard of care. The main outcomes measures were infections and deaths averted, quality-adjusted life years (QALYs), costs, and incremental cost-effectiveness ratio (ICER). Cost-effectiveness was analyzed from a societal perspective, including medical costs to children as well as productivity losses of parents, over a two-year time horizon. Data sources included outbreak surveillance data and published literature.

Results: A 50% efficacious norovirus vaccine averts 571.83 norovirus cases and 0.003 norovirus-related deaths per 10,000 children compared to the observed standard of care. A $200 norovirus vaccine that is 50% efficacious has a net cost increase of $178.10 per child and 0.025 more QALYs, resulting in an ICER of $7,028/QALY. Based on the probabilistic sensitivity analysis, we estimated that a $200 vaccination with 50% efficacy was 94.0% likely to be cost-effective at a willingness-to-pay of $100,000/QALY threshold and 95.3% likely at a $150,000/QALY threshold.

Conclusion: Due to the large disease burden associated with norovirus, it is likely that vaccinating children in daycares could be cost-effective, even with modest vaccine efficacy and a high per-child cost of vaccination. Norovirus vaccination of children in daycare has a cost-effectiveness ratio similar to other commonly recommended childhood vaccines.

1. Introduction

Noroviruses are the leading cause of acute gastroenteritis (AGE) in the United States. It is estimated that approximately 19 to 21 million AGE cases are attributable to norovirus annually, and these cases result in 1.7–1.9 million outpatient visits, 400,000 emergency department visits, and between 570 and 800 deaths annually [1], leading to $10.6 billion in costs [2]. Norovirus vaccines are in late stages of safety and efficacy trials [3] prompting the analysis of potential future vaccination programs. Although norovirus outbreaks are especially severe in pediatric and elderly populations, studies suggest that the potential population-level benefits of norovirus vaccination are likely higher when delivered to a pediatric population relative to the elderly population due to the key role that children play in the transmission of norovirus throughout the population [4,5].

In the United States in 2018, 4.7 million children aged 3–5 attended pre-school (daycare), representing about 39.1 percent of this population [6]. Explosive norovirus outbreaks commonly occur in daycare settings, despite the standard recommendations to exclude symptomatic children from these venues and decontaminate. Children under the age of 5 years old have the highest incidence rates of norovirus AGE and the highest rates of outpatient, emergency department, and inpatient visits associated with norovirus (233, 38, and 9.4 per 10,000 children, respectively) [7,8]. A vaccine for norovirus could potentially reduce the incidence of norovirus in this population; however, further analysis is needed

to determine under what conditions norovirus vaccination of children in daycare would be cost-effective or not cost-effective.

We aimed to determine the cost-effectiveness of norovirus vaccination of children in daycare in addition to the observed standard of practice (excluding symptomatic children from these settings) relative to the observed standard practice alone.

2. Methods

We used a dynamic transmission model of norovirus outbreaks in daycare settings to determine the impact of disease in terms of children's health outcomes [9]. To determine the overall cost-effectiveness of potential vaccination programs, we then used the costs associated with the health outcomes from the dynamic transmission model in an economic model. We compared the outcomes of the children in daycare under two strategies. The first strategy is the observed standard of care (oSOC) in which children are not vaccinated and symptomatic children are excluded from daycare. The second strategy is vaccination of the children in the daycare in addition to the oSOC. Outcomes included the number of norovirus-related infections and deaths; healthcare resource utilization such as the costs of the hypothetical vaccination program, outpatient office visits, emergency department visits, and hospitalizations; and associated non-medical costs such as lost parental productivity.

2.1. Model description

Fig. 1 shows the decision tree used in the model. We consider a two-year period that represents the period over which the vaccine is assumed to be effective and is the typical length of time that children attend daycare. At the beginning of the time horizon, the decision-maker decides whether or not to vaccinate. After the vaccination decision is made, there is some chance that norovirus might be introduced into the daycare setting at a level sufficient to cause an outbreak within the two-year period in the absence of vaccination. Outbreaks cause some of the children to be symptomatically infected. These symptomatic infections can lead to the following outcomes: supportive care, outpatient visits, emergency department visits, hospitalization, or death. The probability of a child in the daycare becoming symptomatic depends on the attack rate which depends on whether or not a vaccination program was implemented (Fig. 1).

To determine the attack rate under the vaccination and no vaccination scenarios, we adapted a transmission model (Havumaki et al., 2021 [9]) that simulates norovirus outbreaks in daycares and was calibrated to observed outbreaks reported via the National Outbreak Reporting System (NORS) to the Centers for Disease Control and Prevention (CDC). These data include 165 daycares with a median size of 80 children (5th percentile: 7 children; 95th percentile: 410 children). The model follows a Susceptible-Exposed-I nfected-Recovered (SEIR-like) framework (see the model schematic in Fig. 2). We adapted the model to include the effects of vaccination on the transmission of norovirus within the daycare, assuming no waning effects over the two-year period.

Under the natural history model of norovirus, individuals start as susceptible (S), partially immune (P) or fully recovered and immune (R) depending on the level of acquired

immunity, from previous exposure or their innate resistance. The force of infection depends on: 1) the number of symptomatic individuals (I) and asymptomatic individuals (A); 2) the level of environmental fomite pathogen contamination (F); and 3) human-to-human and fomiteto-human transmission rates. The model also considers social distancing or individual exclusion (X), in which symptomatic children are removed from the daycare setting, as part of both the oSOC and vaccination strategies. Symptomatic children spend between 1 hour and 1 day in the symptomatic compartment before moving to the individual exclusion (X) compartment. The parameters of the infectious disease model are provided in Havumaki et al. 2021 [9] along with other key model parameters. An outbreak may occur only if norovirus is introduced into the daycare. We use the estimates of community incidence in children under the age of 5 from Phillips et al. 2010 [10] to derive a base-case estimate of 51.9% for the two-year probability that norovirus is introduced into a daycare (see Appendix 1 for details on this derivation) and assume that herd immunity would be achieved after the first outbreak for a two-year period. However, given the variability in reported community-level norovirus incidence [11], we perform a sensitivity analysis to capture this uncertainty.

2.2. Vaccination scenarios

We consider the impact of vaccination on the transmission dynamics of norovirus in the daycare setting. Because we do not know precisely how many doses might be required for a norovirus vaccine, we do not make any assumptions about whether the vaccine would be 1 or 2 doses. Rather we only consider that the total cost and total efficacy of the complete administration of all dose(s). At the individual level, we assumed that, based on vaccine efficacy, either the vaccine completely protects the individual against symptomatic infection or the individual remains completely susceptible; i.e., the vaccine take (immunity) is all or nothing. Although some clinical trials for vaccines that prevent a norovirus infection are in late stages, data on the vaccine take, efficacy, and coverage are not available yet. At the population level, we considered two scenarios, one with a 50% and another with an 80% vaccine efficacy. These two estimates are from vaccine challenge studies that suggested vaccination reduces disease by approximately 50% among vaccinated individuals [12–14]. We also assumed a 90% vaccine coverage for the pediatric daycare population, based on age-specific coverage of measles and influenza vaccines [15,16], which have been used previously to estimate coverage of a norovirus vaccine [4]. Vaccine coverage was varied from 50% to 100% in a one-way sensitivity analysis. A one-year vaccination protection period was also considered as a sensitivity analysis.

2.3. Transition rates

The model was adapted from a previously calibrated transmission model [9]. The model was calibrated to attack rate, outbreak duration, and population size data from the CDC NORS outbreak surveillance system. The model parameters were calibrated by randomly sampling 10,000 parameters and initial condition sets using Latin Hypercube Sampling [9] and using Kullback-Leibler divergence to measure the distance between the calibrated model and the NORS data. Parameter values can be found in Appendix Table A2.

2.4. Costs

The model takes a societal perspective of cost. All costs were converted to a 2019 dollars using the gross domestic product implicit price deflator [17] and future costs were discounted at a rate of 3% per year. We considered medical and non-medical costs related to the hypothetical vaccination program and costs for treatment of symptomatically infected children and productivity costs for their parents. Details are found in Table 1.

2.4.1. Costs associated with vaccination—At baseline, we assumed a net cost of norovirus vaccine dose(s) and administration to be $200 based on existing costs of newer (HPV, Zoster, and rotavirus) vaccines [18]. This cost was varied in sensitivity analysis. In addition, we considered that the administration of the vaccine dose(s) took 1 hour of a parent's time. Of all children receiving vaccination, 4.6% experienced minor side effects (17) which were managed with a children's ibuprofen which costed $3.25 [5].

2.5. Costs associated with infection

We categorize the medical costs associated with a norovirus outbreak as medical (outpatient, inpatient, ED visit oral hydration therapy, over the counter drugs), and nonmedical (transportation costs, parent/caregiver time). Of children symptomatically infected with norovirus, patients utilize the healthcare system through outpatient office visits, emergency department visits, and hospitalization with age-based probabilities listed in [15,16], although some receive supportive care only. The cost of an outpatient office visit was $93.89, the cost of an emergency department visit was $42.12 for physician costs and $124.65 for facility costs and the cost of hospitalization was $3,312.09, and the cost supportive care was $3.23 for over-the-counter medication per day [5,19,20]. We also considered non-medical costs associated with symptomatic infections such as the cost of transportation, parking, and market and non-market productivity of parents taking time off to care for their children.

2.6. Quality-of-life weights

In addition to cost outcomes, we consider the impact of norovirus infection on mortality and quality-of-life (QOL). We assigned event-specific quality-of-life weights from previously published studies of children age 18 months to 5-years of age [21–23] to patients that undergo supportive care, healthcare provider care, emergency care, and hospitalization and assumed that the length of time corresponding to these events was 2 days. We also consider loss in quality-of-life due to norovirus mortality as well as side effects associated with vaccination. Health utility weights are used to generate quality-adjusted life-years (QALYs). Future QALYs were discounted at a rate of 3% per year (Table 1).

2.7. Analysis

Overall costs and QALYs from the two strategies of the oSOC and vaccination were compared using an incremental cost-effectiveness ratio (ICER) which examines the incremental cost of vaccination (compared to the oSOC) divided by the incremental QALYs gained from vaccination (compared to the oSOC) [21]. We also compare the two strategies in terms of intermediate outcomes including cases of norovirus, outpatient visits, emergency department visits, hospitalizations, and deaths.

2.8. Sensitivity analysis

We performed a 1-way sensitivity analysis to estimate the effects of input assumptions (vaccine coverage, costs, event probabilities, and QOL weights) on ICERS. The transmission model is a stochastic model so we evaluated the model with respect to 2500 samples of the infectious disease model parameters (taken from Havumaki et al. 2021 [9] based on the distribution of parameters which best matched the NORS data). We performed probabilistic analysis using 1000 samples of cost, event probability, and QOL weights drawn independently from their respective distributions (see Table 1 for distributions).

3. Results

3.1. Base-case analysis

Table 2 shows norovirus-related outcomes per 10,000 children and norovirus-related outcomes averted per 10,000 children. A 50% efficacious vaccine led to fewer norovirus-related outcomes than the oSOC. Outpatient visits were 102.46 per 10,000 children in the 50% vaccine efficacy scenario compared to 198.53 for the oSOC, whereas emergency department (ED) visits were 12.20 per 10,000 children compared to 23.63 for the oSOC, and hospitalization were 2.61 per 10,000 children compared to 5.06 for the oSOC.

The average-per-person cost was $29.82 for the oSOC while norovirus vaccination accrued costs of $207.02 and $200.08 on average per-person in the 50% and 80% efficacy scenarios when the cost of the vaccine was $200. No vaccination led to 0.052 QALYs lost per child due to norovirus while the vaccination scenarios averaged 0.027 and 0.013 QALYs lost due to norovirus in the 50% and 80% efficacy scenarios.

Table 3 shows that norovirus vaccination is more costly than the oSOC, but leads to more QALYs than the oSOC. In the oSOC, patients lost 0.052 QALYs due to norovirus and incurred $29.82 in costs. When vaccine efficacy is 50%, costs were higher by $178.10 per person with vaccination costs of $192.53 (which accounts for 90% vaccine coverage as well as costs related to side effects and 1 hour of parental time) being offset by lower costs related to managing infections such as outpatient visits (−$3.02), emergency department costs (−$0.49), hospitalization (−$0.88), and supportive care (−$10.47). When vaccine efficacy was increased, norovirus vaccination became more cost-effective with only 0.013 QALYs lost to norovirus per person and $200.08 in total costs per person. Vaccine efficacies of 50% and 80% are expected to have an *incremental cost-effectiveness ratio* (ICER) of $7,028/QALY and $4,350/QALY respectively, when the cost of vaccination is $200.

3.2. Sensitivity analysis

Using 1-way sensitivity analysis, we identified the 10 variables that had the largest effect on ICERs. The ICERs were most sensitive to the probability of norovirus introduction within the vaccination efficacy period, days in supportive care, and quality-of-life being in supportive care. Fig. 3 shows that for the 50% vaccine efficacy and $200 cost scenario, vaccination remains cost-effective using a conventional $100,000 willingness-to-pay (WTP) per QALY threshold [24] when varying key parameters. Appendix Figs. A3 and A4 show the tornado diagrams for the other vaccine efficacy and cost scenarios. Even in the low

efficacy and high cost scenario, vaccination remains cost-effective under the low probability that norovirus is introduced into the daycare.

Because the probability of norovirus introduction was the most sensitive parameter in our analysis, we explored its full variability by conducting a detailed one-way sensitivity analysis. Fig. 4 shows the ICER as the two-year probability of norovirus introduction into the daycare is varied. Even in the more pessimistic scenario, i.e., a 50% vaccine efficacy and a $500 vaccine, norovirus vaccination would be cost-effective at a $100,000 WTP if the probability of norovirus introduction is at least 10%. For scenarios where the cost is lower or the vaccine efficacy is higher, a vaccination program would be cost-effective at the $100,000/QALY threshold for lower values of the probability of norovirus introduction. For a vaccine efficacy of 80% and a moderate cost of $200, a vaccination program would be cost-effective at a $100,000 WTP threshold if the probability of norovirus introduction is at least 3%.

Based on the probabilistic sensitivity analysis, we estimated that a $200 vaccination with 50% efficacy was 94.0% likely to be cost-effective at a WTP of $100,000/QALY threshold and 95.3% likely at a $150,000/QALY threshold (shown in Fig. 5). Under the higher (80%) efficacy scenario and a $200 cost, vaccination was 98.4% likely to be cost-effective at a $100,000/QALY threshold and 99.1% at a $150,000/QALY threshold. As expected, increased vaccination costs lowered the probability of cost-effectiveness; the high ($500) cost, low vaccine efficacy (50%) scenario showed that vaccination was 86.7% likely to be cost-effective at a $100,000/QALY threshold and 90.9% likely at a $150,000/QALY threshold (Fig. 5).

4. Discussion

Due to the large disease burden associated with norovirus, it is likely that vaccinating children in daycares could be cost-effective, even with modest vaccine efficacy and a high per-child cost of vaccination. Even with a high price of $500 per child vaccinated and a modest efficacy of 50%, vaccination is cost-effective at a WTP threshold of $100,000 per additional QALY. Compared to the oSOC, vaccination incurs more costs, but also achieves more QALYs. Vaccination leads to a modest reduction in costs related to managing norovirus infections, but these reductions do not offset the increased costs of vaccination of children. However, even with modest efficacy, vaccination gains 253 QALYs per 10,000 children over the oSOC, leading vaccination to be cost-effective.

To our knowledge, this is the first study to evaluate the health and cost impact of norovirus vaccination of a pediatric population within daycares. Earlier studies suggest that pediatric populations (children under the age of 5) would be the most impactful target population for norovirus vaccination given children's role in the transmission of norovirus [4,5]. However, these studies evaluated norovirus transmission at the national level and did not incorporate the detailed dynamics of transmission among the pediatric population within daycare settings. In contrast, our study focused on the specific transmission dynamics of norovirus outbreaks within daycare settings and is calibrated to the attack rate, duration, and population size of individual outbreaks in daycare centers reported in NORS.

These results are somewhat similar to rotavirus vaccination (another cause of acute gastroenteritis). One study found rotavirus vaccination had an ICER of about $200,000 per life-year saved [25]. Norovirus likely has higher incidence than rotavirus [26], which may contribute to norovirus vaccination potentially having a lower ICER.

The cost-effectiveness of norovirus vaccination is sensitive to the probability of introduction of norovirus into the daycare during the vaccination protection period. One-way sensitivity analyses showed that norovirus vaccination is still cost-effective using conventional thresholds in all scenarios if the probability of norovirus introduction into the daycare during the coverage period is at least 10%. Therefore, the duration of the vaccination protection period and the probability that norovirus would be introduced into a daycare during this period may be important factors to consider. In addition, the results were somewhat sensitive to quality-of-life measures for supportive care and outpatient visits which are the most common management options for symptomatic norovirus infections. The results of the probabilistic sensitivity analysis show that norovirus vaccination is more likely to be cost-effective at conventional thresholds than not, even with high cost and modest efficacy.

Our study has limitations. First, the norovirus outbreak model is calibrated to data that relies on self-reporting. These data may be under-reporting outbreaks which could potentially lead to attack rate, duration, and population size distributions that are not representative of all outbreaks in the U.S. Second, we do not include severe adverse events associated with vaccination, asymptomatic testing, daycare closures, or decontamination of daycares as part of the oSOC which could reduce the cost-effectiveness of vaccination. Third, we ignore the impact of secondary infections caused by infected children to others outside of the daycare. The findings from Steele et al. 2016 [4] suggest that decreasing infection in the pediatric population would also likely reduce illness in the elderly. While our analysis does not include transmission to older individuals, if this were an additional benefit of vaccination, then the cost-effectiveness ratios would be more favorable than in the base case. Of course, our model does include some transmission dynamics and is likely to show more favorable cost-effectiveness ratios than would a static model. Fourth, future research could investigate the transmission of norovirus among children and daycare staff as well as transmission between children and their households to investigate the impact of community burden due to norovirus in daycares. Fifth, we only evaluate the impact of the first introduction of norovirus into the daycare setting during the period of vaccine protection. However, the effects of vaccination on secondary introductions may be limited (see Appendix 1). In addition, our model makes a number of simplifying assumptions due to the available data. We assume that the effects of waning immunity are not significant. We also assume that the probability of introduction of norovirus is independent of the decision to vaccinate or not, but in the long-term, vaccination programs implemented at the national level would likely lower the probability of norovirus being introduced into daycares. There also was a lack of utility data. However, our sensitivity analyses on the utility weights did not appreciably change the ICERs. We also note that our study did not include a narrower healthcare system perspective for the cost-effectiveness analysis. We would expect a healthcare system perspective to be less favorable toward vaccination. However, a societal perspective may be more relevant for this analysis because many of the costs are incurred outside of the healthcare sector. Finally, we do not include spillover effects of infection on children on the

quality-of-life of parents. That may cause us to underestimate the societal cost-effectiveness of norovirus vaccination.

In conclusion, the use of vaccination against norovirus is likely to be cost-effective in children within daycares. Even with modest efficacy and a high cost, vaccination leads to an ICER/QALY value that is most likely cost-effective at conventional thresholds.

Acknowledgments

Appendix 1.: Model description

Here, we summarize the model from Havumaki et al. 2021 [9] and describe how we adapted this model to incorporate potential vaccination scenarios. The ordinary differential equations following the model structure as shown in Fig. 2. When no vaccination is included in the model, the equations are as follows:

Force of infection

$$N_{inf} = I + \beta_A(A_1 + A_2 + A_3) + \beta_{Va}(V_{a1} + V_{a2} + V_{a3})$$

$$\lambda = N_{inf}\beta_{HH} + (F_1 + F_2)\beta_{FH}$$

Human transmission model

$$\frac{dS}{dt} = -\lambda S$$

$$\frac{dV}{dt} = -\lambda V$$

$$\frac{dV_{a1}}{dt} = \lambda V - \rho V_{a1}$$

$$\frac{dV_{a2}}{dt} = \rho V_{a1} - \rho V_{a2}$$

$$\frac{dV_{a3}}{dt} = \rho V_{a2} - \rho V_{a3}$$

$$\frac{dE_1}{dt} = \lambda S - \mu E_1$$

$$\frac{dE_2}{dt} = \mu E_1 - \mu E_2$$

$$\frac{dE_3}{dt} = \mu E_2 - \theta \mu E_3 - (1-\theta)\mu E_3 = \mu E_2 - \mu E_3$$

$$\frac{dI}{dt} = (1-\theta)\mu E_3 - \upsilon I - \phi I$$

$$\frac{dX}{dt} = \upsilon I - \frac{1}{\left(\frac{1}{\phi} - \frac{1}{\upsilon}\right)}X$$

$$\frac{dA_1}{dt} = \phi I + \lambda P + \theta \mu E_3 + \frac{1}{\left(\frac{1}{\phi} - \frac{1}{\upsilon}\right)}X - \rho A_1$$

$$\frac{dA_2}{dt} = \rho A_1 - \rho A_2$$

$$\frac{dA_3}{dt} = \rho A_2 - \rho A_3$$

$$\frac{dR}{dt} = \rho A_3 + \rho V_{a3}$$

$$\frac{dP}{dt} = -\lambda P$$

Venue and pathogens

$$Shedding = \alpha_1 I - \alpha_l \beta_A \left(A_1 e^{-\sigma\left(\frac{1}{\phi}\right)} + A_3 e^{-\sigma\left(\frac{1}{\phi} + \frac{1}{\rho}\right)} + A_3 e^{-\sigma\left(\frac{1}{\phi} + \frac{1}{\rho} + \frac{1}{\rho}\right)} \right)$$

$$- \alpha_1 \beta_{Va} \left(V_{a1} e^{-\sigma\left(\frac{1}{\phi}\right)} + V_{a2} e^{-\sigma\left(\frac{1}{\phi} + \frac{1}{p}\right)} + V_{a3} e^{-\sigma\left(\frac{1}{\phi} + \frac{1}{\rho} + \frac{1}{\rho}\right)} \right)$$

$$\frac{dF1_t}{dt} = Shedding - \xi F1_t$$

$$\frac{dF2t}{dt} = \xi F1t - \xi F2t$$

With the following descriptions:

S = Susceptible to infection

E_1; E_2; E_3 = Exposed to infection

I = Infected with symptoms

A_1, A_2; A_3 = Infected, asymptomatic

R = Recovered, immune to disease and infection

P = Partially immune, immune to disease, but not infection

V = Vaccinated, immune to disease, but not infection

V_a = Vaccinated, asymptomatic

X_t = Excluded

F_{1_t}, F_{2_t} = Contaminated Fomite

V = Vaccinated, partially immunity to disease but not infection due to vaccination

v = Vaccine efficacy

c = Vaccine coverage

The model is represented using continuous time through an ordinary differential equation model. However, when implementing the model, the proportion of individuals across disease states is updated at predefined timesteps (every 1/25 of a day).

Appendix Table A1 shows the initial condition values and uncertainty ranges for the states in the model. Vaccination was modeled by modifying the initial conditions to reflect that

vaccinated children for whom the vaccine took would have partial immunity to norovirus disease.

Probability of norovirus introduction

To estimate the risk of norovirus introduction (at a level sufficient to cause an outbreak in the absence of vaccination), we used data from the United Kingdom estimating norovirus incidence using several methods and examining different age groups [10]. Baseline estimates of overall community incidence in children under the age of 5 was 21.4 per 100 person-years [95% credibility interval: 15.9, 27.7], and in children 0–1 (27.2 [17.9, 38.6]) and 2–4 years old (16.7 [11.4, 23.3]).

Table A1

Initial condition values and uncertainty ranges.

Symbol	Description	Initial Value
T	Total population	Sampled from the NORS Dataset
S	Susceptible	$(1-c^* v)^*(T-P-R)$
E_1 to E_3	Exposed	0 children
I	Symptomatically infected	0 children
A_1 to A_3	Asymptomatically infected	0 children
R	Recovered	0.2^*T
P	Partial immunity	r^*T where r is randomly sampled from the Uniform(0,0.8) [*]
X	Excluded	0 people
F_1, F_2	Contaminated fomite tracking compartments	10 million pathogens (0–100 million)
V	Partially immune due to vaccination	$c^* v^*(T-P-R)$

[*] The percentage starting with partial immunity is varied because there is not an established correlate of protection [31].

Table A2

Input parameter values and ranges in the infectious disease model from Havumaki et al. (2021) [9].

Infectious disease model parameter	Symbol	Estimate/uncertainty ranges	Units	Reference
Outbreak transmission model parameters				
Rate of transition through each latent state	μ	2.6	days^{-1}	[32]
Proportion of latent individuals that do not become symptomatic	θ	0.3	unitless	[13]
Transition rate from symptomatic (I) to asymptomatic (A_1)	ϕ	0.8	days^{-1}	[33]
Recovery rate	ρ	0.2	days^{-1}	[34]
Shedding rate for diseased (I, A, X) individuals	a_I	0.2520 (0.000499–0.5000)	Pathogens /day	[35]
Rate of reduction in shedding,	σ	0.2	unitless	[35]
Biphasic decay rate of norovirus in the environment	ξ	0.763 (0.036 to 1.515)	days^{-1}	[36]

Infectious disease model parameter	Symbol	Estimate/uncertainty ranges	Units	Reference
Reduction factor for asymptomatic shedding and transmission, (relative to symptomatic individuals)	β_A	−2.32 (−4.00 to −0.026)	unitless (sampled in log space)	[35]
Transmission rates				
Human-to-human transmission rates	β_{HH}	$\dfrac{0}{\text{population}}$ to $\dfrac{70}{\text{population}}$	infection/ time	[37]
Fomite-to-human transmission rate derived by multiplying a scaling factor [0,2]	β_{FH}	0 to $2\beta_{HH}$	unitless	Assumption [*]
Exclusion parameters				
Transition rate from symptomatic (I) to excluded (X)	ν	1 to 24	days^{-1}	Assumption

[*] We allow for a wide range of values which can increase or decrease rates relative to *bHH* due to a lack of empirical data on fomite to human transmission.

Base case

Using 16.7 per 100 person-years as a base-case of incidence, if we assume that 50% of norovirus cases are from norovirus outbreaks in daycares, then we have that there are 8.35 new daycare outbreak cases per 100 person-years. Based on our model, we found that a norovirus outbreak leads to a 22.8% attack rate in the absence of vaccination and therefore the annual probability of introduction of norovirus at a sufficient level to cause an outbreak is 0.3662 (0.0835/0.228 = 36.62 persons per 100). This corresponds to rate of norovirus introduction at a sufficient level to cause an outbreak of 0.3662 and therefore a two-year probability of a norovirus introduction at a sufficient level to cause an outbreak is 0.5193. We define a norovirus outbreak in a daycare setting as at least one symptomatic case of norovirus within the daycare.

Ranges

Phillips et al. [10] also report some alternative estimates using (a) accounting for uncertainty in sampling error in the incidence estimate, (b) using a cycle threshold value cutoff, (c) using a cycle Threshold Value Cutoff Plus Probable Cases, (d) subtracting Control Prevalence, (e) Electron Microscopy and (f) all RT-PCR Positive. These estimates are only for the overall age group of < 5. But, the estimates using Electron Microscopy have the lowest estimates (9.1 per 100 person-years [5.1,14.4]) and All RT-PCR Positive had the highest at 44.3 [35.2,54.4]. So, the lowest possible would be 5.1 per 100 person-years and the highest is 54.4 per 100 person-years. However, these are for the overall age group of < 5 and so we adjust this to the group aged 2–4 as compared to the overall age group of < 5 based on what was reported in the base case. In the base case, the lowest possible ratio of rates comparing the overall age group of < 5 to the group aged 2–4 is 27.7/11.4 or 0.41. The highest possible ratio of rates comparing the overall age group of < 5 to the group aged 2–4 is 23.3/15.9 or 1.47. So, if we apply the lowest estimate for the overall age group < 5 of 5.1 and multiply by the lowest possible ratio of 0.41, we get an two-year probability of introduction of 0.2004.

And, if we apply the highest estimate for the overall age group < 5 of 54.4 and multiply by the highest possible ratio of 1.47, we get an two-year probability of introduction of 0.9700.

Distributions for probabilistic sensitivity analysis

Distributions were generally chosen as normal distributions with the mean chosen to represent the base case value and the standard deviation chosen so that the 95% of the time, the variable will cover the range. Most of the time, there was little risk the distribution simulated would give a value outside of a reasonable range (probabilities < 0, probabilities > 1, utilities < 0, utilities > 1, costs < 0). However, we did left truncate the distribution for emergency department visits at 0 as the range was wide enough it could lead to an appreciable risk of giving a value<0. We also used Beta distributions for the utilities and probabilities. These distributions were parameterized with the mean as the base case value and the standard deviation representing a quarter of the range in the one-way sensitivity analysis. We used Gamma distributions for costs, and they were parameterized with the mean as the base case value and the standard deviation representing a quarter of the range in the one-way sensitivity analysis. We selected a lognormal distribution for days for the length of infection symptoms so this time would not be <0.

Assumption regarding two-year period of effective protection

Our analysis assumes that the period of effective protection is two-years. However, we also considered a scenario in which the vaccine's effective protection is only one year, so that daycares would need to vaccinate twice within the two-year period. In this scenario, we assume that all vaccination costs (costs from administering and costs of the vaccine) are doubled relative to the two-year protection scenario. We found that the assumption did not affect the cost-effectiveness. In this case, the ICER for a $200 vaccination cost scenario was $14,380/QALY and $9,105/QALY when the vaccine efficacy was 50% and 80%, respectively. The resulting costs are provided in Appendix Table A7.

Assumption regarding a secondary introduction and outbreak

Our analysis simulates a single introduction during the period of effective protection provided by the vaccine. These simulations show different attack rates under vaccination versus the oSOC. However, more than one outbreak could occur during the period. The key question is, how would infection outcomes be different between the vaccination and the oSOC during a second introduction? To get a sense of how those outcomes could be different during a second introduced outbreak, we look at the differences in the number of susceptible children at the end of the first introduction (and presumably the start of a second introduction), shown in Appendix Fig. A2. Appendix Table A3 (Table A4) show the absolute (relative) number of differences between vaccination and the oSOC for the simulated outbreaks. On average, there were 1.46 fewer susceptible children at the end of an outbreak if the vaccination program was used and vaccine efficacy was 50%. The largest difference between vaccination and the oSOC was a 51.6% difference in terms of the total number of children in the school.
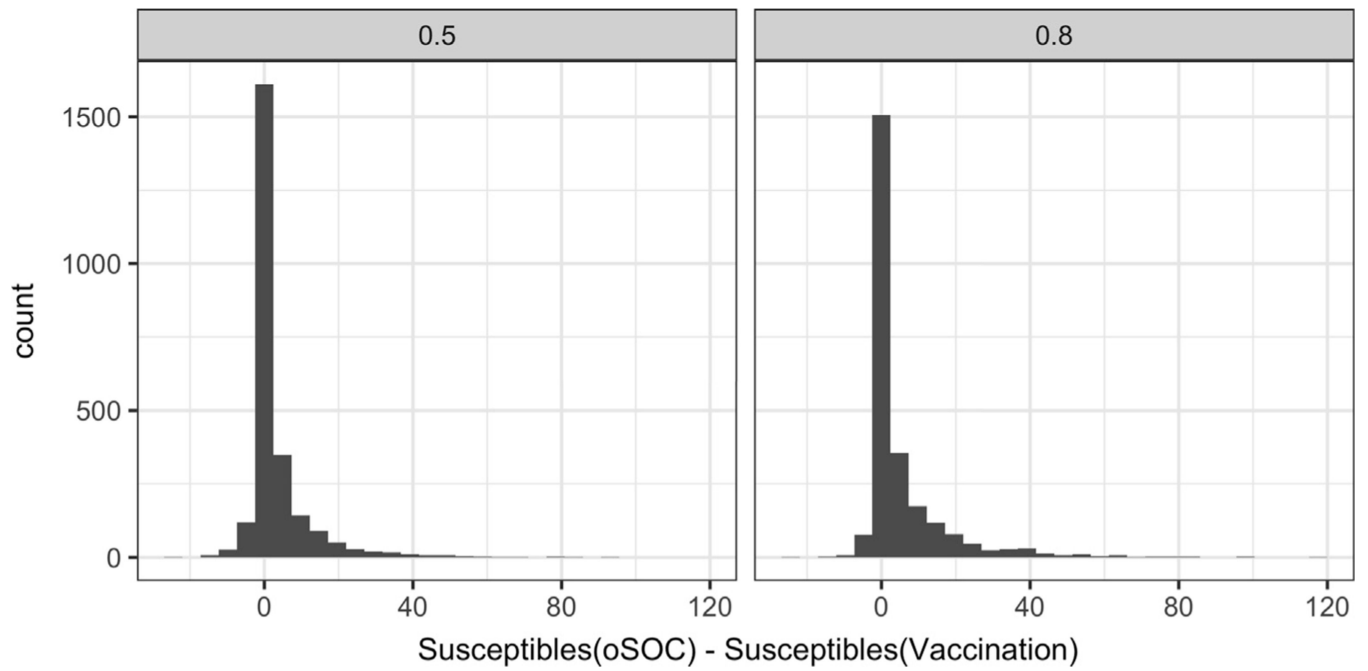
Fig. A2.
Differences of the number of susceptible children after a primary norovirus introduction under the observed standard of care (oSOC) and a vaccination program. For each vaccine efficacy scenario, we show a histogram showing the differences in number of susceptible children after an outbreak with a vaccination program in place versus the oSOC. Most of the time there are small differences in the number of susceptible children, however there are some simulated outbreaks for which these differences are larger.
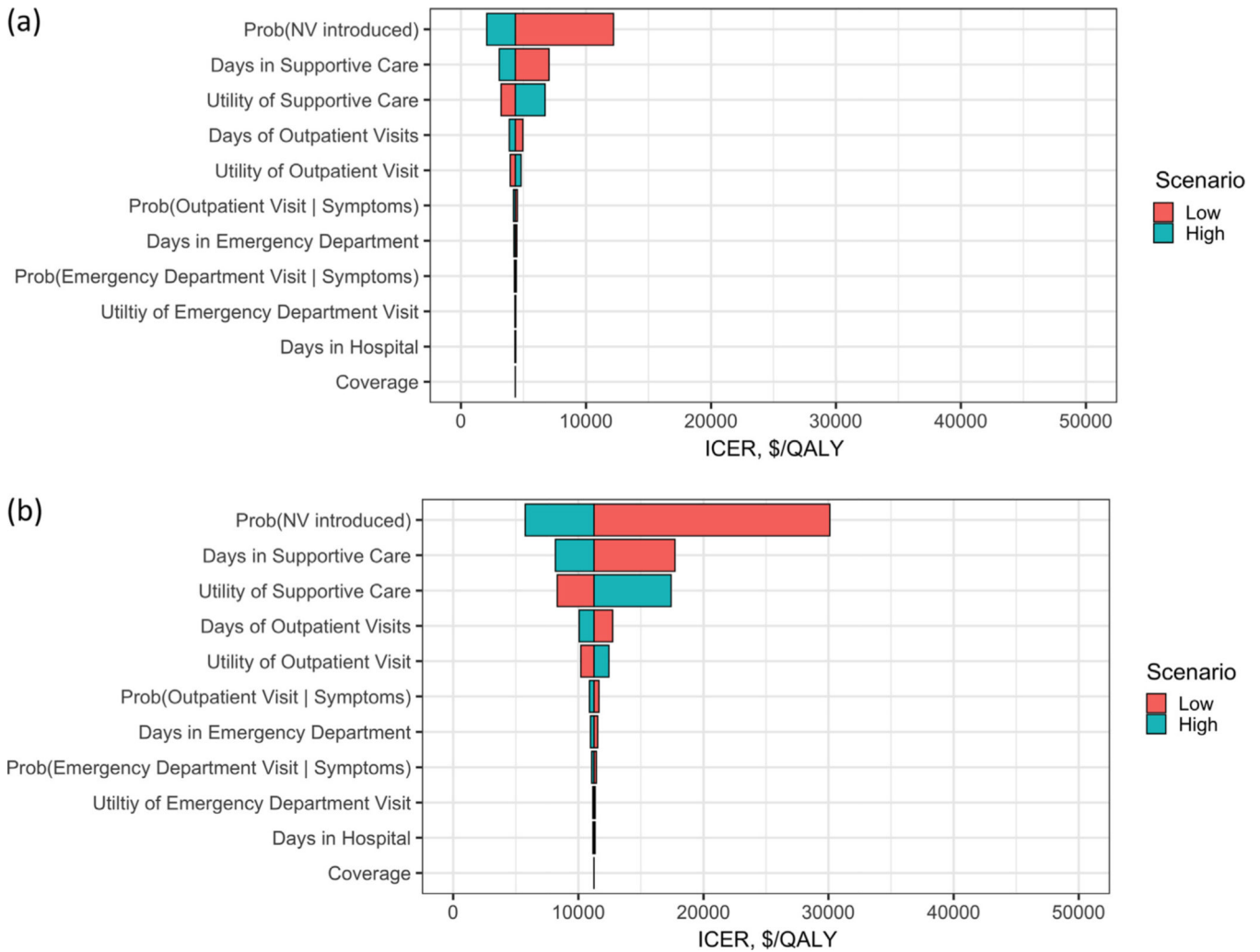
Fig. A3.
One-way sensitivity analyses for the 80% vaccine efficacy scenarios when the net cost of vaccination is (a) $200 and (b) $500. QALY: quality-adjusted life-year. ICER: Incremental cost-effectiveness ratio.

In general, due to either the induced immunity from infection after recovery or residual protection from vaccination, the number of children remaining susceptible prior to a second introduction is very similar between vaccination and the oSOC. Therefore, it would be expected that the disease outcomes in a second introduction are unlikely to be substantially different between vaccination and the oSOC. We believe that omitting a second introduction is unlikely to substantially change the conclusions.
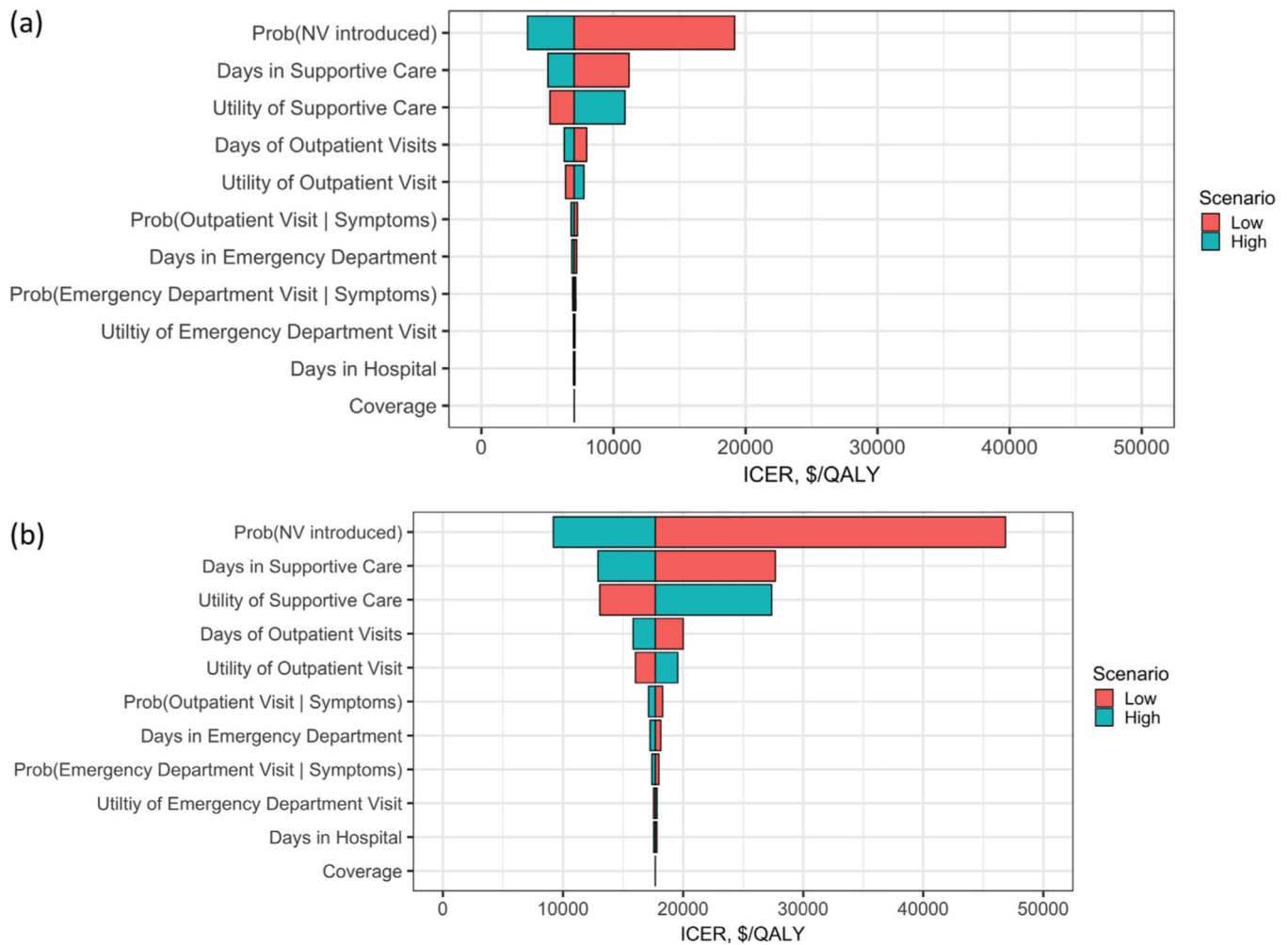
Fig. A4.

One-way sensitivity analyses for the 50% vaccine efficacy scenarios when the net cost of vaccination is (a) $200 and (b) $500. QALY: quality-adjusted life-year. ICER: Incremental cost-effectiveness ratio.

Table A3

Difference in the recovered (R), susceptible (S), partially immune (P) compartments at the end of outbreak between the vaccination strategy (V) and the observed standard of care (oSOC) in terms of the absolute number of children in the daycare.

Vaccine efficacy	$R_{oSOC}-R_V$			$P_{oSOC}-P_V$			$S_{oSOC}-S_V$		
	Average	Min	Max	Average	Min	Max	Average	Min	Max
0.5	3.34	−24	92	−4.75	−85	14	1.46	−29	80
0.8	5.40	−26	116	−8.40	−131	12	3.09	−19	110

Table A4

Difference in the recovered (R), susceptible (S), partially immune (P) compartments at the end of outbreak between the vaccination strategy (V) and the observed standard of care (oSOC) as a percentage of the number of children in the daycare.

Vaccine efficacy	R_{oSOC}-R_V (%)			P_{oSOC}-P_V (%)			S_{oSOC}-S_V (%)		
	Avg	Min	Max	Avg	Min	Max	Avg	Min	Max
0.5	3.3	−21.6	80	4.5	−70	14	1.2	−43.3	38.1
0.8	5.4	−18.9	80	8.1	−75	11.8	2.9	−22.4	52.9

One-way sensitivity analysis on proportion of latent individuals who do not become symptomatic

We conducted a one-way sensitivity analysis on the proportion of latent individuals who do not become symptomatic. We varied this proportion from 10% to 50% while keeping all other model parameters in the infectious disease model constant. We found that, in all cases, the ICER was below $50,000/QALY and did not change our findings.

In the case where 10% of individuals do not become symptomatic, the attack rate in the absence of vaccination was 0.298 and the attack rate with a 50% effective vaccine was 0.154. In this case, vaccination led to an ICER of $1,426 in the case of a $100 vaccine that was 80% effective and an ICER of $13,433 in the case of a $500 vaccine that was 50% effective.

In the case where 50% of individuals do not become symptomatic, the attack rate in the absence of vaccination was 0.157 and the attack rate with a 50% effective vaccine was 0.082. The ICER was $3,256 in the case of a $100 vaccine that was 80% effective and the ICER was $26,402 in the case of a $500 vaccine that was 50% effective.

Supportive care utility

We use 0.8 as the utility weight for supportive care. This value came from [23] which in turn cites [22], but [22] did not have this value. Therefore, the 0.8 utility weight is an assumption based on [23].

Appendix 2.: Health outcomes and associated QALYs and costs

Here, we provide additional details related to the health outcomes and their corresponding QALYs and costs under the base-case analysis and the sensitivity analyses.

Additional base-case analyses

Appendix Table A5 reports norovirus-related outcomes in terms of outcomes averted per 10,000 children relative to the observed standard of care (oSOC).

Appendix Table A6 reports norovirus-related costs per 10,000 children corresponding to each outcome associated with a norovirus infection.

One-way sensitivity analyses for vaccination efficacy and cost scenarios

Appendix Figs. A3 and A4 show the one-way sensitivity analyses for 80% and 50% vaccine efficacy scenarios, respectively.

Table A5

Norovirus-related health outcomes averted per 10,000 children vaccinated.

Vaccine efficacy	Norovirus-related outcomes averted per 10,000 children				
	Cases of norovirus	Outpatient visits	ED visits	Hospitalizations	Deaths
50%	571.83	96.07	11.44	2.45	0.003
80%	882.57	148.27	17.65	3.78	0.005

Table A6

Costs related to the management of norovirus infection.

Vaccine efficacy	Infection-related costs per 10,000 children, $			
	Outpatient visits	ED visits	Hospitalizations	Supportive care
No vaccination(oSOC)	62,376	10,117	18,195	216,447
50%	32,193	5,222	9,390	111,709
80%	15,790	2,561	4,606	54,792

oSOC: observed standard of care.

Table A7

Cost-effectiveness of norovirus vaccination compared with the oSOC in the different vaccination cost and efficacy scenarios, assuming a one-year coverage period.

Vaccine efficacy	Cost of vaccination, $[*]	Attack rate	Cost, $[*]			QALYs[*]	QALYs lost due to norovirus[*]	ICER, $/QALY
			Medical	Non-medical	Total			
No Vaccination (oSOC)	-	0.228	4.55	26.16	30.71	29.967	0.052	NA
50%	100.00	0.117	179.91	37.92	217.83	29.993	0.027	7,384
	200.00	0.117	357.21	37.92	395.13	29.993	0.027	14,380
	500.00	0.117	889.11	37.92	927.03	29.993	0.027	35,370
80%	100.00	0.058	178.72	31.04	209.75	30.006	0.013	4,475
	200.00	0.058	356.02	31.04	387.05	30.006	0.013	9,105
	500.00	0.058	887.92	31.04	918.95	30.006	0.013	22,696

QALY: quality-adjusted life-year.

ICER: incremental cost-effectiveness ratio.

[*] Future costs and QALYs are discounted. ICERs are reported based on unrounded costs and QALY estimates.

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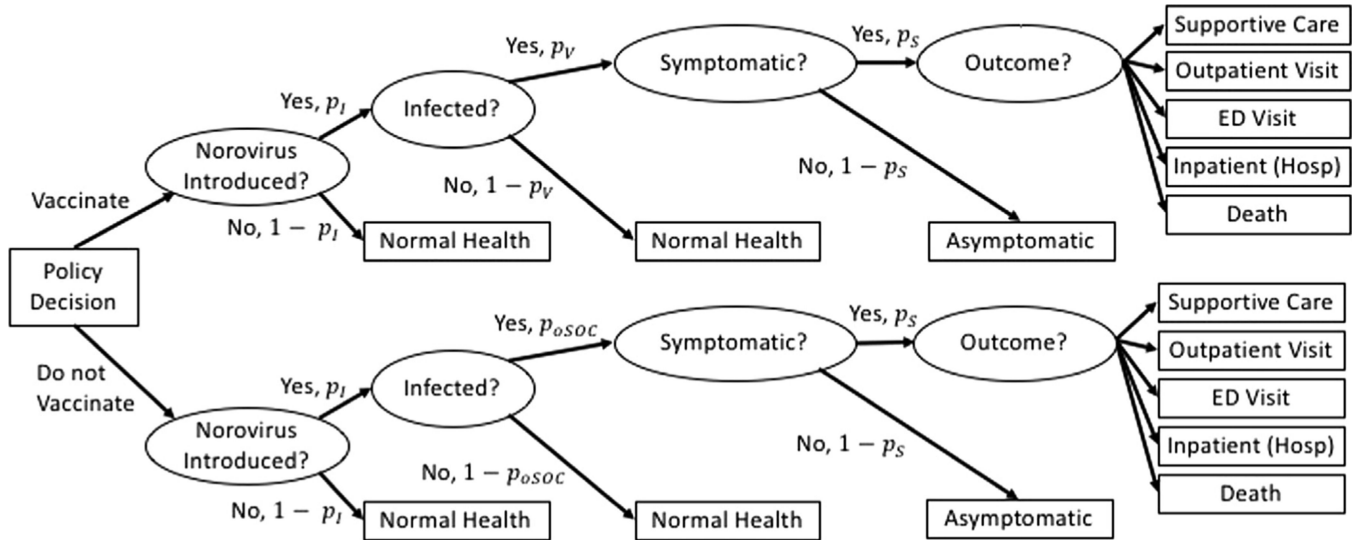
Fig. 1.

High-level decision tree of the decision to vaccinate children in daycare. After deciding whether or not to vaccinate the children in daycare, norovirus may be introduced into the daycare within the two-year period with probability p_I. Then, given that norovirus was introduced into the daycare setting, the infectious disease model determines the fraction of children that become symptomatically infected with norovirus. The fraction of children that get infected depends on their vaccination status. In the case of vaccination, the fraction of children infected given the introduction of norovirus is denoted by p_V and if the policy decision is to not vaccinate and follow the oSOC, then the fraction is denoted by p_{oSOC}. The fraction of infected individuals that develop symptoms is denoted p_S. From there, a fraction of symptomatically infected children will receive supportive care, various levels of medical care, or die. The final branches represent the highest level of care received.
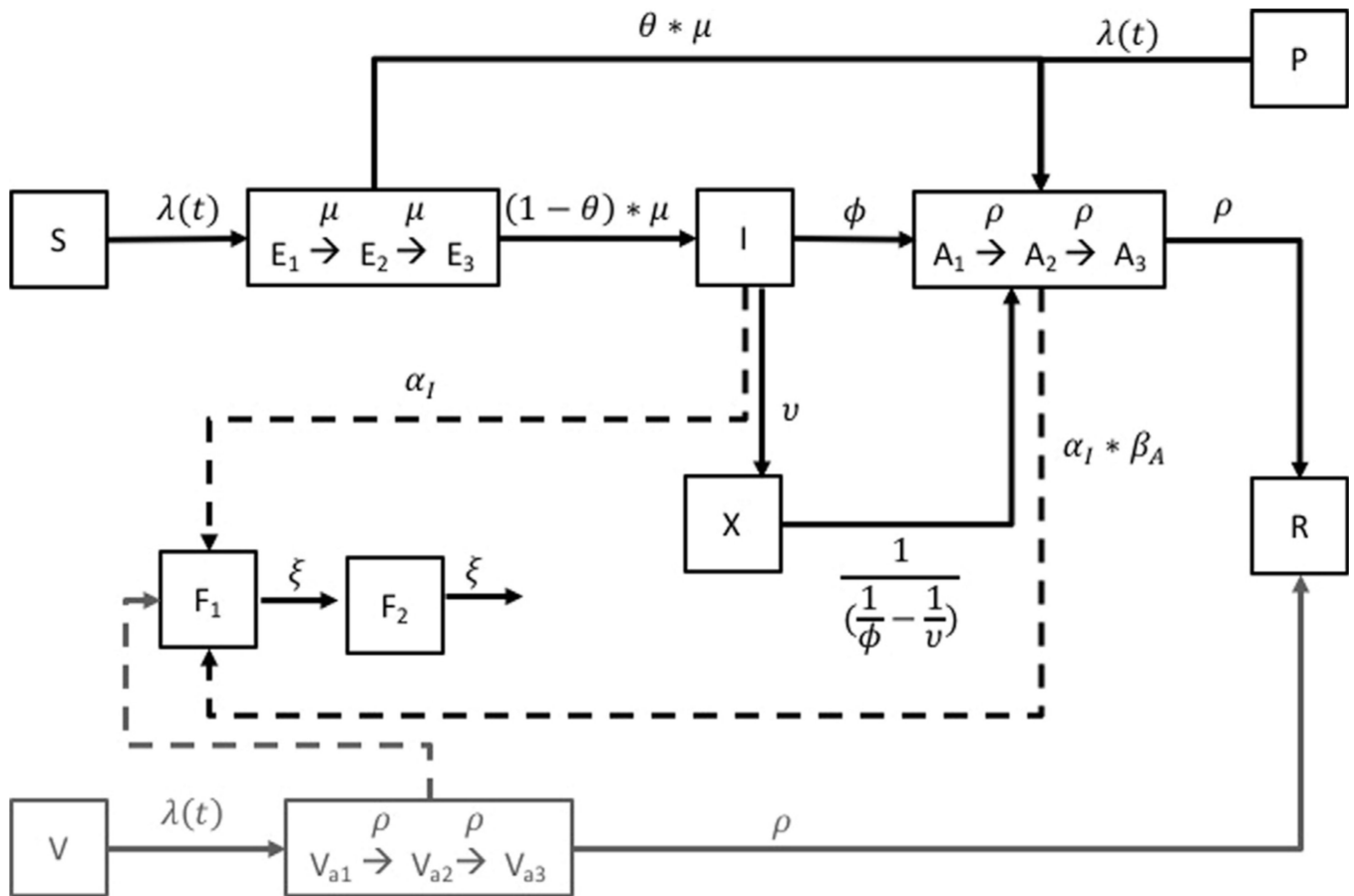
Fig. 2.
Model schematic for a norovirus outbreak in a daycare setting. The black portion of the
schematic shows norovirus outbreak in the absence of vaccination while the dark grey
components of the schematic shows the disease transmission process under vaccination. In
the no vaccination scenario, children begin in the susceptible pool (S) and become exposed
according to the force of infection $\lambda(t)$ and pass through a latent period (E_1 through E_3)
before becoming symptomatically infected or asymptomatically infected (A_1 through A_3).
We consider social distancing or individual exclusion, where children are removed from
the daycare setting, which is represented by (X). During infection, children may shed
pathogens onto environmental fomites (F_1). Pathogens on the fomites decay, moving to F_2
which represents biphasic decay. Individuals may become immune following their infection.
Individuals may also have innate resistance (R) or may be partially immune (P) at the
start of the outbreak. Those starting in (R) do not become infected whereas those starting
in (P) may become asymptomatically infected. Under a vaccination program, individuals
for which the vaccination takes are provided partial immunity (V), although they may
become asymptomatically infectious (V_{a1} to V_{a3}). Like those starting in (P), although these
individuals cannot become symptomatically infected, they may contribute to the force of
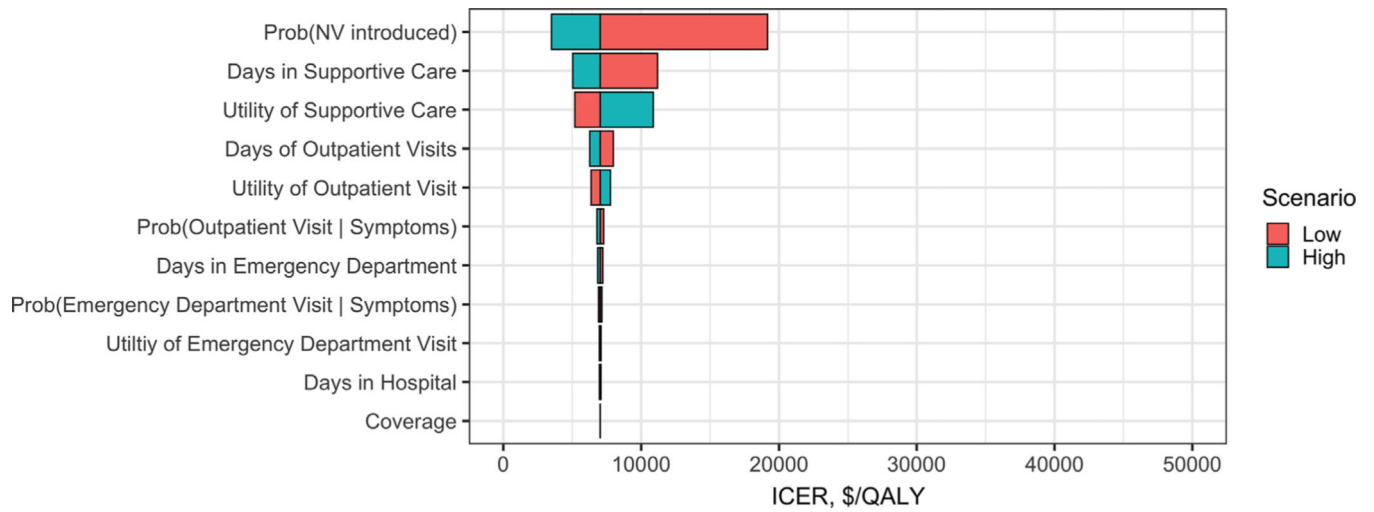infection and shed on fomites. All parameters values are listed in Appendix Table A2.

Fig. 3.
Sensitivity of the Base-case Incremental Cost-effectiveness ratio to key parameters ranked by importance and for the 50% efficacy and $200 cost scenario. NV: norovirus QALY: Quality-Adjusted Life-Year ICER: Incremental Cost-Effectiveness Ratio.

Fig. 4.
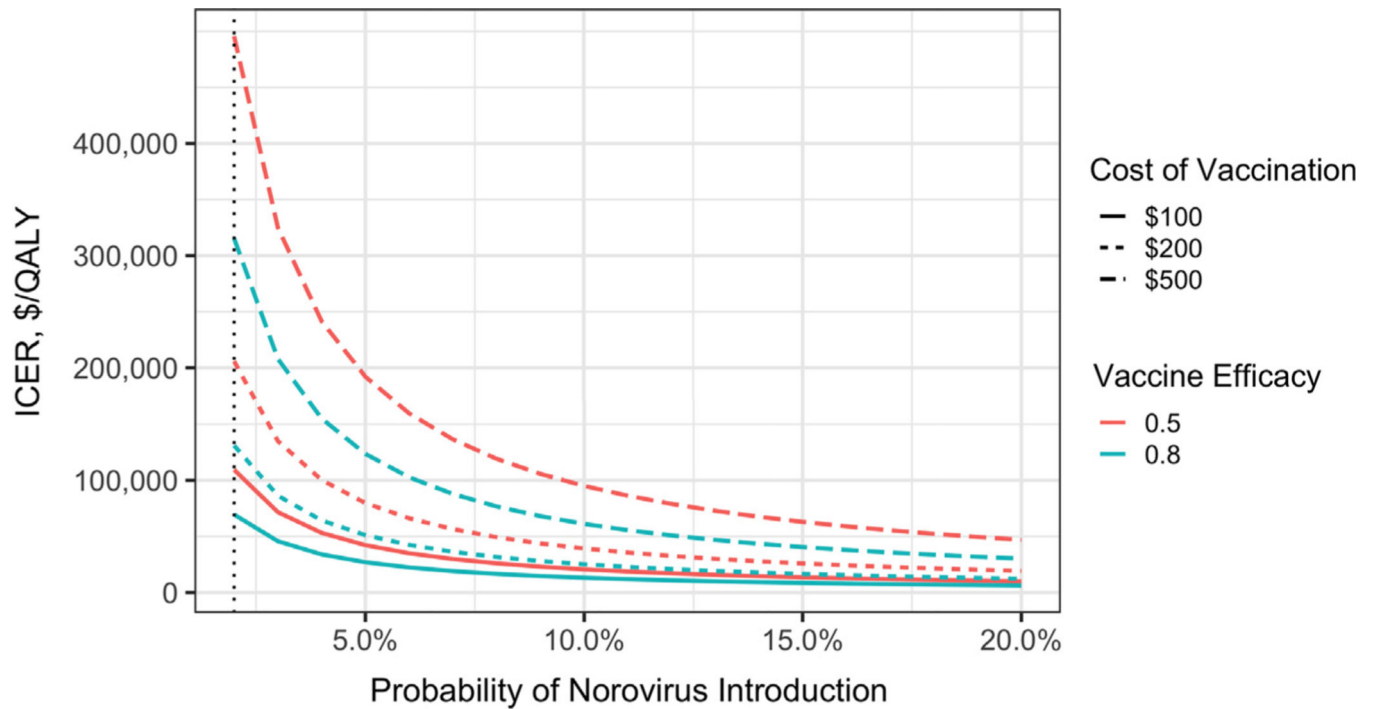Sensitivity of the Incremental cost-effectiveness ratio to the probability that norovirus is introduced into the daycare in the two-year period. The base case probability is 51.9%. The dashed vertical line corresponds to a 2% probability that norovirus is introduced into the daycare setting within the two-year period. QALY: Quality-Adjusted Life-Year ICER: Incremental Cost-Effectiveness Ratio.
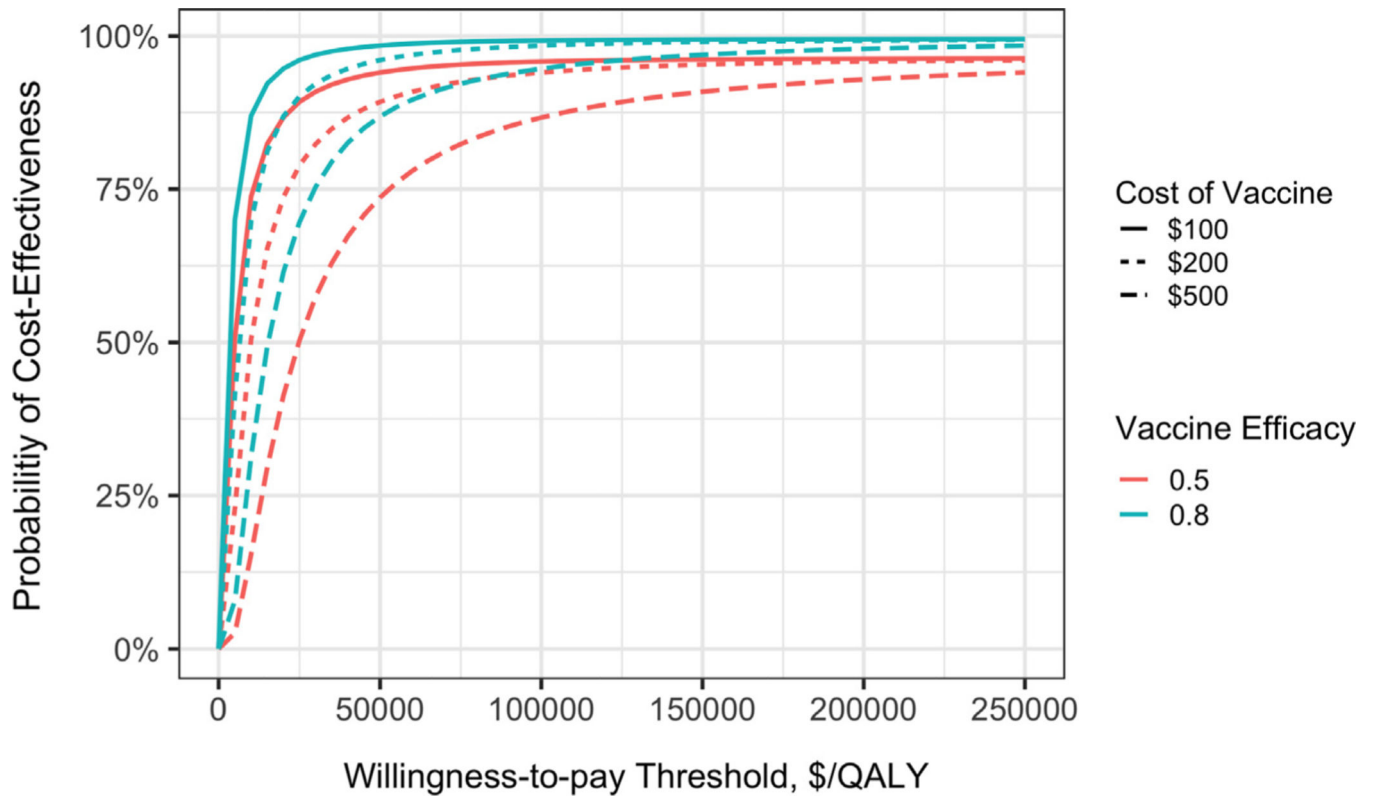
Fig. 5.
Probability of vaccination being cost-effective by willingness-to-pay threshold under various scenarios of vaccine cost and efficacy. QALY: Quality-Adjusted Life-Year.

Table 1

Estimates for key economic model parameters. Costs were converted to a 2019 baseline.

Economic model parameter	Base case	Sensitivity analysis		Reference
		1-way analysis range	Distribution for probabilistic sensitivity analysis*	
Norovirus-outbreak parameters				
Two-year probability of introduction of norovirus into daycare facility	0.5193	0.2004–0.9700	Beta(2.8,2.6)	Assumption†
Probability estimates for healthcare utilization in the event of symptomatic infection				
Outpatient office visit	0.168	0.1008–0.2352	Beta(20,98)	[1,5,26]
Emergency department visits	0.02	0.01–0.03	Beta(15,740)	[8,10]
Hospitalization	0.00428	0.002568–0.005992	Beta(24,5600)	[1,5,23]
Death	0.000006	0.000003–0.000007	Beta(35,5800000)	[1,5,10]
Quality-of-life (health utility weight)				
Perfect health	1.00			[21]
Norovirus episode requiring supportive care	0.80	0.7–0.9	Beta(48,12)	[23]¶
Norovirus episode requiring health provider care	0.69	0.55–0.82	Beta(30,14)	[22]
Norovirus episode requiring emergency care	0.425	0.33–0.52	Beta(30,14)	[27]
Norovirus episode requiring hospitalization	0.2	0.05–0.35	Beta(5.3,21)	[22]
Death	0.00			[21]
Disutility from vaccination side effects	0.001			[28]
Vaccination costs				
Cost of vaccination (administration and all doses)		$100, $200, $500		Assumption
Parental Time, hours	1	0.5–1.1	Gamma(43,0.023)	Assumption
Fraction experiencing minor side effects	0.046	0.026–0.066	NA	[5]
Cost due to minor side effects (Children's ibuprofen)	$3.25	$1.63–4.88	NA	[5]
Infection costs				
Over-the-counter medications (per day)	$3.23	$1.61–4.84	Gamma(15,0.21)	[5]
Days§	2	1–3	Lognormal(0.4, 0.8)	[23,29]
Outpatient visit, ages 0–4	$93.89	$86.24–101.53	Normal(93.89,3.90)	[5]
Emergency department visit, physician	$42.12	+/− 10%	Normal(42.12,2.15)	Medicare (physician) HCPCS 99,282 [20]

Economic model parameter	Base case	Sensitivity analysis		Reference
		1-way analysis range	**Distribution for probabilistic sensitivity analysis**[*]	
Emergency department visit, facility	$124.65	+/− 10%	Normal(124.65,6.40)	Medicare (facility) APC 5022 [19]
Inpatient hospitalization, ages 0–4	$3,312.09	$3,304.98–3,619.19	Normal(3312.33,156.98)	[5]
Productivity costs (Parents)				
Market productivity, daily[†][‡]	$141.64	+/− 10% total	+/− Normal(1,0.05)% total	[30]
Non-market productivity, daily[‡]	$78.66	productivity	productivity	[30]

[*] Numbers in parentheses for Uniform represent the minimum and maximum of the range. Numbers in parentheses for Normal represent the mean and standard deviations. Numbers in parentheses for Lognormal represent the mean and standard deviation of the distribution on a log scale. See Appendix 1 for details on choices of distributions.

[†] See Appendix 1 for the derivation of this estimate.

[‡] Productivity was estimated as an averaged of productivity for adults aged 25–44.

[§] Days refers to the length of symptomatic infection. It is used to calculate total costs of over-the-counter medications with supportive care, as well as loss of quality-of-life associated with all infection outcomes.

[¶] See Appendix 1 for more detail on this estimate.

Table 2

Norovirus-related health outcomes per 10,000 children for the vaccine efficacy scenarios.

Vaccine efficacy	Norovirus-related outcomes per 10,000 children				
	Cases	Outpatient visits	ED visits	Hospitalizations	Deaths
No Vaccination (oSOC)	1181.71	198.53	23.63	5.06	0.007
50%	609.88	102.46	12.29	2.61	0.004
80%	299.14	50.25	5.98	1.28	0.002

oSOC: observed standard of care.

ED: emergency department.

Table 3

Cost-effectiveness of norovirus vaccination compared with the oSOC in the different vaccination cost and efficacy scenarios.

Vaccine efficacy	Cost of vaccination, $	Attack rate	Cost, $*			QALYs*	QALYs lost due to norovirus*	ICER, $/QALY
			Medical	Non-Medical	Total			
No Vaccination (oSOC)	-	0.228	4.42	25.40	29.82	29.967	0.052	NA
50%	100.00	0.117	92.41	25.50	117.92	29.993	0.027	3,476
	200.00	0.117	182.41	25.50	207.92	29.993	0.027	7,028
	500.00	0.117	452.41	25.50	477.92	29.993	0.027	17,629
80%	100.00	0.058	91.25	18.82	110.08	30.006	0.013	2,051
	200.00	0.058	181.25	18.82	200.08	30.006	0.013	4,350
	500.00	0.058	451.25	18.82	470.08	30.006	0.013	11,249

QALY: quality-adjusted life-year.

ICER: incremental cost-effectiveness ratio.

*
Future costs and QALYs are discounted. ICERs are reported based on unrounded costs and QALY estimates.