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A mathematical model of the indirect effects of rotavirus vaccination

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SUMMARY

Rotavirus (RV) infections progressively confer natural immunity against subsequent infection. Similarly to natural infection, vaccination with a live attenuated vaccine potentially reduces RV transmission and induces herd protection. A mathematical transmission model was developed to project the impact of a vaccination programme on the incidence of RV infection and disease for five countries in the European Union. With vaccination coverage rates of 70%, 90% and 95% the model predicted that, in addition to the direct effect of vaccination, herd protection induced a reduction in RV-related gastroenteritis (GE) incidence of 25%, 22% and 20%, respectively, for RV-GE of any severity, and of 19%, 15%, and 13%, respectively, for moderate-to-severe RV-GE, 5 years after implementation of a vaccination programme.

Key words: Herd protection, mathematical model, rotavirus, vaccination.

INTRODUCTION

Rotavirus (RV) is the leading cause of acute gastroenteritis (GE) and one of the major causes of diarrhoea-related hospitalizations and deaths in young children worldwide [1]. RV epidemics that peak during winter and abate during summer occur in developing and developed countries [1]. In developing countries, RV infections account for more than one third of all childhood diarrhoea-related hospitalizations and more than 600 000 childhood diarrhoea-related deaths annually [1]. The RV disease burden is also high in developed countries, including those of the European Union (EU), where up to 700 000 outpatient visits, 87 000 hospitalizations and 230 deaths are expected to occur each year, with impacts on health systems and on society [2]. Recent data from five European countries indicate that RV is responsible for up to 56% of all hospitalized acute GE cases in children aged <5 years [3].

RV infection progressively confers protection against future RV infection (including asymptomatic infection) and RV-GE via natural immunity, as demonstrated by two longitudinal studies conducted in Australia [4] and Mexico [5]. These studies provide the basis for vaccination, which mimics natural infection, as a means to reduce RV infection, disease and transmission in the population.

In recent years, two new RV vaccines have been successfully developed: a live attenuated G1P[8] two-dose human RV vaccine (Rotarix™, GlaxoSmithKline Biologicals, Belgium), and a live bovine-human reassortant vaccine: G1P[5], G2P[5], G3P[5], G4P[5] and G6P[8] three-dose vaccine (Rotateq™, Merck &

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Co. Inc., USA). Large randomized clinical trials have assessed the safety, immunogenicity and direct effects of these vaccines in different populations, showing comparable and high efficacy overall for RV-GE and severe RV-GE in the first and second year post-vaccination [6, 7].

To optimize the public health impact of these vaccines, high coverage rates are critical, as demonstrated by the eradication of smallpox in 1980, and the introduction of routine vaccination programmes for other infectious agents including poliomyelitis, diphtheria/pertussis/tetanus, measles, pneumococcal, and meningococcal disease [8]. High RV vaccine coverage has the potential to substantially reduce RV infection and disease in populations, prevent disease outbreaks and limit disease transmission.

RV vaccination programmes have already been implemented in several Latin American countries, Australia, the USA and in some EU countries. The European Society for Paediatric Infectious Diseases (ESPID) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Rotavirus Expert Working Group have produced recommendations for RV vaccination and are encouraging the incorporation of RV vaccine into all European vaccination schedules [9]. The WHO has recently made recommendations to include RV vaccination of infants into all national immunization programmes [10].

Most existing models for RV have been developed to evaluate the cost-effectiveness of a vaccination programme based on a 'cohort model', where the number of cases averted by vaccination is evaluated by comparing the number of cases in a vaccinated cohort *vs*. a non-vaccinated cohort over a specified period of time [11–14]. Most cohort models account only for the direct effects of vaccination in vaccinated individuals and do not account for the effects of herd protection. A recent cohort model did account for herd protection indirectly using estimates of herd protection obtained from dynamic models [15]. Because vaccination is expected to reduce disease transmission in the population, indirect effects or 'herd protection' may be conferred to the total population in addition to the direct effect of vaccination in those vaccinated. Mathematical 'dynamic' models allow for evaluation of both direct and indirect effects induced by vaccination [16, 17].

We developed a mathematical dynamic transmission model of RV to project the population-level impact of RV vaccination in children within a national vaccination programme in Europe. The model is based on current knowledge of the natural history of RV, transmission within the population, and RV age-specific incidence [18], adjusted for under-reporting. The model also accounts for both direct and indirect herd protection effects induced by vaccination, under the assumption that human strain-derived vaccination mimics natural infection. We evaluated the potential for spread of RV in the population and estimated the magnitude of herd protection with different vaccine coverage rates.

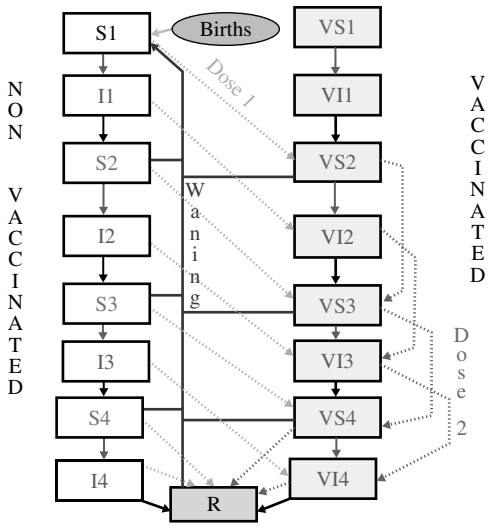

Fig. 1. Structure of the model.

MATERIALS AND METHODS

A dynamic, deterministic compartmental model [19] was developed to represent RV natural history and transmission. The model simulates the flow of individuals through different states of susceptibility and infectivity and accounts for the progressive build-up of natural immunity to RV infection and RV-GE (the model was developed using the mathematical software Matlab 7.3.0). We describe first the model prior to vaccine introduction, and then evaluate the impact of a vaccination programme in Europe using different vaccine coverage rates.

Prior to vaccine introduction

Natural history of RV infection and disease

The model accounts for the progressive build-up of natural immunity against RV infection, RV-GE and infectiousness after first and subsequent RV infections, as shown in Figure 1 (non-vaccinated pathway).

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Table 1. *Risk ratios (RR) and 95% confidence intervals (CI) for RV infection and RV-GE (any severity) compared to no prior infections, used for immunity parameters. Estimates are from a study of RV natural protection in 200 Mexican infants* [5]

Type of infection	No. of prior infections	RR	95% CI
RV	0	1	
	1	0·62	0·50–0·83
	2	0·40	0·28–0·59
	3	0·34	0·17–0·67
RV-GE	0	1	
	1	0·23	0·12–0·40
	2	0·17	0·08–0·36
	3	0·08	0·01–0·56

Individuals move through four susceptible states (S states) and four infectious states (I states), with progressive decreases in susceptibility and infectivity as they progress to each subsequent state. More specifically, non-vaccinated infants are susceptible to a first RV infection (state S1). When infected for the first time, infants move to state I1 and subsequently move to state S2, in which they are again susceptible, but at reduced risk compared to state S1. Individuals can be re-infected a second time (state I2), but have lower infectiousness than in state I1, etc. The model assumes that individuals are fully protected against re-infection after four prior infections (state R). However, the protection acquired by prior natural RV infections is also assumed to wane with time, with individuals in the partially or fully protected states (S2, S3, S4 and R) moving back to the fully susceptible state S1 after a period of temporary protection, with mean duration that was varied across a large range of values (see base case and sensitivity analyses).

The reductions in risk for RV infection and RV-GE (immunity parameters) included in the model were derived from risk ratios (RR) and 95% confidence intervals (CI) estimated in a longitudinal study of natural protection in Mexican infants (Table 1) [5]. This well-known study of RV natural history is one of the few conducted thus far [4, 5, 20, 21]. Protection by maternal antibodies, acquired either placentally or by breastfeeding, was accounted for by assuming that protection decayed exponentially from 100% at birth to 50% at age 1 month and 0% at age 6 months and was based on estimates of the biological half-life of maternal antibodies observed for various viral infections [22–25].

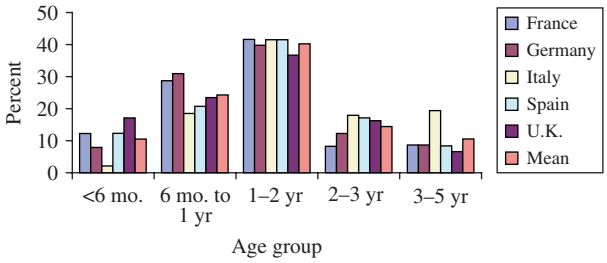

Fig. 2. Distribution of RV-GE cases (any severity) in <5-year-olds used in the model. The mean is across the five EU countries considered in the model.

RV-GE incidence

RV-GE burden of disease estimates were obtained from the Reveal study, a study of seven EU countries, including Belgium, France, Germany, Italy, Spain, Sweden and the UK [18]. The model incorporated data from five of these countries; Belgium and Sweden were excluded because incidence rates for infants aged <6 months were less reliable. Data on the burden of disease came from multiple sources, including hospitalizations, emergency-room visits and primary-care visits. The reported mean annual RV-GE incidence rate in children aged <5 years for the five countries included in the model was 42·3/1000 [18]. Although incidence rates were variable across countries [mean annual incidence in children aged <5 years varied from 20·7/1000 (95% CI 13·7–28·7) in the UK to 49·6/1000 (95% CI 37·3–63·5) in France], the age distribution across countries was consistent and we therefore incorporated the mean RV-GE age distribution in the model (Fig. 2).

Reported incidence rates are underestimates of the true RV-GE incidence as they do not include RV-GE that occurred outside of the hospital, emergency department and primary-care setting. To estimate the true RV-GE incidence we used data from a recent survey of EU countries, which reported the median annual incidence of acute GE hospitalizations to be 4·8/1000 in children aged <5 years living in EU high-income countries [26]; across the five countries included in the model, the highest median number of hospitalizations caused by RV infection was 55·6% [26]. Assuming that for each RV-GE hospitalization there are eight primary-care visits, and for each primary-care visit there are four RV-GE cases treated at home [2], we estimated the true annual incidence of

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Table 2. *Age-specific annual RV-GE* (*any severity*) *incidence per 100 000 for the base case* (*incidence rate 120/1000*) *in children aged <5 years and sensitivity analysis* (*using two additional incidence rates: 100/1000 and 140/1000 in children aged <5 years*)

	RV-GE incidence per 100 000		
Age category	With incidence rate 100/1000 in <5-year-olds	With incidence rate 120/1000 in <5-year-olds (base case)	With incidence rate 140/1000 in <5 year-olds
0–6 months	10 371	12 445	14 519
6 months to 1 year	24 556	29 467	34 378
1–2 years	20 192	24 230	28 268
2–3 years	7168	8601	10 035
3–5 years	2589	3107	3625
>5 years	51	51	51

RV-GE to be 109/1000 in children aged <5 years. For the base case we used a more conservative estimate of annual RV-GE incidence (120/1000 in <5 year-olds), and performed sensitivity analyses to examine lower and higher incidence rates (range 100–140/1000).

A single age category was included in the model for those aged ⩾5 years (5–80 years), for whom incidence of RV-GE disease is significantly lower. Mean annual incidence of RV-GE for this age group was estimated at 16/100 000, based on Robert Koch Institute (RKI) surveillance data for Germany [27]. Although the age distribution of RV-GE in Germany was similar for Reveal and RKI data, the number of cases aged 3–5 years in the Reveal data was about 3·2 times higher than the RKI data. We applied this correction factor to the ⩾5 years age group, which gave us an adjusted incidence rate of 51·2/100 000. Incidence rates used for the base case model are provided in Table 2.

Transmission dynamics

RV infection is acquired primarily by direct person-to-person transmission via the faecal–oral route [28, 29]. Hence, the greatest proportion (95% pre-vaccination) of the rate of acquiring RV infection per susceptible (the force of infection) was assumed to be caused by direct person-to-person transmission (including delayed transmission via fomites on surfaces such as toys and furniture), varied over time as an age-specific function of the number of infectious individuals in the population [19]. This important feature allowed the model to account for indirect herd protection effects induced by vaccination. The remaining proportion of the force of infection (5% pre-vaccination) was also assumed to be age-specific but fixed over time and accounted for all alternative routes of transmission (e.g. importation of RV, primary transmission from an animal reservoir, virus of common-source origin, etc.).

The rate at which susceptible individuals are infected was assumed to depend on the individual's level of susceptibility [5] and infectivity, both of which depended on the number of prior RV infections, and the ages of these susceptibles and infectives using age-specific transmission parameters [19]. These parameters were estimated from age-specific RV-GE incidence rates as described above (see Appendix 1 for more details about transmission).

The model also assumes that individuals infected by RV remain infected and infectious for an average of 10 days [30]. As some RV infections are asymptomatic, the proportion of symptomatic infections (RV-GE of any severity) was assumed to be 39% at first infection [5, 20] and to decrease for subsequent infections (the risk reduction induced by prior infections is greater for RV-GE than for RV infection, as shown in Table 1).

Mixing patterns between individuals

We assumed a 'preferred mixing' pattern within and between the six age groups (0–6 months, 6 months to <1 year, 1–2 years, 2–3 years, 3–5 years and >5 years), which allowed for the exploration of different types of 'mixing' patterns between individuals across age groups by varying the percentage p of mixing with 'proportionate mixing' (with individuals having

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contacts with others in proportion to the number of contacts supplied from each age group), and the remaining proportion $(1-p)$ for 'assortative mixing' (contacts with individuals of the same age group) [31]. While a more assortative mixing is often used between different age groups in a population for viral diseases like varicella or measles, it is less realistic across the fine age strata (aged <5 years) included in the RV model. Proportionate mixing allows for the effect of age on virus spread (infectives) and contact (susceptible) to be accounted for more accurately than assortative mixing. To evaluate a plausible range for p, we estimated the mixing matrix across the full range of values of p, under different combinations of the other parameters. The mean of the five intra-group transmission rates was compared with the mean of the 10 inter-groups transmission rates in <5year-olds and it was observed that the ratio of the intra-group mean to the inter-group mean increased sharply with the value of p. Based on a European survey of close contact patterns for directly transmitted infections [32], which reported this ratio to be between 1 and 2 in <5-year-olds, we restricted the range of possible values for p to lie between 50% and 100% in the base case, and considered different ranges in sensitivity analyses.

Estimation of RV transmission parameters

The model was fit with six transmission parameters and six age-specific RV-GE incidence rates with exact matching. The transmission parameters were estimated by fitting the age-specific RV-GE incidence rates projected by the model at pre-vaccination steady state to observed age-specific incidence rates (Table 2).

Demography

Infants flow into the model as susceptibles at birth (with decreasing partial protection induced by maternal antibodies during the first few months of life), age into each age class, and flow out at age 80 years. The model uses 75 age classes (60 age classes of 1 month in children aged <5 years and 15 classes of 5 years in individuals aged >5 years) with individuals moving continuously from one age class to the next over time. The model assumes that each age cohort is the size of the current birth cohort with a lifespan of 80 years [33].

Pre-vaccination model outcomes

The model was used to evaluate the potential for spread of RV infection within the population by estimating its basic reproduction number (R_0). R_0 is defined as the average number of new infectious cases generated by one primary infected case introduced into a fully susceptible population [19]. The closer the value of R_0 to 1 (i.e. the lower the potential for spread), the easier it becomes to control the disease using preventive measures such as vaccination.

Model with introduction of a vaccination programme

The impact of RV vaccination was modelled to estimate the reduction in RV-GE cases with implementation of a two-dose RV vaccination programme across medium (70%) and high (90% and 95%) coverage rates. The model focused on the impact of RV-GE *of any severity*. However, given the importance of severity, especially for the cost-effectiveness evaluations of vaccination, the model was also used to evaluate the impact of vaccination on moderate-to-severe RV-GE for the base case. Pre-vaccination incidence rates were assumed to be at epidemiological steady state in each age group at the time of implementation. The effect of RV vaccine was assumed to be similar to that of natural infection with first and subsequent RV infections (natural or vaccine-induced) progressively reducing the risk of future RV infection and RV-GE in every individual (Fig. 1, vaccinated pathway). The first dose at age 2 months was considered equivalent to one natural RV infection at age 2 months, and the second dose at age 4 months equivalent to a second natural RV infection at age 4 months (doses do not lead to RV-GE or infectiousness). For example, at the time of the first dose, an infant in state S1 (S2, …) will flow to state VS2 (VS3, …) (Fig. 1). At the time of the second dose, infants will flow from state VS2 (VS3, …) to state VS3 (VS4, …). Natural or vaccine-induced immunity is assumed to wane after a period of temporary protection after which individuals flow back to state S1. The duration of protection was varied across a wide range of values (from 5 to 50 years, as well as lifelong immunity) and assumed to be the same whether induced by natural infection or by vaccination. RV-GE specific deaths prevented by vaccination are not accounted for by the model because RV-specific mortality rates are low in the developed world.

Model outcomes

Model outcomes included the percent reduction in the annual incidence rate of RV-GE following a 5-year vaccination programme, and the indirect herd

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Table 3. *Projected percent reduction in RV-GE incidence after 5 years vaccination programme compared to pre-vaccination*

	Percent reduction in RV-GE incidence Vaccination coverage rate		
	70% mean (range)	90% mean (range)	95% mean (range)
Any severity RV-GE			
Direct effects only*	52%	67%	71%
Projected from model	77% (69–85%)	89% (83–94%)	91% (85–96%)
Moderate-to-severe RV-GE			
Direct effects only†	59%	76%	80%
Projected from model	78% (70–86%)	91% (85–97%)	93% (87–98%)

* Assumes 79% vaccine efficacy against RV-GE (any severity) [6].
† Assumes 90% vaccine efficacy against moderate-to-severe RV-GE, based on 90% efficacy observed for severe RV-GE [6].

protection benefit of vaccination after a 5-year vaccination programme. Indirect effects were estimated by comparing the outcomes from the dynamic model with a simpler projection accounting for direct effects only.

Base case

The base case assumes: (1) point estimates for reduction in susceptibility to infection and RV-GE as a function of the number of prior infections (Table 1), (2) age-specific incidence rates of RV-GE (any severity) are based on an annual incidence of 120/1000 in <5-year-olds and mean age distribution from Reveal (see 'RV-GE incidence' section), and (3) RV direct person-to-person transmission accounts for 95% of the force of infection pre-vaccination.

There are no quantitative data to inform the parameters related to the duration of protection (whether natural or vaccine-induced) and the reduction in infectiousness after first and subsequent RV infections. Quantitative data on the structure of the contact pattern is also sparse. Model outcomes were therefore evaluated for different combinations of values for these model parameters. More precisely, (1) the duration of protection (whether induced by natural immunity or by vaccination) was assumed to be at least 5 years in the base case with waning ranging between 0 and 0·2 with steps of 0·02, corresponding to 5–50 years of protection as well as lifelong protection, (2) 20 different combinations of values were used for the reduction in RV infectiousness after 1, 2 and 3 prior infections compared to first infection, each ranging between 0·25 and 1, and 3) the proportion p of 'proportionate mixing' in the preferred mixing pattern was varied between 50% and 100%, with steps of 10% based on the assumption that mixing is not likely to be very assortative by age group in the <5-year-olds (see 'Mixing patterns between individuals' section). Model outcomes were evaluated for three different vaccination coverage rates: 70%, 90% and 95%.

Sensitivity analyses

We assessed the sensitivity of model outcomes to the base case assumptions by ranging: (1) annual incidence rates from 100 to 140/1000 in <5-year-olds (Table 2), (2) the duration of protection (whether induced by natural immunity of vaccination) from 2 to 4 years, (3) the percentage of 'proportionate mixing' p from 20% to 40% or, in the most assortative scenarios, from 0% to 10%, and (4) immunity parameters for reduction in risk of RV infection and RV-GE after first and subsequent RV infections using confidence limits from Table 1. We did not conduct sensitivity analyses across different severity types, as the main focus of the model was to investigate RV-GE of any severity.

RESULTS

RV infections and disease prior to the introduction of vaccination

The mean model-based estimate of the basic reproduction number R_0 across the different scenarios

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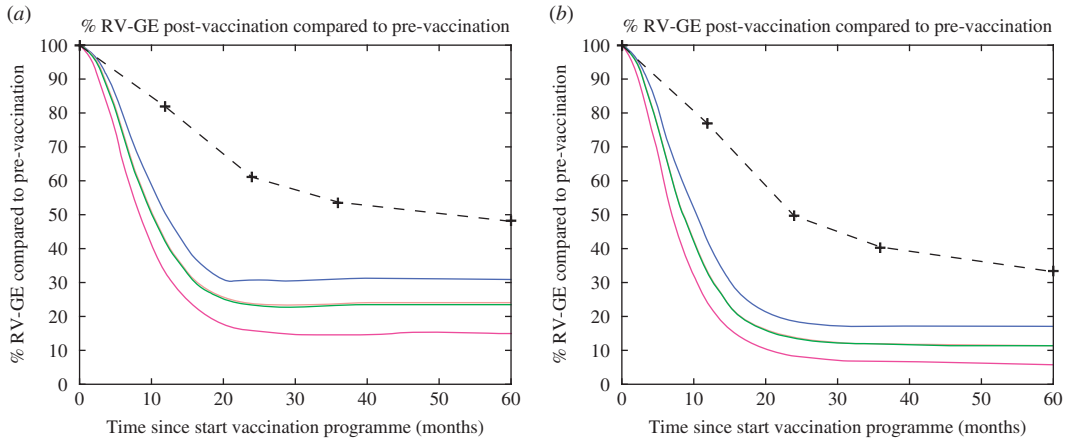

Fig. 3. RV-GE (any severity) annual incidence, by month, as a percentage of incidence pre-vaccination over first 5 years of a vaccination programme, with (*a*) 70% coverage and (*b*) 90% coverage. Minimum (purple), median (red), mean (green) and maximum (blue) percent reduction across all scenarios considered. Dotted line (black) shows projected reduction after 1, 2, 3 and 5 years vaccination programme using a simple estimate without herd protection.

considered for the base case was 1·84 and ranged between 1·44 and 4·17.

Impact of vaccination on RV-GE any severity

As expected, the projected reduction in RV-GE incidence increased with higher vaccination coverage rates following a 5-year vaccination programme (Table 3). Figure 3 shows the projected monthly RV-GE incidence over a 5-year vaccination programme compared with the RV-GE incidence pre-vaccination for vaccination coverage rates of 70% (Fig. 3*a*) and 90% (Fig. 3*b*).

To evaluate the impact of herd protection, we compared overall RV-GE reduction in the population with reduction induced by the direct effect of vaccination only. For example, with 70% coverage and 79% efficacy against any RV-GE [6], accounting for direct effects only, a 5-year vaccination programme is expected to reduce RV-GE by 55% (i.e. $0{\cdot}70 \times 0{\cdot}79$) in children aged <5 years and by 52% in the total population (with <5-year-olds accounting for 94% of RV-GE cases, Table 2). Similarly, vaccination is expected to reduce RV-GE in the total population by 67% with 90% coverage and by 71% with 95% coverage. Table 3 shows that herd protection is projected to induce an additional reduction in RV-GE of 25%, 22% and 20% with 70%, 90% and 95% coverage, respectively, on top of direct effect. Even under the most conservative scenario, the additional reduction in RV-GE is still projected to be 17%, 16% and 14% with 70%, 90% and 95% coverage, respectively.

Impact of vaccination on moderate-to-severe RV-GE

To estimate the reduction in incidence of moderate-to-severe RV-GE 5 years after implementation of a vaccination programme we assumed that 11% of first infections and 3% of second infections caused moderate-to-severe RV-GE, and that no subsequent infections caused moderate-to-severe RV-GE [5].

Following a 5-year vaccination programme, the model projected moderate-to-severe RV-GE incidence reductions very similar to those projected for RV-GE any severity (Table 3). Herd protection induced an additional reduction in moderate-to-severe RV-GE of 19%, 15% and 13% with 70%, 90% and 95% coverage, respectively, on top of the direct effect of vaccination.

Sensitivity of model outcomes to model parameters

Potential for spread

We investigated the sensitivity of the model-based estimate of R_0 to (1) incidence of RV-GE pre-vaccination in children aged <5 years of (100, 120 and 140/1000), (2) duration of protection (whether acquired by natural infection or vaccination) ($\geqslant 5$ years, base case; and 2-4 years), and (3) mixing patterns (p ranging from 50% to 100% for the base case, 20–40% and 0–10% for the most assortative scenarios). Table 4 shows that the estimated value for R_0 is greater if the incidence of RV-GE pre-vaccination is higher, the mixing pattern is more assortative (lower value of p), or the duration of protection is longer. Figure 4 shows the estimated R_0 as a function of

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Table 4. *Sensitivity analysis of model-based estimates of the basic reproduction number, R_0, for a range of RV-GE (any severity) incidence rates in <5-year-olds pre-vaccination, duration of protection and mixing pattern parameter*

Duration of protection	Mixing (% proportionate)	Basic reproduction number R_0 Incidence in <5-year-olds 100/1000 Mean (range)*	120/1000 Mean (range)*	140/1000 Mean (range)*
⩾5 years	50–100%	1·57 (1·33–2·66)	1·84 (1·44–4·17)†	2·30 (1·58–7·97)
	20–40%	1·68 (1·34–4·31)	2·08 (1·46–7·36)	2·88 (1·61–14·20)
	0–10%	2·01 (1·39–6·53)	2·62 (1·53–11·09)	3·89 (1·73–23·97)
2–4 years	50–100%	1·39 (1·25–1·81)	1·52 (1·32–2·14)	1·69 (1·40–2·59)
	20–40%	1·42 (1·26–1·91)	1·56 (1·33–2·30)	1·75 (1·41–2·81)
	0–10%	1·51 (1·35–2·20)	1·67 (1·36–2·71)	1·90 (1·44–3·36)

* The mean and the range are across all scenarios considered (varying the duration of protection, the infectiousness and the contact pattern, as described in the 'Sensitivity analyses' section).
† Base case.

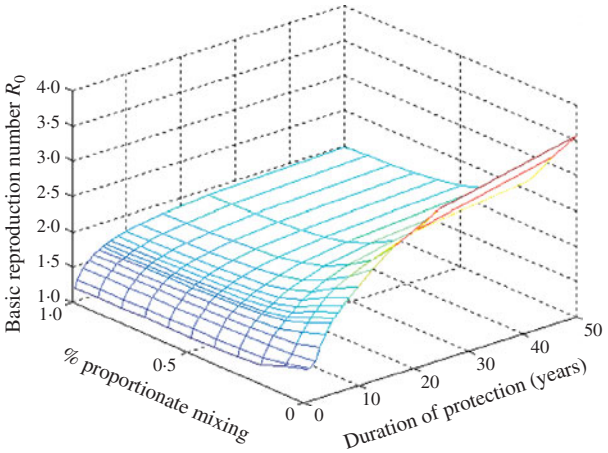

Fig. 4. Sensitivity analysis: basic reproduction number R_0 as a function of the duration of protection and the contact pattern parameter p (mean across 20 scenarios for infectiousness).

the duration of protection and the mixing parameter p (mean across the 20 scenarios considered for infectiousness parameters).

Reduction in RV-GE by vaccination

Table 5 shows the estimated mean and range for the percent reduction in the RV-GE cases (any severity) following a 5-year vaccination programme, across vaccination coverage rates (70%, 90% and 95%), RV incidence rates pre-vaccination (100, 120 and 140/1000), duration of protection (⩾5 years as in base case and 2–4 years), and mixing pattern (p ranging from 50% to 100% in base case, 20–40% and 0–10%. The percent reduction in RV-GE following a 5-year vaccination programme was greater when the incidence of RV-GE pre-vaccination was lower, when the duration of protection (induced by natural infection or by vaccination) was longer and when the mixing was less assortative (higher values of p). Even under very conservative conditions, with incidence of 140/1000 pre-vaccination, the minimal reductions projected are 57%, 75% and 79% with 70%, 90% and 95% coverage, respectively, provided that protection lasted for a minimum of 5 years and p was ⩾50% (as assumed in the base case). These projected reductions are still higher than reductions accounting for direct protection only (i.e. 52%, 67% and 71% with 70%, 90% and 95% coverage, respectively). Figure 5 shows the projected percent reduction of RV-GE following a 5-year vaccination programme as a function of the duration of protection and the mixing parameter (p) for the base case incidence of 120/1000 with 70% coverage (Fig. 5*a*) and 90% coverage (Fig. 5*b*) (mean across the 20 scenarios for infectiousness).

Sensitivity to immunity parameters

We evaluated the sensitivity of the outcomes to the immunity parameters by evaluating the percent reduction in RV-GE (any severity) for the base case, with incidence of 120/1000, mixing pattern parameter (p) of 0·8 and a waning rate of 0·10 (i.e. a mean duration of 10 years protection). Percent reduction in

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Table 5. *Sensitivity analysis of projected percent reduction in RV-GE incidence (any severity) following a 5-year vaccination programme compared to pre-vaccination for a range of RV-GE (any severity) incidence in <5-year-olds pre-vaccination, duration of protection, and mixing pattern parameter, with 70%, 90% and 95% vaccination coverage*

			Percent reduction in RV-GE incidence after 5 years vaccination Incidence in <5-year-olds		
			100/1000	120/1000	140/1000
Vaccination coverage	Duration of protection	Mixing (% proportionate)	Mean (range)*	Mean (range)*	Mean (range)*
70%	⩾5 years	50–100%	84% (78–90)	77% (69–85)†	66% (57–76)
		20–40%	81% (72–89)	72% (59–82)	60% (52–70)
		0–10%	72% (54–86)	60% (48–71)	51% (43–56)
	2–4 years	50–100%	79% (72–86)	72% (63–82)	64% (55–75)
		20–40%	75% (65–85)	68% (56–79)	59% (48–70)
		0–10%	64% (47–80)	55% (42–70)	47% (37–57)
90%	⩾5 years	50–100%	92% (87–96)	89% (83–94)†	83% (75–91)
		20–40%	91% (86–96)	86% (78–94)	77% (66–87)
		0–10%	85% (69–95)	77% (60–91)	65% (55–76)
	2–4 years	50–100%	87% (81–92)	83% (77–90)	78% (70–87)
		20–40%	85% (78–91)	80% (70–89)	73% (61–84)
		0–10%	75% (57–89)	68% (51–84)	60% (46–74)
95%	⩾5 years	50–100%	93% (89–97)	91% (85–96)†	86% (79–93)
		20–40%	92% (88–96)	89% (82–95)	81% (70–91)
		0–10%	87% (72–96)	81% (64–94)	69% (58–82)
	2–4 years	50–100%	89% (83–93)	85% (79–92)	81% (73–89)
		20–40%	87% (80–92)	82% (73–90)	76% (64–87)
		0–10%	77% (60–90)	71% (53–86)	63% (49–78)

* The mean and the range (% values) are across all scenarios considered (varying the duration of protection, the infectiousness and the contact pattern, as described in the 'Sensitivity analyses' section).
† Base case.

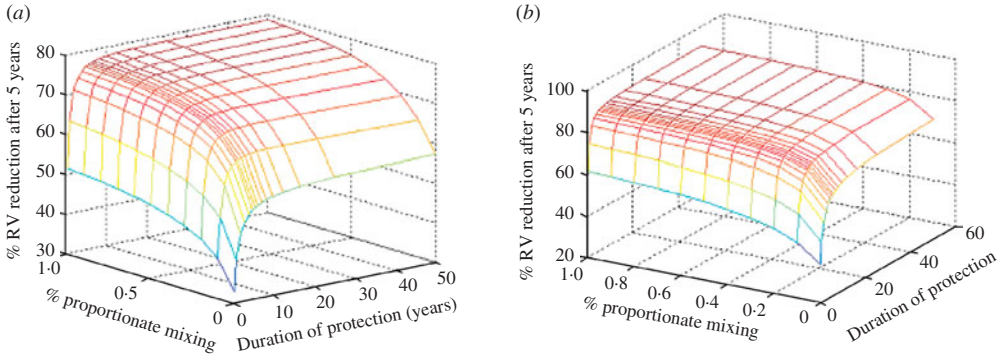

Fig. 5. Sensitivity analysis: percent reduction in RV-GE (any severity) incidence following a 5-year vaccination programme as a function of the duration of protection and the contact pattern parameter p (mean across 20 scenarios for infectiousness) with (*a*) 70% and (*b*) 90% vaccination coverage.

RV-GE was estimated across a total of 1160 different scenarios. Figure 6 shows histograms of the percent reduction in RV-GE incidence after a 5-year vaccination programme across those 1160 scenarios with 70% (Fig. 6*a*) and 90% (Fig. 6*b*) vaccination coverage. The median values from the sensitivity analysis were similar to the base case for 70% coverage (75% and 75%, respectively) and 90% coverage (89% and 88%, respectively). Although the minimal reduction could be quite low, the distributions were

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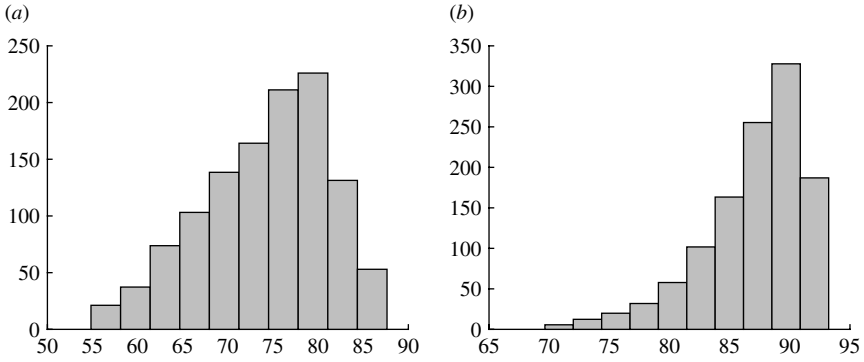

Fig. 6. Sensitivity to immunity parameters. Histograms of the percent reduction in RV-GE (any severity) incidence after a 5-year vaccination programme across the 1160 scenarios considered with (*a*) 70% and (*b*) 90% vaccination coverage.

right-skewed. Percent reduction in RV-GE reached its lowest value when there was low immunity against infection but high immunity against RV-GE.

DISCUSSION

Using a mathematical model of RV natural history and transmission in five countries in Europe, we estimated a substantial reduction in incidence of RV-GE in the years following implementation of a vaccination programme. The projected reduction was substantially higher when accounting for indirect herd protection effects induced by vaccination compared to direct effects only. For example, following a 5-year vaccination programme with 90% coverage, the model projected that 89% of RV-GE cases of any severity would be averted accounting for direct and herd protection effects, compared to 67% accounting for direct effects only. Hence, herd protection is expected to reduce RV-GE by an additional 22%. These population-level reductions are not comparable to outcomes from a model using a traditional cohort approach [11–14] since the latter usually evaluate the impact of vaccination in a single birth cohort.

A major assumption of the model is that vaccination mimics natural infection. Data on RV natural history [5] were used to quantify the impact of prior RV infection on future RV infection (symptomatic and asymptomatic) and RV-GE. Clinical trials conducted in Europe with Rotarix report efficacy following two vaccine doses against RV-GE of any severity of 87·1% and 78·9% over the first year of life and the first two years of life, respectively [6]. This is comparable to the protection induced by two prior natural infections, which has an efficacy of 83% (Table 1; $1-\mathrm{RR}=1-0{\cdot}17=0{\cdot}83$).

The model reveals a relatively low potential for RV spread in Europe, with an estimated R_0 ranging between only 1·44 and 4·17 in the base case. Although low compared to estimates for other infections acquired during childhood, a low R_0 is common for infections that do not confer full natural immunity after the first episode of infection or carriage [34]. Hence, vaccination early in life has the potential to dramatically decrease RV incidence rates in a relatively short time.

Sensitivity analysis showed that although RV-GE reduction estimates depend on assumptions about RV-GE incidence pre-vaccination, duration of protection, mixing pattern and immunity parameters, herd protection is projected to induce an additional reduction in RV-GE incidence across a large range of assumptions. Reduction in RV-GE was most sensitive to RV-GE incidence pre-vaccination and mixing pattern but only for very assortative type of mixing, which is not very plausible in <5-year-olds. Reduction in RV-GE was not very sensitive to duration of protection. It should be noted that lower vaccine efficacy observed in vaccine trials during the second *vs*. first year of life [6] may be a reflection of acquired natural immunity from prior infections acquired also in placebo group during the first year of life, rather than waning of vaccine protection.

We pooled the population aged >5 years because RV disease burden is considerably lower in this group compared to children aged <5 years. Although some epidemiological data show a slight increase in persons aged >70 years [27, 35–37], the incidence rate in that age group is still much lower than the incidence of RV-GE in the first year of life. Under-reporting is more likely in the elderly compared with infants, resulting in the potential for additional reduction of

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RV infection in the elderly by reduced transmission from infants. This was observed, for example, with the reduction of invasive pneumococcal disease in older adults following infant vaccination with the 7-valent vaccine in the USA [38].

A prior version of the model developed using data from Germany [39] explored the impact of accounting for seasonality with time-varying transmission rates or of using different vaccination schedules. Results were similar whether the model accounted for seasonality or not. We used a conservative schedule of 2 and 4 months in the model in order to account for the diversity in RV vaccination schedules in European countries, although the first dose of Rotarix may be administered as early as age 6 weeks, and the second dose at least 4 weeks later [40]. The prior version of the model showed that outcomes were similar with both schedules.

The magnitude and duration of protection by maternal antibodies, whether placentally transferred or acquired by breastfeeding, during the first months of life, is uncertain [1]. In the model, we assumed that protection by maternal antibodies decayed exponentially from 100% at birth to 50% around age 1 month and 0% at age 6 months. Sensitivity analyses performed for the first version of the model indicated that the outcomes of the model are not sensitive to the magnitude and duration of protection conferred by maternal antibodies.

A limitation of the model is that it does not account for antigenic diversity of RV types. Antigenic diversity is limited in the EU, however [18, 41], and the efficacy of Rotarix vaccine against these RV types is high [6, 42].

A low percent of risk for infection was chosen for non-direct person-to-person transmission. The rationale is that the epidemiology of RV in Europe, in particular the strong seasonal pattern of RV-GE incidence, indicates that RV behaves very similarly to airborne-transmitted infections. Moreover, primary transmission from animal reservoir is probably very low in Europe, as the prevalence of RV from animal origin in the EU is very low [43].

To our knowledge, very few mathematical models of RV transmission have been developed thus far to evaluate the impact of RV vaccination accounting for herd protection effects. José *et al.* [44] used a compartmental model of diarrhoeal diseases to project the impact of different prevention and control strategies. This model assumes the force of infection to be a constant and does not account for the indirect herd protection effects induced by vaccination. Shim *et al.* [45] describe an age-stratified compartmental model for RV in which they analyse the stability of the disease-free endemic steady state and the existence of an endemic steady state; however, they do not apply their model to evaluate quantitatively the impact of vaccination. Shim & Galvani [46] also use a transmission model of RV to evaluate the cost-effectiveness of Rotateq in the USA However, the structures of these models do not capture the progressive build-up of natural immunity with increasing number of prior infections.

Pitzer *et al.* [47] developed a RV dynamic model accounting for the progressive build-up of natural immunity to better understand the causal factors of the spatio-temporal pattern of RV incidence observed in the USA and to explore the relative importance of direct and indirect protection, using epidemiological US data prior to and during the first two years post-vaccination.

Studies of disease natural history suggest that vaccination may induce additional benefits via herd protection. RV-GE surveillance data from countries in which RV vaccination has already been introduced permits evaluation of the extent of the herd protection amplification over the direct effects of vaccination. Preliminary data from a US study conducted post-vaccination in 2007–2008 [48, 49] and from a prospective surveillance study of RV-GE hospitalizations in Brazil [50] both suggest indirect protection induced by vaccination to unvaccinated children.

Although we apply this model in the context of a developed country, the same approach may be followed to evaluate the impact of RV vaccination in developing countries. As observed for some other oral vaccines (e.g. polio, cholera), the efficacy of RV vaccination is consistently lower in populations with low socioeconomic status. The explanation for this observation is still unclear and is probably multifactorial (e.g. maternal antibodies, breastfeeding, multiple gut pathogens, etc.). Challenges to applying these models to developing countries include sparse epidemiological data and different natural immunity and contact patterns.

In summary, using a mathematical model that projects the impact of RV vaccination on RV infection and RV-GE, we show that vaccination with a two-dose vaccine mimicking natural infection (i.e. Rotarix), not only reduces burden of disease by direct effects, but also has the potential to induce strong

indirect herd protection effects on RV disease within just a few years of implementation.

APPENDIX 1: Per-susceptible rates of RV infection

Direct person-to-person transmission

The rate at which susceptible individuals in age class a_1 with p_1 prior infections are infected by infectives in age class a_2 with p_2 prior infections:

$$\mathrm{RRS}(p_1) \times \mathrm{T}(a_1,\ a_2) \times \mathrm{RRI}(p_2),$$

Similarly, the rate at which susceptible individuals in age class a_1 with p_1 prior infections are infected by infectives in age class a_2 with p_2 prior infections *and* experience symptomatic disease (RV-GE of any severity):

$$\mathrm{SR} \times \mathrm{RRD}(p_1) \times \mathrm{T}(a_1,\ a_2) \times \mathrm{RRI}(p_2),$$

where

- $\mathrm{RRS}(p_1)$ = risk ratio to be infected after p_1 prior infections, compared to no prior infections (see Table 1) [5];
- $\mathrm{RRD}(p_1)$ = the risk ratio to be infected and experience RV-GE (any severity) after p_1 prior infections, compared to no prior infections (see Table 1) [5];
- SR is the percentage of first RV infections that cause RV-GE (any severity). The value used for SR in the model is 39% [5];
- $\mathrm{T}(a_1,\ a_2)$ = age-specific transmission rate between infectives in age class a_2 and susceptibles in age class a_1 (Appendix 2);
- $\mathrm{RRI}(p_2)$ = the ratio of infectiousness after p_2 prior infections (compared to no prior infections).

Non-direct person-to-person transmission

The rate at which susceptible individuals in age class a_1 with p_1 prior infections are infected by *non*-direct person-to-person transmission:

$$\mathrm{RRS}(p_1) \times \mathrm{ND}(a_1).$$

Similarly, the rate at which susceptible individuals in age class a_1 with p_1 prior infections are infected by non-direct person-to-person transmission and experience symptomatic disease (RV-GE of any severity):

$$\mathrm{SR} \times \mathrm{RRD}(p_1) \times \mathrm{ND}(a_1),$$

where $\mathrm{RRS}(p_1)$, $\mathrm{RRD}(p_1)$ and RS are as defined above, and $\mathrm{ND}(a_1)$ = specified proportion of the force of infection in age class a_1 which is *not* caused by direct person-to-person transmission (as estimated from age-specific force of infection prior to vaccination).

APPENDIX 2: Structure of the mixing matrix

W is a 6×6 matrix with entries

$$W_{ij} \text{ (for } i = 1,\ 2,\ \ldots,\ 6, \quad \text{and} \quad j = 1,\ 2,\ \ldots,\ 6).$$

$$W_{ij} = p * (c_i * c_j / D) + (1 - p) * (c_i * \delta_{ij} / N_j),$$

where $D = \sum c_k N_k$; N_k = population in age group k, $\delta_{ij} = 1$ if $i = j$, 0 if $i \neq j$; c_1, c_2, …, c_6 are the six transmission coefficients estimated by calibration to incidence data, and p is the contact pattern parameter = proportion of 'proportionate mixing' in the 'preferred mixing' pattern.

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DECLARATION OF INTEREST

Dr Van Effelterre, Dr Soriano-Gabarró and Dr Debrus are employed by GlaxoSmithKline Biologicals. Dr Newbern was employed by GlaxoSmithKline Biologicals at the time the modelling project was initiated.

REFERENCES

1. **Parashar UD, *et al.*** Global illness and deaths caused by rotavirus disease in children. *Emerging Infectious Diseases* 2003; **9**: 565–572.
2. **Soriano-Gabarro M, *et al.*** Burden of rotavirus disease in European Union countries. *Pediatric Infectious Diseases Journal* 2006; **25** (Suppl. 1): S7–S11.
3. **Forster J, *et al.*** Hospital-based surveillance to estimate the burden of rotavirus gastroenteritis among European

children aged <5 years. In: Abstract from the 25th Annual Meeting of the European Society for Paediatric Infectious Diseases, Porto, Portugal, 2007.
4. **Bishop RF, *et al.*** Clinical immunity after neonatal rotavirus infection. A prospective longitudinal study in young children. *New England Journal of Medicine* 1983; **309**: 72–76.
5. **Velazquez FR, *et al.*** Rotavirus infections in infants as protection against subsequent infections. *New England Journal of Medicine* 1996; **335**: 1022–1028.
6. **Vesikari T, *et al.*** Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. *Lancet* 2007; **370**: 1757–1763.
7. **Vesikari T, *et al.*** Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *New England Journal of Medicine* 2006; **354**: 23–33.
8. **Heymann DL, Aylward RB.** Mass vaccination: when and why. *Current Topics in Microbiology and Immunology* 2006; **304**: 1–16.
9. **Vesikari T, *et al.*** European Society for Paediatric Infectious Diseases/European Society for Paediatric Gastroenterology, Hepatology, and Nutrition evidence-based recommendations for rotavirus vaccination in Europe: executive summary. *Journal of Pediatric Gastroenterology and Nutrition* 2008; **46**: 615–618.
10. **Anon.** Meeting of the immunization Strategic Advisory Group of Experts, April 2009 – conclusions and recommendations. *Weekly Epidemiological Record* 2009; **84**: 220–236.
11. **Goossens LM, *et al.*** The cost-utility of rotavirus vaccination with Rotarix (RIX4414) in the Netherlands. *Vaccine* 2008; **26**: 1118–1127.
12. **Jit M, Edmunds WJ.** Evaluating rotavirus vaccination in England and Wales. Part II. The potential cost-effectiveness of vaccination. *Vaccine* 2007; **25**: 3971–3979.
13. **Melliez H, *et al.*** Cost and cost-effectiveness of childhood vaccination against rotavirus in France. *Vaccine* 2008; **26**: 706–715.
14. **Newall AT, *et al.*** The cost-effectiveness of rotavirus vaccination in Australia. *Vaccine* 2007; **25**: 8851–8860.
15. **Jit M, *et al.*** The cost-effectiveness of rotavirus vaccination: Comparative analyses for five European countries and transferability in Europe. *Vaccine* 2009; **27**: 6121–6128.
16. **Brisson M, Edmunds WJ.** Economic evaluation of vaccination programs: the impact of herd-immunity. *Medical Decision Making* 2003; **23**: 76–82.
17. **Edmunds WJ, Medley GF, Nokes DJ.** Evaluating the cost-effectiveness of vaccination programmes: a dynamic perspective. *Statistics in Medicine* 1999; **18**: 3263–3282.
18. **Van Damme P, *et al.*** Multicenter prospective study of the burden of rotavirus acute gastroenteritis in Europe, 2004–2005: the REVEAL study. *Journal of Infectious Diseases* 2007; **195** (Suppl. 1): S4–S16.
19. **Anderson RM, May RM.** *Infectious Diseases of Humans. Dynamics and Control*. Oxford University Press, 1991.
20. **Fischer TK, *et al.*** Protective immunity after natural rotavirus infection: a community cohort study of newborn children in Guinea–Bissau, west Africa. *Journal of Infectious Diseases* 2002; **186**: 593–597.
21. **Moulton LH, *et al.*** The protective effectiveness of natural rotavirus infection in an American Indian population. *Journal of Infectious Diseases* 1998; **178**: 1562–1566.
22. **Hartter HK, *et al.*** Placental transfer and decay of maternally acquired antimeasles antibodies in Nigerian children. *Pediatric Infectious Diseases Journal* 2000; **19**: 635–641.
23. **Lee MS, *et al.*** Half-life of human parainfluenza virus type 3 (hPIV3) maternal antibody and cumulative proportion of hPIV3 infection in young infants. *Journal of Infectious Diseases* 2001; **183**: 1281–1284.
24. **McLean B, Holmes IH.** Transfer of antirotaviral antibodies from mothers to their infants. *Journal of Clinical Microbiology* 1980; **12**: 320–325.
25. **Watanaveeradej V, *et al.*** Transplacentally transferred maternal-infant antibodies to dengue virus. *American Journal of Tropical Medicine and Hygiene* 2003; **69**: 123–128.
26. **Williams CJ, Lobanov A, Pebody RG.** Estimated mortality and hospital admission due to rotavirus infection in the WHO European region. *Epidemiology and Infection* 2009; **137**: 607–616.
27. **Robert Koch Institute.** Survstat (http://www3.rki.de/SurvStat).
28. **Bishop R.** Natural history of human rotavirus infections. In: Kapikian AZ, ed. *Viral Infections of the Gastrointestinal Tract*, 2nd edn. New York: Marcel Dekker, 1994, pp. 131–167.
29. **Desselberger U, Gray J.** *Viral Gastroenteritis*. Amsterdam: Elsevier Science, 2003.
30. **Centers for Disease Control and Prevention.** *Epidemiology and Prevention of Vaccine-Preventable Diseases*, 10th edn. Washington, DC: Public Health Foundation, 2007.
31. **Hethcote HW.** Modeling heterogeneous mixing in infectious disease dynamics. In: Isham V, Medley G, eds. *Models for Infectious Human Diseases: Their Structure and Relation to Data*. Cambridge: Cambridge University Press, 1996, pp. 215–238.
32. **Mossong J, *et al.*** Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS Medicine* 2008; **5**: e74.
33. **U.S. Census Bureau.** International Data Base (http://www.census.gov/ipc/www/idb/informationGateway.php).
34. **Trotter CL, Gay NJ, Edmunds WJ.** Dynamic models of meningococcal carriage, disease, and the impact of serogroup C conjugate vaccination. *American Journal of Epidemiology* 2005; **162**: 89–100.
35. **Carraro E, *et al.*** Rotavirus infection in children and adult patients attending in a tertiary Hospital of Sao Paulo, Brazil. *Brazilian Journal of Infectious Diseases* 2008; **12**: 44–46.
36. **Hrdy DB.** Epidemiology of rotaviral infection in adults. *Review of Infectious Diseases* 1987; **9**: 461–469.

37. **Iijima Y, *et al.*** An outbreak of rotavirus infection among adults in an institution for rehabilitation: long-term residence in a closed community as a risk factor for rotavirus illness. *Scandinavian Journal of Infectious Diseases* 2006; **38**: 490–496.
38. **Lexau CA, *et al.*** Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. *Journal of the American Medical Association* 2005; **294**: 2043–2051.
39. **Van Effelterre TP, Standaert BA.** Potential impact of a high vaccine coverage against rotavirus diarrhea in Belgium. In: Abstract from the Vaccine Global Congress. Amsterdam, Netherlands, 2007.
40. **Electronic Medicines Compendium (eMC).** (http://emc.medicines.org.uk/document.aspx?documentId = 17840).
41. **Forster J, *et al.*** Hospital-based surveillance to estimate the burden of rotavirus gastroenteritis among European children younger than 5 years of age. *Pediatrics* 2009; **123**: e393–400.
42. **De Vos B, *et al.*** Live attenuated human rotavirus vaccine, RIX4414, provides clinical protection in infants against rotavirus strains with and without shared G and P genotypes: integrated analysis of randomized controlled trials. *Pediatric Infectious Diseases Journal* 2009; **28**: 261–266.
43. **Iturriza-Gómara M, *et al.*** Rotavirus surveillance in Europe 2005–2008: web-enabled reporting and real-time analysis of genotyping and epidemiological data. *Journal of Infectious Diseases* (in press).
44. **Jose MV, Bobadilla JR.** Epidemiological model of diarrhoeal diseases and its application in prevention and control. *Vaccine* 1994; **12**: 109–116.
45. **Shim E, *et al.*** An age-structured epidemic model of rotavirus with vaccination. *Journal of Mathematical Biology* 2006; **53**: 719–746.
46. **Shim E, Galvani AP.** Impact of transmission dynamics on the cost-effectiveness of rotavirus vaccination. *Vaccine* 2009; **27**: 4025–4030.
47. **Pitzer VE, *et al.*** Demographic variability, vaccination, and the spatiotemporal dynamics of rotavirus epidemics. *Science* 2009; **325**: 290–294.
48. **Centers for Disease Control and Prevention.** Delayed onset and diminished magnitude of rotavirus activity – United States, November 2007–May 2008. *Morbidity and Mortality Weekly Report* 2008; **57**: 697–700.
49. **Payne DC, *et al.*** Decline in rotavirus hospitalizations in 3 US counties after introduction of rotavirus vaccine In: Abstract from the Pediatric Academic Societies Meeting, Baltimore, MD, 2009.
50. **Safadi M, *et al.*** Hospital-based surveillance to evaluate the impact of rotavirus vaccination in Brazil. In: Abstract from the 27th Annual Meeting of the European Society for Paediatric Infectious Diseases,. Brussels, Belgium, 2009.