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Quantifying Parameter and Structural Uncertainty of Dynamic Disease Transmission Models Using MCMC: An Application to Rotavirus Vaccination in England and Wales

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Background. *Two vaccines (Rotarix and RotaTeq) are highly effective at preventing severe rotavirus disease. Rotavirus vaccination has been introduced in the United Kingdom and other countries partly based on modeling and cost-effectiveness results. However, most of these models fail to account for the uncertainty about several vaccine characteristics and the mechanism of vaccine action.* ***Methods.*** *A deterministic dynamic transmission model of rotavirus vaccination in the United Kingdom was developed. This improves on previous models by 1) allowing for 2 different mechanisms of action for Rotarix and RotaTeq, 2) using clinical trial data to understand these mechanisms, and 3) accounting for uncertainty by using Markov Chain Monte Carlo.* ***Results.*** *In the long run, Rotarix and RotaTeq are predicted to reduce the overall rotavirus incidence by 50% (39%–63%) and 44% (30%–62%), respectively but with an increase in incidence in primary school children and adults up to 25 y of age. The vaccines are estimated to give more protection than 1 or 2 natural infections. The duration of protection is highly uncertain but has only impact on the predicted reduction in rotavirus burden for values lower than 10 y. The 2 vaccine mechanism structures fit equally well with the clinical trial data. Long-term postvaccination dynamics cannot be predicted reliably with the data available.* ***Conclusion.*** *Accounting for the joint uncertainty of several vaccine characteristics resulted in more insight into which of these are crucial for determining the impact of rotavirus vaccination. Data for up to at least 10 y postvaccination and covering older children and adults are crucial to address remaining questions on the impact of widespread rotavirus vaccination.* ***Key words:*** *rotavirus; vaccination; uncertainty; dynamic transmission model; Markov Chain Monte Carlo.* ***(Med Decis Making 2015;35:633–647)***

Rotavirus is the most common cause of acute gastroenteritis in children younger than 5 y worldwide.[1] Two vaccines are highly effective at preventing severe rotavirus disease: a monovalent human attenuated vaccine (Rotarix) and a pentavalent bovine-human reassortment vaccine (RotaTeq).[2,3] Several countries have introduced or are considering introduction of 1 of the 2 vaccines into their infant vaccination schedule.[4] Decisions about whether to and which vaccine to introduce are being informed by economic models, which project the impact of introducing either vaccine.

Cost-effectiveness analyses have drawn contrasting conclusions on the cost-effectiveness of introducing the vaccines in the United Kingdom.[5–9] The UK's Joint Committee on Vaccination and Immunization concluded that rotavirus vaccines were not cost-effective at their list prices (http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_095177.pdf). However, following a competitive tender, it was announced that Rotarix would be introduced into the United Kingdom's routine infant vaccination schedule on 1 July 2013.

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We present a new model of rotavirus transmission and vaccination. The model considers both the monovalent and pentavalent vaccine as it was used to inform the United Kingdom's decision on which vaccine to introduce. Furthermore, the model incorporates potential important aspects that have not been considered by previous published dynamic models.[10–15] Specifically, our model allows for a different mode of action of the monovalent and pentavalent rotavirus vaccine, which may result from their different valency, composition, efficacy against various disease endpoints, recommended schedule, and number of doses required.[2,3] Furthermore, we included the option that vaccine failures still can benefit from a second or third successful dose and consider the effects of between-dose immunity. This is potentially important as both vaccines have been shown to have partial efficacy prior to administration of a full course,[3,16] and omitting this between-dose efficacy could potentially underestimate the impact of a vaccination program.

With this improved model, we aim to estimate the proportion of vaccinated persons that successfully responds to each of the rotavirus vaccines, the duration of vaccine protection, the likelihood of different vaccine mechanisms, and the uncertainty around these estimates. These results are useful in their own right but also demonstrate the value of evaluating the transmission dynamics of vaccination within a formal framework to capture the uncertainty involved. This information is then used to assess the long-term impact of a universal vaccination program in England and Wales with Rotarix and RotaTeq and the uncertainty around it.

METHODS

The model was implemented in R version 2.15.2,[17] with differential equations solved using the package deSolve.[18] The code is available upon request.

Model Structure

The model structure is depicted in Figure 1, and the parameters of the model are explained in Tables 1 and 2.

Model Structure without Vaccination

We developed a deterministic age-structured dynamic model similar to a previous model used to evaluate rotavirus vaccination in England and Wales.[10] Our model estimates the age-specific incidence of rotavirus infections, symptomatic disease, and severe disease over time (in days). Thirty-eight age groups are monitored: children younger than 2 y are followed by month, 2- to 4-y-olds are followed by year, 5- to 30-y-olds are followed in 5-y age groups, and adults aged 31 y and older are monitored in 10-y age groups. Age intervals are restricted to reduce the computational budget for Markov Chain Monte Carlo (MCMC; see below) and were chosen to be similar to the data sources used for fitting but finer for children younger than 5 y, who experience most of the rotavirus burden.

Briefly, the model is structured so that children are immune at birth (maternal protection, compartment M), after which they move through 4 susceptible

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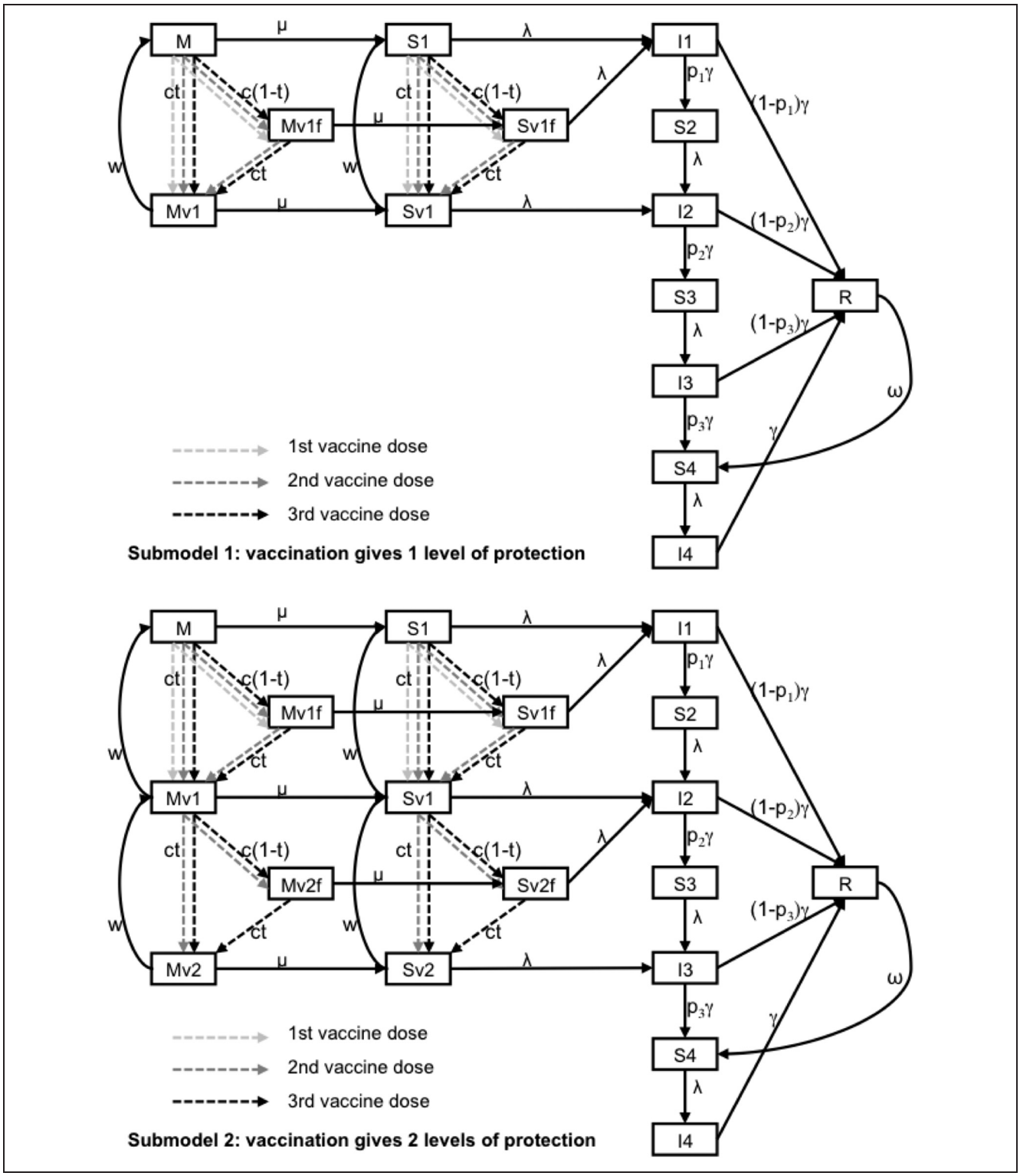

Figure 1 Age-structured rotavirus transmission model incorporating the effects of vaccination on the status of individuals in the rotavirus-related epidemiological classes. Parameter c represents the coverage of a vaccine dose. The other parameters are defined in Tables 1 and 2. A full description of the model is given in the Methods section.

Table 1 Epidemiological Parameter Definitions and Estimated Values with 95% Credible Intervals for the Model without Vaccination

Parameter	Symbol	Parameter Value	Reference
Rate of loss of maternal immunity (per day)	μ	1/90	19
Rate of recovery from infection (per day)	γ	1/8	20
Risk of becoming resusceptible after nth rotavirus infection	p_n	n = 1: 0.62 n = 2: 0.40 (0.40/0.62)[a] n = 3: 0.34 (0.34/0.40)[a] n = 4: 0[a]	21
Scaling factor proportion of infections that are symptomatic	θ	0.63 (0.24/0.38)	22
Proportion of nth infections that are symptomatic	α_n	n = 1: 0.47[a] * θ n = 2: 0.25[a] * θ n = 3: 0.32[a] * θ n = 4: 0.20[a] * θ	21
Proportion of nth infections that are severe	$sev\alpha_n$	n = 1: 0.28[a] * α_1 n = 2: 0.19[a] * α_2	21
Rate of loss of natural immunity (per year)	ω	1/90 [1/13 to 1/90]	Parameter set with highest log likelihood based on 4 Markov chain Monte Carlo chains of 150 000 samples each + 95% credible interval for each parameter
Infectivity parameter	q	0.76 [0.48 to 0.98]	
Seasonal amplitude of infectivity parameter[b]	b_1	0.11 [0.0074 to 0.15]	
Phase of cosine function in seasonal transmission[b]	ϕ	−0.53 [−2.0 to −0.04]	
Reporting rate 0–1 y old		0.07 [0.022 to 0.19]	
Reporting rate 1–4 y old		0.04 [0.025 to 0.10]	
Reporting rate 5 y and older		0.02 [0.022 to 0.023]	Based on reporting rate all ages and estimates for 0–1 and 1–4 y olds

a. Risk given that they did not become immune at the last infection.

b. Used in the equation that determines the seasonality of the rotavirus force of infection (λ), with $\lambda_{a_i t_j} = I_{a_i t_j} * \theta * b_{a_i a_i} * \varphi * b_1 * \cos(\frac{2\pi t_j}{360} + \varphi)$, where $I_{a_i t_j}$ is the number of newly infected persons of age group i on day j and $b_{a_i a_i}$ is the age-specific contact probability based on age-mixing patterns collected as part of a large European study (POLYMOD).[23] The $b_{a_i a_i}$ matrix reflects the probability of contact between persons of 4 different age groups (<1 y, 1 up to (including) 4 y, 5 up to (including) 24 y, and persons older than 24 y). The contact probabilities are presented in Appendix C.

Table 2 Estimated Vaccine Parameters for Rotarix and RotaTeq, for Models Assuming 1 or 2 Levels of Protection from a Full Vaccination Course[a]

Vaccine	Assumed Levels of Protection	Log Likelihood	Take[b] (*t*)	Duration of Protection (1/w; y)	Additional Case Protection (%)[c]
Rotarix	1	−2.38	0.93 [0.80–1.00]	9.5 [4–63]	99.998 [73–99.7]
	2	−2.48	0.99 [0.80–1.00]	3.7 [2–36]	93 [68–99.6]
RotaTeq	1	−1.71	0.94 [0.57–0.99]	67.5 [2–55]	69 [25–99]
	2	−1.77	1.00 [0.58–0.99]	3.2 [1–36]	74 [8–98]

a. Parameter sets with the highest log likelihood based on 2 Markov chain Monte Carlo chains of 150 000 samples are presented together with 95% credible intervals.
b. Take is the proportion of successfully vaccinated persons (no vaccine failures).
c. Additional case protection refers to the additional protection against becoming symptomatic in vaccinated persons compared with unvaccinated persons. Successfully vaccinated persons are assumed to have the same probability of being infected as unvaccinated individuals who experienced already 1 or 2 previous infections but to have a lower probability to become symptomatic.

(S1–S4) and infected (I1–I4) compartments (Figure 1). After each infection, a proportion of individuals enter the recovered compartment R (where they are temporarily but completely immune to re-infection), and the remainder enter the next susceptible class. The proportion of individuals assumed to move into the next susceptible class after each infection (p1–p3) decreases with the number of previous infections an individual has experienced. Immunity for individuals in the recovered compartment can wane (ω), so that they are again susceptible to reinfection but have a lower probability of becoming a symptomatic or severe case than individuals with no previous infections (this probability is assumed to be equal to having had 3 previous infections). The probability for disease transmission is seasonal to account for the winter peak of rotavirus incidence. The risk of an infected individual becoming symptomatic decreases with increasing number of previous infections and is calculated based on 2 studies. An observational study of Mexican infants[21] found that 47% of first, 25% of second, 32% of third, and 20% of fourth infections are symptomatic and that the percentage of symptomatic infections associated with severe disease is 28% of first, 19% of second, and 0% of subsequent symptomatic infections. Separately, a meta-analysis estimated the global rotavirus disease incidence in children younger than 2 y to be 0.24 symptomatic rotavirus infections per person-year.[22] This is different from the incidence of 0.38 in the Mexican infants from the study by Velazquez and others.[21] Hence, Velazquez and others' proportions of first, second, third, and fourth infections that are symptomatic are rescaled so that the overall probability for a symptomatic infection matches the global estimate (scaling parameter $\theta = 0.24/0.38$).

Adding Option for Vaccination

Although clinical trials report the reduction in rotavirus disease endpoints at various time intervals following each dose of vaccine (Table 3),[6,7,21] the exact mechanism of action of both vaccines is still uncertain. Our model incorporates 2 different vaccine mechanisms (submodels).

- Vaccine mechanism 1 assumes that there is only 1 level of protection offered by the vaccine and that a single successful dose is sufficient to generate this. The only advantage conferred by the second (or third) dose of vaccine is to reduce the overall number of vaccine failures (individuals who fail to respond to vaccination). Hence, it is assumed that at least 1 successful vaccine dose provides the same protection from infection as having had 1 natural infection (Figure 1, submodel 1).
- Vaccine mechanism 2 is the same as 1, but individuals can gain additional protection from a second or third successful dose of vaccine if already protected by a first successful dose. Hence, it is assumed that 2 successful vaccine doses provide the same protection from infection as having had 2 natural infections (Figure 1, submodel 2).

In both submodels, upon the initiation of vaccination, a proportion of those receiving a first vaccine dose are successfully vaccinated and enter the first susceptible vaccinated class (Sv1); those who are not successfully vaccinated go to the vaccine failure class (Sv1f). It is also possible to gain primary protection from a second or third vaccine dose if the first- and/or second dose is not successful. Although a German case-control study found a significant association between breast-feeding and rotavirus breakthrough infections,[24] other studies have shown that vaccine efficacy is comparable in breast-fed and

Table 3 Vaccine Efficacy Data for Rotarix[3] and RotaTeq[2,16] and Model Predictions Based on the Parameter Set with Highest Log Likelihood from 2 MCMC Chains of 150 000 Samples[a]

Vaccine Outcome Measure	Data (95% CI)	Model: 1 Level of Protection	Model: 2 Levels of Protection
Rotarix			
VE against any severity RVGE between 2 doses	0.90 (0.09–1.00)	0.92 [0.76–0.96]	0.93 [0.73–0.94]
VE against any severity RVGE first season	0.87 (0.80–0.92)	0.87 [0.76–0.88]	0.86 [0.72–0.88]
VE against severe RVGE first season	0.96 (0.90–0.99)	0.94 [0.85–0.96]	0.94 [0.85–0.95]
VE against any severity RVGE second season	0.72 (0.61–0.80)	0.70 [0.58–0.74]	0.75 [0.63–0.80]
VE against severe RVGE second season	0.86 (0.76–0.92)	0.87 [0.74–0.93]	0.86 [0.74–0.93]
RotaTeq[b]			
VE against severe RVGE after first dose	0.82 (0.39–0.97)	0.83 [0.29–0.85]	0.80 [0.21–0.80]
VE against severe RVGE after second dose	0.87[c]	0.88 [0.39–0.89]	0.89 [0.37–0.93]
VE against any severity RVGE first season	0.70[c]	0.70 [0.22–0.73]	0.74 [0.26–0.83]
VE against severe RVGE first season	1.00 (0.91–1.00)	0.89 [0.31–0.88]	0.87 [0.38–0.94]
VE against any severity RVGE second season	0.57[c]	0.57 [0.08–0.54]	0.64 [0.16–0.74]
VE against severe RVGE second season	0.94 (0.64–1.00)	0.88 [0.11–0.83]	0.76 [0.19–0.89]

a. Ninety-five percent credible intervals are constructed based on 5000 of these 150 000 samples. MCMC = Markov chain Monte Carlo; VE = vaccine efficacy; RVGE = rotavirus gastroenteritis; CI = confidence interval.
b. Per-protocol analysis.
c. Vaccine efficacy shown here is calculated from the incidence rates of the vaccinated and placebo group reported in ref. 2 and therefore not equal to the adjusted vaccine efficacy estimates as reported in ref. 2. This is because parameters were fitted against the incidence rates, not directly against vaccine efficacy estimates.

non–breast-fed infants.[25,26] Therefore, we assumed that vaccinated infants could be successfully immunized prior to waning of maternal antibodies. These individuals enter the Mv1 class, where they are still immune. Upon the waning of maternal antibodies, they enter the vaccinated susceptible Sv1 class. Waned individuals can still benefit from a subsequent dose, with the same benefit as when the first dose would have been successful (although this would happen only if the duration of protection from the vaccine is less than 2 mo, which is rather unlikely). Individuals vaccinated successfully with 1 or 2 doses have the same risk of becoming infected as unvaccinated individuals who have experienced either 1 or 2 previous natural rotavirus infections.

Estimating Model Parameters

Model parameters that could be directly informed by data are kept fixed (Table 1). All other parameters are estimated using MCMC in 2 steps: 1) estimate 4 epidemiological parameters and 2 reporting rates and 2) fix the 4 epidemiological parameters at their most likely value and estimate 3 vaccine parameters for Rotarix and RotaTeq and for each of the 2 vaccine mechanisms. The epidemiological and vaccine parameters could not be estimated within a single framework, because they were fitted to separate data sets requiring distinct model settings: the model needed to allow for rotavirus transmission when fitting epidemiological parameters based on national surveillance data but could not allow for transmission when fitting vaccine parameters based on clinical trial data (as trial participants are unlikely to contact each other). The estimation procedure is explained in more detail in the following paragraphs.

Epidemiological Parameters and Data Sets Used for Estimating Them

Four epidemiological parameters and 2 reporting rates were estimated by fitting the model to the following 3 data sets.

Data set 1: A study of rotavirus immunoglobulin M (IgM) class antibodies from 1768 routinely collected serum samples tested in Birmingham, United Kingdom, in 1997 to 1998[27] provided information on the incidence of rotavirus infection in elderly patients (where surveillance is poor). IgM is generally understood to be short lived, and therefore, we assumed it to be a marker of recent infection and therefore incidence. We explored different cutoff values for IgM titer, and at the value of 2.5, the seasonality in the data matched the known seasonality of rotavirus best (Appendix Figure A1). Hence, for fitting, we used the annual proportion of study individuals with an IgM titer greater than 2.5 in 2 age groups (0 up to 70 y old and 71 y or older; the sample size was too small to look at more than 2 age groups).

Data set 2: Rotavirus incidence in the placebo arm of a clinical trial for Rotarix[3] was used to inform the

age distribution of (severe) rotavirus incidence in children younger than 2 y. The data points corresponding to 5 trial outcomes used for fitting are shown in Appendix Table A1.

Data set 3: From Public Health England, the daily number of reported rotavirus cases was available for persons aged less than 1 y, 1 y up to (and including) 4 y, and 5 y and older for 1998 up to 2008.

The epidemiological parameters we estimated by fitting the model to the 3 data sets described above are the rate at which naturally induced immunity against rotavirus wanes (ω), the probability of transmitting rotavirus infection per contact made (q), and the amplitude (b_1) and offset (ϕ) of the forcing term, which determines the seasonality of the rotavirus force of infection (see the footnote in Table 1). Within the same fitting procedure, we also estimated 2 additional parameters: the reporting proportion to rotavirus national surveillance (data set 3) in children younger than 1 y and in children aged 1 up to (including) 4 y. Tam and others[28] showed that only 1 out of 43 (30–62) symptomatic cases were reported to national rotavirus surveillance. As it is likely that the reporting rate differs by age, we estimated the reporting proportions for the 2 youngest age groups, and based on these estimates and the estimate for all age groups from Tam and others,[28] we calculated the reporting rate for persons 5 y and older.

Because the age distribution of the seroprevalence sample differed from the age distribution of the England and Wales population in our model, fitting on this data set was weighted by age. Similarly, the overall incidence of symptomatic rotavirus infections of the placebo group of the clinical trial was slightly lower than the global estimate we used in our model (0.20 compared with 0.24 symptomatic rotavirus infections per person-year). Therefore, we did not fit our predictions directly to the clinical trial data but adjusted them first (by dividing the predictions by 0.24 and multiplying them by 0.20). Unlike our model, the clinical trial follows a single cohort over time. Hence, we summed the predicted number of symptomatic and severe rotavirus cases in 2-mo-olds in September with the cases in 3-mo-olds in October, and so on. This way, the predictions can be compared with the observed number of cases in the age cohorts of the placebo group of the clinical trial.

Vaccine Parameters and Data Sets Used for Estimating Them

We estimated separately for Rotarix and RotaTeq the proportion of individuals receiving each dose of the vaccine who successfully respond (vaccine take) and the waning of vaccine-induced protection, using the number of symptomatic and severe cases at 5 and 6 data points available from Rotarix and RotaTeq clinical trials, respectively, as shown in Table 3.[2,3,16] During the fitting procedure, the 4 epidemiological parameters were held fixed at their most likely value, because estimating the vaccine parameters conditional on the joint posterior distribution of the epidemiological parameters was computationally too expensive. Initially, we assumed, as others have, that a successful vaccine dose confers protection against becoming a symptomatic case similar to 1 or 2 natural rotavirus infections.[15] However, with this assumption, it was impossible to match the highly efficacious trial results: model efficacy estimates were well below those observed in the trial even with vaccine take at 100% and no waning of vaccine efficacy. Therefore, we decided to further assume that vaccination reduces the probability of being a symptomatic case in successful vaccine responders. In other words, we added to our model the option that vaccination protects better against symptomatic infection than natural infection (''additional case protection''). We also explored the possibility of including 2 other parameters: a reduced probability for infected vaccinees to experience severe disease (''additional severe case protection'') and/or a reduced probability to become susceptible for subsequent infection (''additional resusceptible protection''). However, there were too few data points in the vaccine trial data to concurrently estimate all 5 parameters. Also, we found that including additional severe case protection and/or resusceptible protection without including additional case protection was not sufficient to reproduce the high vaccine trial estimates. Hence, we estimate 3 vaccine parameters: waning of vaccine efficacy (w), take (t), and additional case protection.

To estimate these parameters, the model was set up in a different way than for the estimation of the epidemiological parameters: we used the model to directly replicate the vaccine clinical trials. A single birth cohort of individuals at 100% vaccine coverage was followed over a defined period (starting with 2-mo-olds getting their first dose for Rotarix on 1 January and for RotaTeq on 1 July), and the force of infection was fixed at prevaccination levels to remove the effect of herd protection since only a tiny fraction of the population is likely to be vaccinated. Because the overall incidence of symptomatic rotavirus infections of the placebo groups of the clinical trials differed slightly from the global estimate we used in our model, we did not fit our predictions directly to

the clinical trial data but adjusted them first (i.e., we divided the incidence of symptomatic cases predicted from the model with vaccination by the incidence predicted from the model without vaccination and multiplied this by the incidence of the placebo group of each clinical trial).

Estimating Parameters Using MCMC

Parameters were estimated using the Metropolis-Hastings algorithm.[29] The log likelihood for a single parameter set was calculated as the sum of log likelihoods for all data sets used for fitting, weighted by the sample size of each data set. The log likelihood per data point was based on a binomial distribution for incidence data (seroprevalence and vaccine trial data) and a Poisson distribution for count data (daily reported cases from Public Health England). Uniform priors are used for all parameters. Also, uniform proposals are used for all parameters, that is, a new sample in the MCMC chain is drawn from a uniform distribution with as minimum the current sample minus delta and as maximum the current sample plus delta, where delta for each parameter was chosen so that the acceptance rate of the MCMC chain was about 25% to 30% and so that no (strong) autocorrelation existed (based on visually checking autocorrelation plots). Samples outside the boundaries of a parameter were ''bounced back'' (i.e., new sample value = 2 $\times$ boundary value − old sample value, a method used often in MCMC analyses). Boundaries for all rate and proportion parameters were set to be between 0 and 1 (q, ω, reporting rate 0- to 1-y-olds, reporting rate 1- to 4-y-olds, *t*, additional case protection). Boundaries for the seasonal parameters ϕ and b_1 were [–pi,pi[and [0,minimum(1 − q,q)[, and the possible duration of protection of the vaccine was set between 1 day and lifelong. The estimated posterior distribution for each parameter was based on 4 (epidemiological parameters) or 2 (vaccine parameters) independent MCMC chains with different starting values spanning parameter space. Groups of chains of 150 000 samples (excluding burn-in time of 50 000 samples) were sufficiently long to obtain good mixing according to 5 criteria: visual inspection of trace plots, minimum effective sample size of 6300, passing Geweke, Heidelberg and Welch tests, and Gelman-Rubin potential reduction factor smaller than 1.2.

To estimate the epidemiological parameters, model outcomes were fitted to the data after running for 20 y. Computational time increases for increasing number of years the model is run. Preliminary runs showed that for most of the parameters sets (about 84%), equilibrium was reached after 20 y. Parameter sets for which this was not the case were rejected in the MCMC procedure.

Predictions

Because 1) we were unable to estimate the epidemiological and vaccine parameters within a single framework and 2) estimating the vaccine parameters conditional on the joint posterior distribution of the epidemiological parameters was computationally too expensive, only the uncertainty around the estimated vaccine parameters is reflected in the predictions. This was done as follows: 2 parameter sets were sampled from the joint posterior distribution of the vaccine parameters (1 for each vaccine mechanism), but only the parameter set that had the highest log likelihood was retained. In this way, the vaccine mechanism that was more poorly fitting was less likely to be sampled and retained. This procedure was repeated 5000 times, resulting in 5000 sampled and selected parameter sets for each of the vaccines. Each of these sets was used to generate epidemic time courses with vaccination. Each dose of vaccine was assumed to be administered to 91% of children at age 2 and 3 (and 4) mo, based on 2005 to 2009 coverage levels by first birthday for the diphtheria, tetanus, polio vaccine, which has a similar schedule to rotavirus.[30] All infants that started a vaccine course were assumed to complete it. Vaccination was assumed to start after 2 full years of endemic equilibrium, in the month of July (since the UK rotavirus vaccination program began in July 2013, joint DH, PHE, and NHS England letter, https://www.gov.uk/government/collections/rotavirus-vaccination-progarmme-for-infants).

Postvaccine epidemiology generated by each of the parameter and model sets was investigated in depth, and the impact of the uncertainty of the vaccine parameters and vaccine mechanism on postvaccine epidemiology was assessed.

The funders had no role in the study.

RESULTS

Epidemiological Parameters

The average probability of transmitting rotavirus when making contact is estimated to be 76% (95% credible interval, 48%–98%), and immunity from natural infection is estimated to be long (Table 1). Model predictions based on the parameter set with the highest log likelihood fit the surveillance and

vaccine trial data well; only the incidence of severe rotavirus is underestimated, whereas the rotavirus incidence in persons aged 5 y or older is overestimated (Appendix Figure A2; Appendix Table A1). Also, the seroprevalence data contribute very little to the likelihood because the rotavirus incidence in adults is largely determined by the surveillance data because of its larger sample size.

Estimated Effectiveness of Rotarix and RotaTeq and Most Probable Vaccine Mechanism

Estimated vaccine parameters are shown in Table 2 (parameter values with the highest likelihood + 95% credible intervals) and Appendix Figure A3 (posterior distributions). The best fitting parameter estimates for Rotarix replicate the vaccine trial data extremely well (Table 3). Those for RotaTeq reproduce between-dose trial vaccine efficacy values (against severe rotavirus) and vaccine efficacy against any rotavirus extremely well but underestimate vaccine efficacy against severe rotavirus after 1 and 2 seasons (Table 3). This difference is likely caused by the larger sample size of the between-dose vaccine efficacies compared with the other endpoints related to severe rotavirus gastroenteritis. The best estimates for vaccine take and especially for the waning rate and the additional case protection depend heavily on the assumed vaccine mechanism and the vaccine. The uncertainty around these estimated parameters (width of estimated posterior distribution) is greater for RotaTeq than for Rotarix and larger for the model assuming 2 levels of protection instead of only 1 level of vaccine protection (Appendix Figure A3). Models assuming 1 level of protection produced the parameter set with the highest log likelihood, which may indicate a better fit at first glance. However, once the uncertainty in parameter estimates is considered, the range of likelihoods from fitting each model to data overlapped largely, suggesting that the mechanisms of action cannot be determined with the currently available data. Indeed, when weighted according to the likelihood, almost half of the samples were drawn from each of the submodels (44% of samples for the model with Rotarix and 47% for the model with RotaTeq were drawn from submodel 2).

Predictions for England and Wales

Averaged over 20 to 50 y after vaccination, the best-fitting models predict a 50% (39%–63%; Rotarix) or 44% (30%–62%; RotaTeq) reduction in the overall burden of rotavirus disease of any severity and a 71% (60%–82%; Rotarix) or 66% (47%–82%; RotaTeq) reduction in severe rotavirus disease compared with prevaccination years. Without vaccination, more than half of all symptomatic rotavirus cases and almost 80% of severe cases are estimated to occur in children younger than 2 y. A vaccination program with Rotarix/RotaTeq is predicted to reduce symptomatic cases in this age group (2 mo up to 2 y of age) by 88% (79%–94%)/79% (60%–92%) and severe cases by 91% (83%–95%)/85% (69%–94%). In addition, it will reduce symptomatic and severe cases by 71% (61%–81%)/63% (48%–78%), by 71% (61%–81%)/63% (49%–78%) in infants aged 0 to 1 mo, and by 46% (19%–75%)/32% (0.2%–68%) and 48% (20%–74%)/37% (4%–73%) respectively, in children 2 to 4 y old. For schoolchildren aged 5 y and older, to young adults aged 25 y, all models predict an increase of 97% (65%–114%)/68% (9%–105%) in the average annual number of rotavirus cases postvaccination, which is largest in primary school children (5–10 y: 131% [83%–158%]/95% [23%–144%]; Figure 2). For severe rotavirus, the percentage increase in annual numbers is largest for the elderly but negligible in terms of absolute numbers (less than 1 person per year). The absolute increase in the number of severe rotavirus cases after vaccination is highest in 5- to 10-y-olds (Appendix Figure B1).

Following vaccination at levels of coverage expected in the United Kingdom, the best-fitting models for Rotarix and RotaTeq predict multiannual epidemics (Figure 3). Only 0.2% (Rotarix) or 0.8% (RotaTeq) of 5000 sampled parameter sets from the joint density distribution generate regular annual epidemics. Hence, the long-term postvaccination epidemiology is expected to generate major peaks interspersed with smaller, irregular epidemics (Figure 3). Importantly, there is a lot of uncertainty in these postvaccination dynamics (Appendix B, Figure B2).

From the 4 sources of uncertainty accounted for in the predictions (take, waning, additional case protection, levels of protection from vaccine), uncertainty around the waning rate has the largest impact on the predicted reduction in rotavirus disease burden postvaccination (Figure 4). The overall reduction in the number of rotavirus cases is predicted to be 50% higher when the duration of vaccination protection is 10 y instead of 1 y. However, for durations of protection of 10 y or more, there is almost no difference in the expected reduction in rotavirus cases. Longer protection from the vaccine results in a smaller increase in rotavirus incidence in schoolchildren and young adults and a higher probability

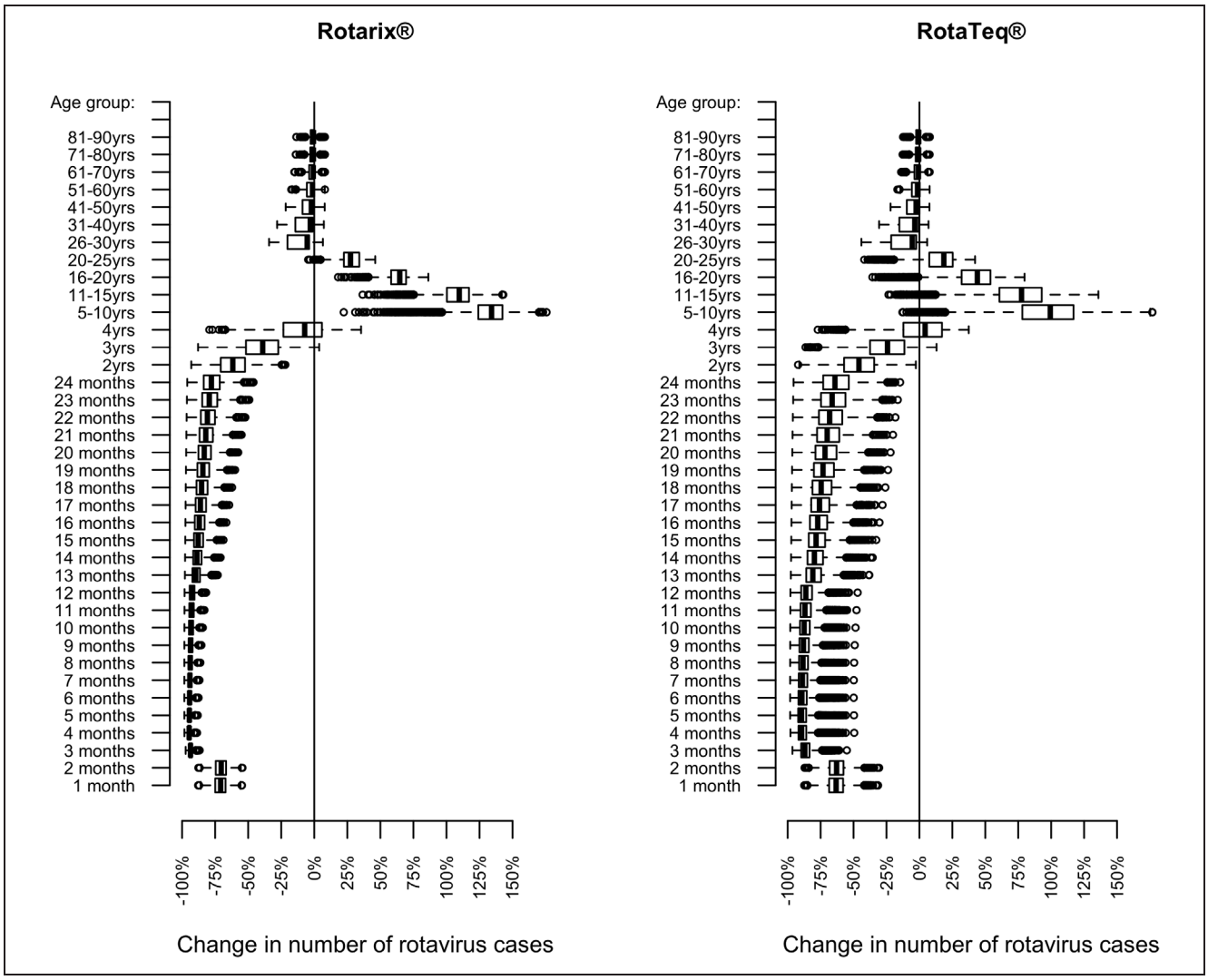

*Figure 2 Boxplots showing the percentage change in symptomatic rotavirus cases averaged over 20 to 50 y postvaccination as compared with prevaccination predicted by the model with Rotarix (left) and RotaTeq (right), based on 5000 sampled parameter sets for each vaccine (1 or 2 levels of protection sampled according to log likelihood). Boxplots: median (horizontal line within box); 50% credible interval (rectangle = interquartile range going from lower quartile q1 to higher quartile q3); q1-1.5*interquartile range and q3 + 1.5*interquartile range (whiskers); and outliers (open circles).*

for regular annual cycles. Assuming additional protection from a second (or third) vaccine dose, lower probabilities for infected vaccinees to become symptomatic induce a similar (but slightly smaller) effect.

DISCUSSION

Characteristics of Rotarix and RotaTeq

The clinical trial data are not sufficient to assess the most probable vaccine mechanism of action for Rotarix and RotaTeq. However, several other vaccine characteristics could be estimated with our approach.

The estimated proportion of children who respond successfully to the vaccines varies between 93% (80%–100%) and 100% (58%–99%). Posterior distributions are wider for RotaTeq than for Rotarix. This is because higher proportions of vaccine failures for RotaTeq as compared with Rotarix can result in a similar number of children protected, as failures of the first RotaTeq dose can obtain full vaccine protection from the second or third dose, whereas failures of the first Rotarix dose have only the second dose to get protection. Previous models have assumed percentages of successful vaccine responders ranging

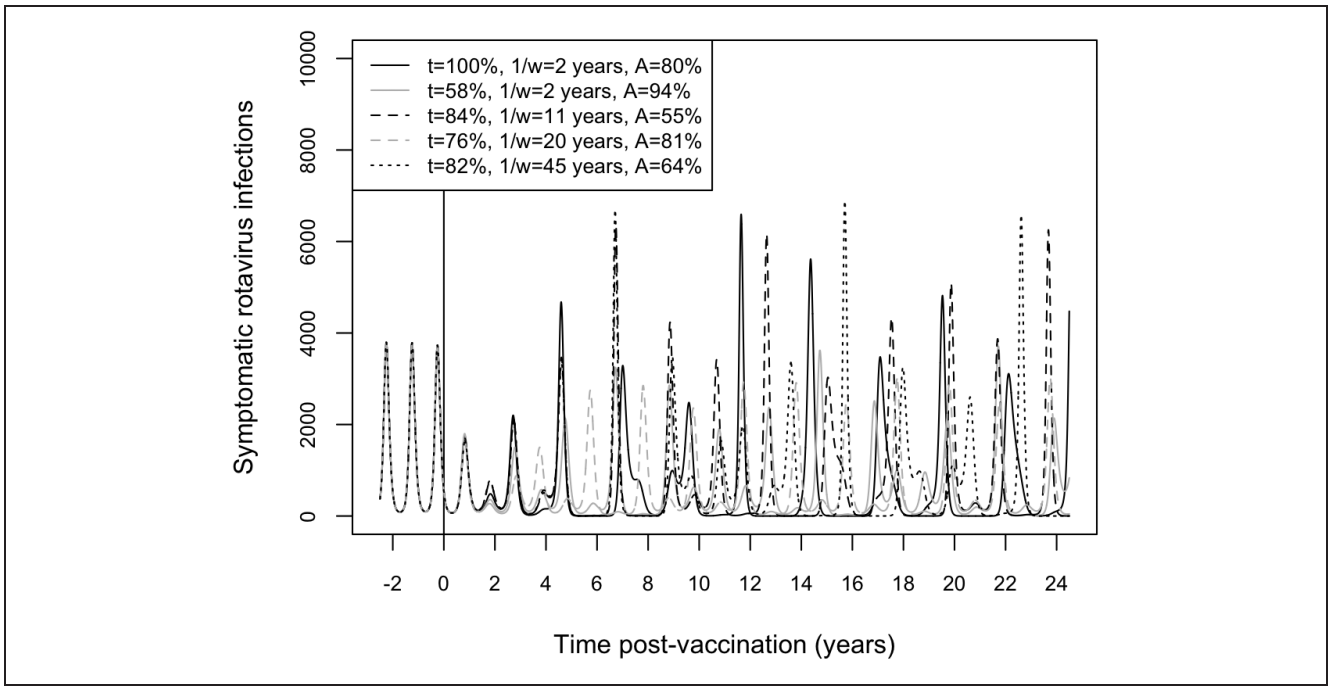

Figure 3 Model predictions for the number of symptomatic rotavirus infections for RotaTeq over time (model predictions for Rotarix are similar and therefore not shown), based on 5 randomly sampled set of values from the joint distribution of the 3 vaccine parameters (percentage responding successfully [t], duration of vaccine protection [1/w], and additional case protection [A]).

from 95%[12] to 100%,[15] hence falling within our estimated credible intervals.

Our model allows for complete waning of vaccine-induced immunity: if vaccinated, children have the same protection as having had 1 or 2 natural infections, but this protection can wane entirely. Best estimates for this duration of partial protection vary between 3.2 (1–36) and 67.5 (2–55) y. Published post-vaccination data show a sustained effectiveness against rotavirus hospitalizations up to 3 y after vaccination.[31–33] Clearly, the short follow-up period of the vaccine trial data and postmarketing studies do not allow determining the duration of vaccine protection accurately. However, by quantifying the uncertainty of this parameter explicitly and propagating this uncertainty into the model outcome (the predictions), we were able to deduce that the uncertainty in this parameter is influential only for values smaller than 10 y (Figure 4). Based on our results, the assumption of 1 y of protection made by Shim and Galvani[14] may be rather low; however, assuming no complete waning of immunity as was done by the other models[10–13,15,34] may have overestimated the impact of vaccination.

We estimated that vaccination, on top of giving the same protection as 1 (or 2) natural infections, decreases the probability of becoming symptomatic. This result suggests that previous models may have underestimated the impact of vaccination. Most of these models assumed that when vaccinated persons are infected for the first time, they have the same probability of becoming infected and developing (severe) symptoms as when they would get infected for the second (or third) time without being vaccinated.[10,12,13,15,34] We found that this assumption was not sufficient to obtain the high vaccine efficacy estimates measured in the vaccine trials of Rotarix and RotaTeq.[2,3,16] Previous modeling studies also obtained rather low vaccine efficacies against rotavirus of any severity (i.e., 64% or lower[10,14,34,35]). Only Pitzer and others[34] observed a higher vaccine efficacy (74%) when assuming 2 vaccine doses provide the same protection as 2 natural infections. With similar assumptions, we obtained a lower vaccine efficacy because we assumed a lower overall probability for an infected person to become symptomatic than Pitzer and others[34] (i.e., unlike Pitzer and others,[34] we adjusted the values from Velazquez's study[21]; see the methods in the ''Model Structure without Vaccination'' section). Alternatively, we may have overestimated vaccine effectiveness by using vaccine efficacy data from clinical trials with strict inclusion

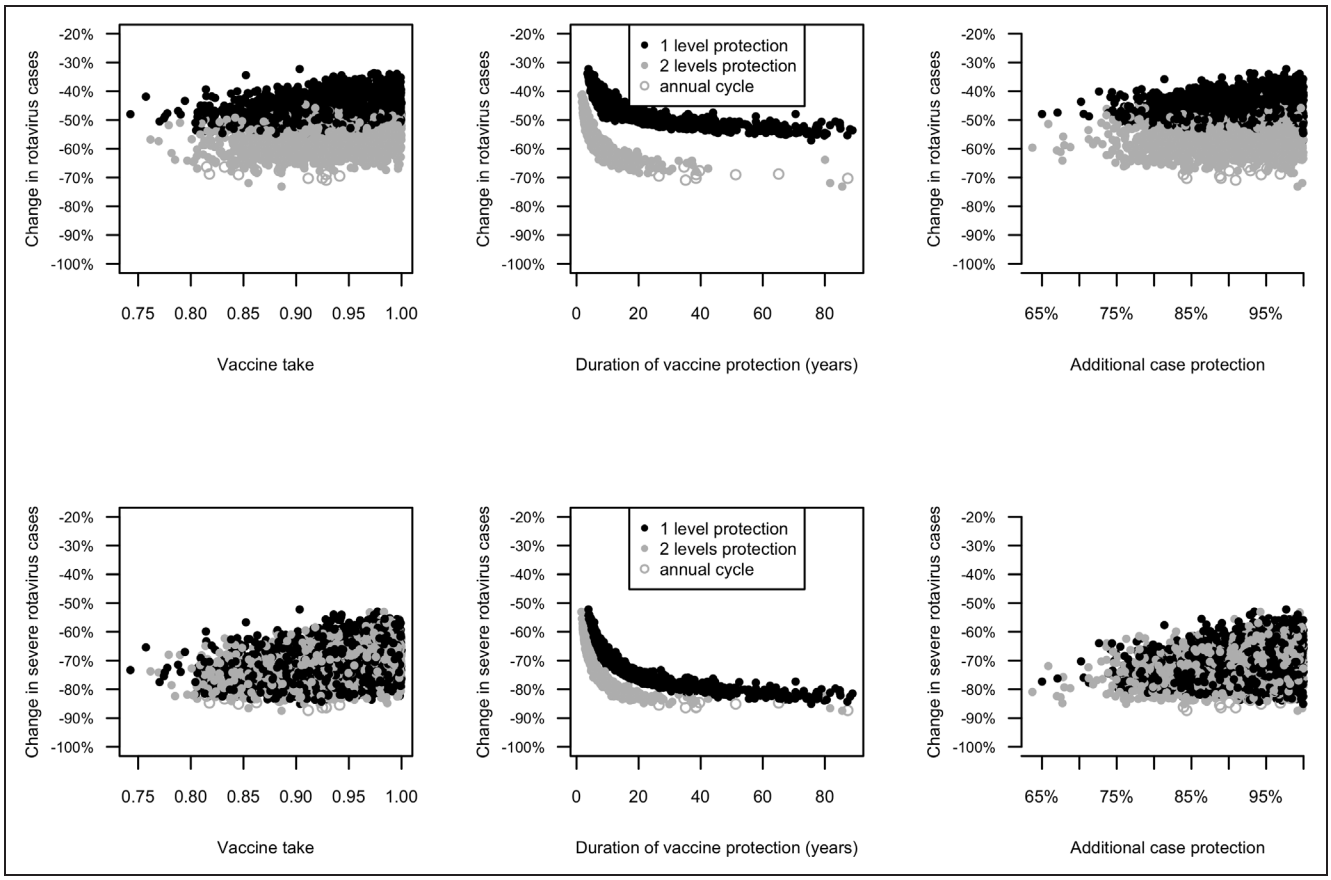

Figure 4 Predicted reduction in the number of symptomatic (top) and severe (bottom) rotavirus cases as a function of vaccine take, duration of protection from the vaccine, the additional case protection, and the assumed levels of protection. Predictions from 5000 parameter sets drawn from their estimated joint distribution. Predictions resulting in annual cycles are marked with open circles. Predictions for RotaTeq are very similar to the ones for Rotarix and therefore not shown.

criteria. However, studies from developed countries show effectiveness values against hospital admission similar to the efficacy values estimates in the clinical trials (e.g., refs. 36 and 37).

Predicted Impact of Vaccination

The impact of vaccination is predicted to be slightly larger for Rotarix than for RotaTeq, but credible intervals overlap substantially. Both vaccines will likely induce a large reduction in the overall burden of rotavirus disease but also an increased incidence in primary school children and young adults up to 25 y (average over 20 to 50 y postvaccination). This increase is predicted because our model assumed the probability of infection to depend on the number of previous infections (cf. refs. 10, 12, 13, 34). Therefore, children become susceptible to (re-)infection at older ages because they were (temporarily) protected by the vaccine when infants. When using an age-dependent infection probability, no shift in rotavirus burden toward the older age groups is expected (e.g., refs. 11, 14, 15, 34). US surveillance data have shown a decline in rotavirus infections and/or hospitalizations in older children and adults the first seasons after vaccine licensure (e.g., refs. 38, 39). This may indicate that the probability of infection and/or severe infection decreases with increasing age. However, data are available for only several years, and the long-term impact of rotavirus vaccination on unvaccinated individuals remains unclear.[40]

Although the expected decrease in rotavirus disease burden after vaccination is consistent for both vaccines and vaccine mechanisms, the size, timing, and frequency of postvaccination rotavirus epidemics are highly uncertain (Figure 3). As Pitzer and others[34] noted, the amplitude of the seasonal forcing

is estimated to be quite low, indicating that most of the cycling of the incidence is induced by the interaction of susceptible and infected persons. Depending on the model structure and/or the assumed vaccine coverage, published models predicted regular annual cycles or more irregular postvaccination dynamics.[34] None of these models, however, accounted for joint parameter uncertainty. Therefore, it is unclear if these predicted postvaccination dynamics are specific to a certain model structure and/or if they are the result of the chosen parameter values. In this study, the uncertainty of the vaccine parameters dominated the uncertainty resulting from the 2 different vaccine mechanisms (structural uncertainty). Postvaccination data from the United States indicate the emergence of biennial patterns.[38,41,42] In a few years, incidence data for 5 to 10 y postmarketing from other countries may shed more light on rotavirus postvaccination dynamics.

Accounting for Model Structure and Parameter Uncertainty Using MCMC

This is one of the first studies that used MCMC to account for uncertainty involved in a transmission dynamic model. Although the procedure remains computationally expensive and capturing all (possibly relevant) uncertainties was therefore not possible, our approach gave more insight in several aspects of the rotavirus vaccines.

One of the main reasons MCMC is not often used for estimating parameters of complex dynamic disease transmission models is that it is computationally costly. Running one MCMC chain to estimate our epidemiological parameters took about 2 wk on a PC with an Intel Xeon(R) CPU W5580 processor at 3.20 GHz (23.5 GiB memory). The computational time increases rapidly with the increasing number of differential equations and longer time frames over which to solve them. For the epidemiological parameters, time to equilibrium depends on the parameter set, so each parameter set has to be evaluated for a sufficiently long time, which is why this step takes so long. However, the disadvantage of a long runtime may be outweighed by the advantages of precise estimation of parameters and their joint uncertainty distribution, which allows for more precise identification of the information available and still lacking and of how important each source of uncertainty is in determining the predictions. Indeed, we show that although the 3 estimated vaccine parameters have relatively large credible intervals, only the uncertainty around the duration of vaccine protection strongly affects the expected reduction in rotavirus disease burden after vaccination.

Although our model is the first to incorporate several important aspects and sources of uncertainty related to rotavirus transmission and vaccination, we were unable to capture all uncertainty, mainly because that would be computationally too expensive. For instance, to consider the uncertainty around the reporting rate of rotavirus to national surveillance,[28] the global estimate of the incidence of symptomatic rotavirus infection,[22] and the UK contact data,[23] we would need to run the MCMC for every combination of values of the uncertainty distributions of these parameters. We decided to keep them fixed, as relative good data exist. The social contact data we included in our analysis resulted in the best fit to the UK national surveillance data in another analysis.[10] Furthermore, we assumed that breast-feeding had no effect on vaccine efficacy, that the vaccine mechanism was ''leaky-or-nothing,'' that only symptomatic cases transmit rotavirus, and that transmission is not dependent on disease severity. A German case-control study[24] found a significant association between breast-feeding and breakthrough rotavirus infection, although no difference in vaccine efficacy was found in a European clinical trial.[26] When more evidence becomes available, our assumption of no impact of breast-feeding on vaccine efficacy may need to be reconsidered. We assumed that a proportion (take) of vaccinated individuals seroconverted and hence benefitted from vaccination, whereas another proportion (1-take) did not receive any protection (i.e., leaky-or-nothing[43]). The exact way of how the vaccine works is difficult to determine; however, our assumption is the same as previous rotavirus models (e.g., ref. 34). If asymptomatic cases have a nonnegligible contribution to the transmission process, we may have overestimated the probability to get infected and consequently the impact of vaccination on this. Recently, Weidemann and others[44] estimated the infectiousness of symptomatically infected individuals to be 10 times higher than that of asymptomatically infected individuals, based on a modeling study. However, little is known about how much rotavirus transmission depends on disease severity, and previous models have made different assumptions. Therefore, ideally, the uncertainty around this assumption should be accounted for. Unfortunately, this was not feasible within the time available for our analysis. Lastly, and maybe most importantly, we were unable to capture uncertainty in prevaccination rotavirus natural history

and epidemiology, as well as vaccine action, within the same framework. This is because the 2 aspects of the model were fitted to separate data sets requiring distinct model settings. Pitzer and others[34] showed that different epidemiological model structures can result in different predictions for the impact of vaccination. Hence, a key area for future modeling work when sufficient data become available spanning both the pre- and postvaccination era will be to account for both epidemiological and vaccine parameter uncertainty at the same time.

Epidemiological Parameters

The model without vaccination has a rather poor fit to the reported cases in persons older than 4 y and to the incidence of severe cases in the placebo group of the vaccine clinical trial. One explanation for the difference in predicted and reported daily reported rotavirus cases is that older individuals are less likely to be recorded or tested for rotavirus. Also, the small number of cases in older age groups means that the model fitting procedure takes little notice of the results for this age group. The difference in the predicted and reported incidence of severe cases is probably due to a different probability of becoming severe in the clinical trial study as opposed to the one we used in our model.[21]

CONCLUSION

Accounting for the joint uncertainty of several vaccine characteristics resulted in more insight as to which of these are crucial for determining the impact of rotavirus vaccination. Best-fitting models suggest that rotavirus vaccines provide more protection than 1 or 2 natural infections do, and the duration of protection of the vaccine is very influential if it is lower than 10 y. Long-term postvaccination data that also cover older children and adults will be crucial to address remaining questions on the impact of widespread rotavirus vaccination.

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