Quantitative benefit-risk models used for rotavirus vaccination: a systematic review

Hugo Arlegui\textsuperscript{1,2,3}, Gaelle Nachbaur\textsuperscript{3}, Nicolas Praet\textsuperscript{4}, Bernard Bégaud\textsuperscript{1,2}

\textsuperscript{1}University of Bordeaux, UMR1219, 33000 Bordeaux, France.
\textsuperscript{2}INSERM, UMR1219, Bordeaux Population Health Research Centre, Pharmacoepidemiology team, 33000 Bordeaux, France.
\textsuperscript{3}GSK, 92500 Rueil-Malmaison, France.
\textsuperscript{4}GSK, B-1300 Wavre, Belgium.

Corresponding author

Hugo Arlegui: hugo.arlegui@gmail.com

GSK
23 Rue François Jacob
92500 Rueil-Malmaison
France

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Abstract

Background: While rotavirus vaccines have proven to prevent the risk of rotavirus gastroenteritis (RVGE) in children under 5 years old, they are also associated with an increased transient risk of intussusception (IS). Several quantitative benefit-risk models (qBRm) are performed to measure this balance in hospitalisations and deaths prevented versus the ones induced.

Objectives: To provide a complete overview of qBRm used for rotavirus vaccination.

Method: For this study, three medical literature databases were systematically searched to identify relevant articles, in English, published between 2006 and 2019.

Results: Of the 276 publications screened, 14 studies using qBRm for rotavirus vaccination were retained, based on pre-selected criteria. Four were performed in low-middle-income countries (LMICs). Almost all (13/14) displayed the following characteristics: force of infection assumed to be constant over time (static model), indirect effect of rotavirus vaccination (herd effect) not considered, closed model (individuals not allowed to enter/exit the model over time) and aggregated level (no tracking of individual’s behaviour). Most of the models were probabilistic (9/14) and reported sensitivity/scenario analyses (12/14). Input parameter values varied across studies. Selected studies suggest that, depending on the models used; for every IS hospitalisation and death induced, vaccination would prevent, respectively, 190–1,624 and 71–743 RVGE-related hospitalisations and deaths.

Conclusions: The benefits of rotavirus vaccination were shown to largely exceed the increased risk of IS, across all studies. Future research aiming to harmonise qBRm for rotavirus vaccination, should ensure the comparability of studies and provide additional information for regulatory authorities, physicians and patients.

Keywords: vaccines and immunisation; benefit-risk; model; rotavirus; intussusception; systematic review.
Background

Infection with rotaviruses is the most common cause of severe diarrhoea and dehydration in young children. Although spread worldwide, rotavirus infection induces a higher burden in low-income countries (LICs) (1). These highly contagious viruses virtually infect all children before they reach the age of five (2). Rotavirus was responsible for an estimated 258 million [95% confidence interval (CI) 193-341 million] episodes of gastroenteritis and 128,000 [95% CI: 104,500-155,600] deaths in children under the age of five in 2016 (3).

Historically, nine months after an oral rhesus-human reassortant rotavirus tetravalent vaccine (RotaShield, Wyeth) was licensed in the United States (US) in October 1998, the immunisation programme was suspended because of a temporal association between rotavirus vaccination and occurrence of intussusception (IS) (4). The estimated relative risk (RR) of IS during the 3–7 days after RotaShield administration was 58.9 [95% confidence interval (CI): 31.7–109.6] postdose 1 and 11.0 [95% CI: 4.1–29.5] postdose 2 (5). IS is a rare but serious medical condition observed when a segment of the intestine invaginates into an adjacent distal segment (6, 7) resulting in blood vessel compression and leading to pain, bowel oedema and - if arterial supply is compromised - intestinal ischemia, necrosis and even perforation. If left untreated, IS can be fatal. Although rare, IS is the most common cause of acute intestinal obstruction in infants, occurring usually between 4 and 10 months of age (1). IS occurs without rotavirus vaccination with an average worldwide background incidence rate estimated at 74 cases per 100,000 children under 1 year of age, and was shown to range between 9–328 per 100,000 across countries (7). Surgical rates of IS are substantially higher in Africa (77%) and Central and South America (86%) compared to other regions (13–50%) (7, 8).

Since 2006, two live-attenuated rotavirus vaccines have been licensed in more than 100 countries (9): Rotarix (Glaxosmithkline Biologicals), a two-dose schedule oral human rotavirus vaccine and RotaTeq (Merck & Co., Inc), a three-dose schedule oral human-bovine reassortant rotavirus vaccine (10-13). The two established vaccines have proven to be effective, and have led to a significant decline in rotavirus gastroenteritis (RVGE)-related morbidity and mortality (10, 11). Two new rotavirus vaccines have received prequalification from the WHO in 2018 (Rotavac, Bharat Biotech International Limited and Rotasiil, Serum Institute of India Limited) (14). Moreover, other rotavirus vaccines have been licensed for national markets in China (Lanzhou Lamb rotavirus vaccine (LLR), Lanzhou Institute of Biological Products) and in Vietnam (Rotavin-M1 rotavirus vaccine, Center for Research and Production of Vaccines) (15). In 2009, the World Health Organization (WHO) recommended rotavirus vaccination to all children, especially in countries with high diarrhoea-
related mortality rates (1). By the end of 2018, 92 countries had introduced rotavirus vaccination into their routine immunisation programmes for children (16).

Several observational post-licensure surveillance studies have been undertaken to assess the risk of intussusception after vaccination with Rotarix and RotaTeq in real-life settings (8, 17-24). Data from epidemiological studies suggest that between 1 and 6 cases of IS per 100,000 vaccinated children may be attributable to rotavirus vaccination (25). A meta-analysis has reported an overall estimate of RR of IS postdose 1 of 5.4 [95 % CI: 3.9-7.4] and 5.5 [95 % CI:3.3-9.3] and postdose 2 of 1.8 [95 % CI: 1.3-2.5] and 1.7 [95 % CI: 1.1-2.6], after vaccination with Rotarix and RotaTeq respectively (26). These overall estimates were further confirmed by two recent meta-analyses (22, 27).

Given the increased risk of IS associated with rotavirus immunisation, it is crucial to balance it with the benefits of vaccination in reducing RVGE-related hospitalisations and deaths (28, 29). In this context, several studies have been conducted in various geographical settings to investigate the benefit-risk (BR) profile of rotavirus vaccination. These studies using quantitative benefit-risk models (qBRm) provided key information for regulatory authorities, physicians and parents (30-33).

The aim of the present systematic literature review was: (1) to provide a comprehensive overview of published qBRm focusing on rotavirus vaccination and of their methodological approaches; (2) to characterise the BR profile of rotavirus vaccination on the basis of available scientific evidence.

Methods

Search strategy

Medline, Scopus and the Institute for Scientific Information (ISI) Web of Knowledge databases were systematically searched in order to identify original studies on qBRm for rotavirus vaccination published from 1 January 2006 to 13 December 2019. The search strategy used pre-specified terms (‘benefit-risk’ and ‘rotavirus vaccines’) as detailed in Appendix Table 1, and was limited to publications in English.

Two reviewers (H.A and N.P) independently screened all titles and abstracts using pre-defined criteria (Appendix Table 2). Subsequently, the assessment for eligibility of identified publications was carried out by examining their full-text. Disagreements between the two reviewers were resolved through discussion. In addition, reference lists of eligible articles were screened (i.e. ‘snowballing’) in order to identify potential additional publications. Finally, a grey literature search of public health organisation websites and Google was performed using the pre-specified search terms.

All citations were downloaded and imported in EndNote (version X7-Thomson-Reuters Corp, New York, USA).
Data extraction and analysis

The following data were extracted and summarised: the qBRm general information, the model characteristics, the input parameters and the BR estimates.

General information includes the studied vaccine(s), the alternative(s) to the studied vaccine(s), the vaccine funding sources, the income category of the countries for which the BR was estimated.

The model characteristics were classified according to eight attributes (34-36):

1. Simulation versus Non-Simulation model: the BR estimates were either derived from modelling approach using simulation techniques of various degrees of complexity (e.g. cohort or microsimulation models) including as many components and interaction as possible (simulation) or from a simple computation, mathematical function or statistical model (non-simulation).

2. Dynamic versus Static model: the force of infection was assumed to change over time (dynamic) or not (static).

3. Model considering Herd effect or Not: a potential herd effect of rotavirus vaccination was considered (yes) or not (no).

4. Model considering Waning effect or Not: a potential waning effect (i.e. vaccine efficacy/effectiveness decrease with time) was considered (yes) or not (no).

5. Open versus Closed model: an open model allows individuals to enter and exit the model over time (open), while a closed model does not allow for new entrances over time (closed).

6. Probabilistic versus Deterministic model: the model takes into account the uncertainty around the input parameters (probabilistic) or not (deterministic).

7. Model integrating Aggregate versus Individual-based data: the population’s behaviour in the model was simulated using aggregate variables of which values are population averages (aggregate data) or the behaviours of individuals in the population were tracked (individual-based data).

8. Model including Scenario/Sensitivity analyses or Not: scenario (using analyses to investigate different epidemiological or health care scenarios of interest) and/or sensitivity (using analyses to quantify the range of uncertainty) analyses were conducted or not. Sensitivity analyses were categorised between deterministic (using point estimates) and probabilistic (using probability distributions).
Input parameters used to perform qBRm along with benefit, risk and benefit-risk ratio (BRR) following rotavirus vaccination were extracted from analysed studies. The benefit of rotavirus vaccination was reported as the annual number or proportion of RVGE-related hospitalisations or deaths prevented by vaccination in children before 5 years. The risk of rotavirus vaccination was reported as the annual number or proportion of IS-related hospitalisations or deaths attributed to vaccination in children under one year of age. The BRR following rotavirus vaccination was expressed as the ratio of the annual number of RVGE-related hospitalisations or deaths prevented (benefit) and the annual number of IS-related hospitalisations or deaths attributed to vaccination (risk).

Results

Study selection

After removing duplicates, the search strategy yielded 276 unique records, from which 248 were excluded based on titles and/or abstracts that were not relevant to the present analysis. The full-text review of the 28 selected articles led to the consensual exclusion of 14 of them by both reviewers, leaving 14 publications for data extraction and analysis (Figure 1).

General information and model characteristics of selected studies

qBRm used for rotavirus vaccination were published from 2009 onwards (Table 1) (17, 18, 37-48). Among the fourteen selected studies, eight investigated Rotarix (6/14) (18, 37, 41, 44) or RotaTeq (2/14) (38), while five assessed both rotavirus vaccines (17, 39, 40, 42, 43). The last study (47) investigated all currently licensed vaccines (Rotarix, RotaTeq, ROTAVAC, ROTASIL and RV3-BB) and were assumed to be equivalent in terms of vaccine efficacy, effectiveness, or impact, or IS risks. All studies focused on rotavirus vaccines administered according to the national or WHO recommended vaccination schedule. Five of the fourteen studies also considered rotavirus vaccination without age restriction (37, 42, 43, 46, 47) and one study (45) considered a targeted strategy with selective rotavirus vaccination of infants with medical risk conditions (prematurity, low birth weight, or congenital conditions). Only two studies were reported as funded by a pharmaceutical company (GlaxoSmithKline) (41, 48) while the others were classified as “other sources of funding” (such as academic institutions or health authorities). Nine studies were performed in high income countries (HICs) (17, 37, 38, 40, 41, 44-46, 48), and five in low and/or middle-income countries (LMICs) (18, 39, 42, 43, 47). Studies in HICs were country-specific and mainly used local data, whereas those in LMICs were conducted across several countries: in 2, 14, 117, 135 and 158 LMICs, respectively. In the studies which included 117, 135 and 158 LMICs, a generic model using data provided by geographic area (not country-specific), was used to calculate the different estimates (42, 43, 47).
Studies included in the review used simulation (9/14) or non-simulation models (5/14) to estimate final BR outcomes. All simulation models used a cohort model as modelling approach, i.e. simulated a hypothetical cohort of individuals through a set of health states over time. A few studies (5/14) considered a waning effect over time following rotavirus vaccination. Three attributes were identical across all studies, i.e. all models were static, closed, and reported results at an aggregate/population average level. Only one study took herd effect into account. Models were probabilistic in nine studies and deterministic in the remaining ones. Most studies reported results from additional analyses: scenario analyses (9/14), probabilistic sensitivity analyses (PSA) (9/14) and deterministic sensitivity analyses (DSA) (4/14). General information for each study and a description of the different models are summarised in Table 1.

**Summary of input parameters**

Almost all (13/14) included the following input parameters: vaccine efficacy or effectiveness (VE), vaccine coverage (VC), relative risk (RR) of IS after vaccination during a given risk period (Table 2), and the baseline incidence of hospitalisations or deaths (related to RVGE or IS) in children under 5 years (for RVGE) or 1 year of age (for IS) in the absence of vaccination (Table 3). One study considered baseline incidence for RVGE under <15 years (45). VE varied according to the number of doses administered (one to three), the age of immunisation (e.g. VE >6 months and >12 months following vaccination), the vaccine used (mainly Rotarix or RotaTeq) and the health outcome of interest (hospitalisation or death). VC considered for a full vaccination schedule was low in LMICs (about 50%) and high in HICs (about 90%). All studies considered a 7-day risk period for the risk of IS following vaccination, while half of them also investigated an additional risk period of up to 21 days (17, 18, 37, 40, 44, 46, 47). The RR of IS ranged between 1.1 (95% CI: 0.3;3.3) (Brazil) and 9.9 (95% CI: 3.7;26.4) (Australia and France) after the first dose with a 7-day risk period. The RR of IS ranged from 1.7 (95% CI: 1.2;2.4) (158 LMICs assessed in the Patel et al. (43)) to 3.1 (95% CI 0.4;23.4) (Singapore) after the second dose with a 7-day risk period. Only one study analysed a RR of IS after the third dose with a risk period of 7 days (42). Details on RRs used according to the different risk periods are available in Table 2. The baseline incidence of hospitalisations or deaths (number and rate) for RVGE and IS in the absence of vaccination were country or area-specific, and were higher in LMICs for deaths (Table 3 and Appendix Table 3).

**Benefit-risk estimates of rotavirus vaccination**

Based on the 14 selected publications, vaccination would prevent 59.0% (Australia) to 89.9% (England) of RVGE-related hospitalisations, and 32.1% (mean percentage in 135 LMICs assessed by Clark et al. (47)) to 87.5% (Lamrani et al. (40) in France) of RVGE-deaths expected to occur in a no
vaccination scenario in children under 5 years of age. On the other hand, the IS-related hospitalisation rate and the IS-related death rate would increase by 2.1% (Ledent et al. (48) in France) to 21.9% (Lamrani et al. (40) in France), and 2.2% (Ledent et al. (48) in France) to 17.8% (Lamrani et al. (40) in France) as a result of vaccination in children under 1 year of age, respectively. BRRs ranged from 190 (Singapore) to 1,624 (Ledent et al. (48) in France) RVGE-related hospitalisations prevented for every additional vaccine-related IS hospitalisation, whilst 71 (US) to 743 (Ledent et al. (48) in France) RVGE-related deaths would be prevented for every additional IS-death caused by the vaccine (Table 3 and Figure 2).

Discussion

To our knowledge, the present review is the first to gather available evidence on qBRm used for rotavirus vaccination. It had two main objectives: (1) to describe methodological approaches used in the selected models (i.e. their model characteristics and input parameters) and (2) to characterise the BR profile of rotavirus vaccination based on the available scientific evidence.

Although a herd effect has been observed for rotavirus vaccination (49-54), only one study considered it as a model characteristic, among the fourteen selected studies. Some authors argued that this choice intended to make the approach more conservative. In addition, more complex modelling techniques such as transmission dynamic models were not used at all while PSA were only conducted in 9/14 of the qBRm. Choosing for simpler approaches might be explained by the fact that some studies were not conducting qBRm as primary but as secondary objective. While five studies considered a waning effect of rotavirus vaccination (37, 40, 45-47), their estimates of the proportion of RVGE-related hospitalisations or deaths prevented by vaccination in children aged less than 5 years were similar to figures reported in the other studies. This might be explained by the fact that the majority of severe RVGE cases occurs during infancy (2), before the protective effect of vaccination starts to wane.

Comparing input parameters across the different studies showed that lower VC figures were considered in LMIC than in HIC studies. This might be linked to the year of publication, i.e. between 2009 and 2012, the WHO recommended administration of the first dose of rotavirus vaccines with an upper age limit of 12-14 weeks to minimise the potential risk of IS. This strict age restriction may have reduced VC in some developing countries where the timeliness of paediatric vaccination varies widely (55). In 2013, WHO removed this age restriction in order to improve VC (56). It is worth noting though that the use of different VC figures had no impact on BRR estimates, since none of the selected qBRm considered transmission dynamic modelling.
The annual number of IS-related hospitalisations or deaths in children less than 1 year of age used as input parameter also varied across studies. The etiology of IS is not yet clearly understood. Differences in infant diet, breastfeeding, maternal antibody levels, association with several pathogens including adenoviruses might all contribute to the variances in background rates of IS (7, 57, 58). A higher number of IS-related deaths are observed in LMICs compared to HICs among selected studies. This finding might be due to differences in healthcare infrastructure or delays in care (7).

The present review systematically collected the published information on qBRm for rotavirus vaccination, which allowed further characterising its BR profile. All selected studies concluded that vaccine-prevented RVGE-related hospitalisations and deaths outweigh vaccine-induced IS-related hospitalisations and deaths, with no marked difference between LMICs and HICs. Differences in BRR noted across studies included in this review can be explained by (1) the choice of model attributes (e.g. simulation versus non-simulation models), (2) varying epidemiology of RVGE and IS observed across countries and areas, (3) data availability at the time of the study, and (4) differences in the choice of input parameter values. Though it is crucial to consider those differences when comparing models and their outputs. For example, despite the fact that they used similar modelling approaches, the two qBRm studies conducted in France showed differences with BRRs of 214 and 273 in Lamrani et al. (2017) and 1,624 and 743 in Ledent et al. (2018), for hospitalisations and deaths, respectively (40, 48). This might be explained by the value of some input parameters (e.g. risk period duration and relative risk of IS). In this specific example, the use of scenario analysis by Ledent et al. considering the same risk period of 21 days as Lamrani et al. resulted in similar BRR between both studies (48).

This systematic literature review has some limitations. First, the search strategy may have not identified all relevant studies, notably due to the lack of limited specific keywords for qBRm. In addition, some studies conducted by or for local governments or pharmaceutical companies may not have been made publicly available or indexed. Secondly, the data from included studies were not pooled in a meta-analysis to estimate an overall BRR for rotavirus vaccination, since 95% CI were not available for all studies. Nevertheless, a forest plot allowing a visual assessment of differences between BRRs is depicted without providing overall BRR estimate (Figure 2).

**Conclusion**

The present review provides a comprehensive overview of publications reporting on qBRm for rotavirus vaccination. This evidence confirms the favorable safety profile of rotavirus vaccines. However, the observed differences in qBRm approaches between studies complexified the comparison of their outputs and warrant the need for harmonisation in such analysis in order to
ensure comparability. In addition, since most studies focused on HICs, there is a need to increase BRR estimations in LMICs considering setting-specific input parameters and including sensitivity and/or scenario analyses to fully capture their effect.

Notes

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Declaration of financial interests

Hugo Arlegui, Gaëlle Nachbaur and Nicolas Praet are employed by the GSK group of companies which produces one of the two vaccines of interest (Rotarix) in this review. Gaëlle Nachbaur and Nicolas Praet also hold shares in the GSK group of companies. Bernard Bégaud, who acted as the academic PhD supervisor of this study, has no conflicts of interest to declare.

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Table 1. General information and model characteristics of studies using quantitative benefit-risk models for rotavirus vaccination.

| Source                  | Vaccine(s)       | Alternative(s)                                      | Funding Income category | Simulation model | Static/Dynamic model | Herd Waning effect | Close/Open model | Deterministic/Probabilistic model | Aggregate/Individual-based model | Scenario/Sensitivity analyses |
|-------------------------|------------------|----------------------------------------------------|-------------------------|------------------|----------------------|--------------------|------------------|-----------------------------------|-------------------------------|-------------------------------|
| Patel MM, et al. 2009   | Rotarix/RotaTeq | No vaccination No age restriction to vaccination   | Other LMICs             | No               | Static               | No                 | No               | Closed/Deterministic              | Aggregate                     | Scenario                      |
| Patel MM, et al. 2011   | Rotarix          | No vaccination                                     | Other LMICs             | No               | Static               | No                 | No               | Closed/Deterministic              | Aggregate                     | No                            |
| Desai R, et al. 2012    | Rotarix/RotaTeq | No vaccination                                     | Other LMICs             | Yes              | Static               | No                 | No               | Closed/Probabilistic             | Aggregate                     | PSA                           |
| Patel MM, et al. 2012   | Rotarix/RotaTeq | No vaccination No age restriction to vaccination   | Other LMICs             | Yes              | Static               | No                 | No               | Closed/Probabilistic             | Aggregate                     | Scenario/PSA                   |
| Carlin JB, et al. 2013  | Rotarix/RotaTeq | No vaccination                                     | Other HIC               | No               | Static               | No                 | No               | Closed/Deterministic              | Aggregate                     | No                            |
| Desai R, et al. 2013    | RotaTeq          | No vaccination                                     | Other HIC               | Yes              | Static               | No                 | No               | Closed/Probabilistic             | Aggregate                     | DSA/PSA                       |
| Clark A, et al. 2014    | Rotarix          | No vaccination No age restriction to vaccination   | Other HIC               | Yes              | Static               | No                 | Yes              | Closed/Probabilistic             | Aggregate                     | Scenario                      |
| Yung CF, et al. 2015    | Rotarix          | No vaccination                                     | Other HIC               | No               | Static               | No                 | No               | Closed/Deterministic              | Aggregate                     | Scenario                      |
| Ledent E, et al. 2016   | Rotarix          | No vaccination                                     | Pharma HIC              | Yes              | Static               | No                 | No               | Closed/Probabilistic             | Aggregate                     | DSA/PSA                       |
| Study Authors               | Vaccine Type          | Vaccination Strategy                                      | Region Type | HIC Status | Model Type   | Sensitivity Analyses | Scenario Type + PSA/DASA Scenario |
|----------------------------|-----------------------|------------------------------------------------------------|-------------|------------|--------------|----------------------|------------------------------------|
| Lamrani A, et al. 2017     | Rotarix/RotaTeq       | No vaccination                                             | Other       | Yes        | Static       | No                   | Closed Probabilistic Aggregate PSA Scenario |
| Ledent E, et al. 2018      | Rotarix               | No vaccination                                             | Pharma HIC  | Yes        | Static       | No                   | Closed Probabilistic Aggregate DSA/PSA Scenario |
| Bruijning-Verhagen P, et al. 2018 | RotaTeq              | No vaccination, Targeted vaccination                        | Other       | Yes        | Static       | Yes                  | Closed Probabilistic Aggregate DSA/PSA Scenario |
| Bruun T, et al. 2019       | Rotarix               | No vaccination, No age restriction to vaccination           | Other       | No         | Static       | No                   | Closed Deterministic Aggregate Scenario |
| Clark A, et al. 2019       | Rotarix/RotaTeq/RV3-BB/ROTAVAC/ROTASII | No vaccination, No age restriction to vaccination           | Other       | LMICs      | Static       | No                   | Closed Probabilistic Aggregate PSA Scenario |

HIC, High-income country; LMICs, Low-middle-income countries; PSA, Probabilistic sensitivity analyses; DSA, Deterministic sensitivity analyses.
Table 2. Input parameters of quantitative benefit-risk models used for rotavirus vaccination.

| Source              | Location               | Vaccine(s)              | Vaccine efficacy/effectiveness | Vaccine coverage | IS risk period (days): Relative risk | Birth Cohort |
|---------------------|------------------------|-------------------------|-------------------------------|-----------------|-------------------------------------|--------------|
| Patel MM, et al.    | LMIC (117)             | Rotarix/RotaTeq         | D1: 50%                       | 54%             | D1[1-7]: 6.0                        | NR           |
|                     |                        |                         | D2&3: 75%                     |                 | D2[1-7]: 3.0; D3[1-7]: 1.0          |              |
| Patel MM, et al.    | Brazil                 | Rotarix                 | D1&2: 85%                     | 50%             | Brazil: 5.3; Mexico: 5.3            | 3,068,249    |
|                     | Brazil                 | Rotarix                 |                                |                 |                                      |              |
| Patel MM, et al.    | LMIC (158)             | Rotarix/RotaTeq         | 'Hosp': 66% [31;83] to 85%    | 80%             |                                      |              |
|                     |                        |                         | 'Death': 80% [59;90] to 100%  |                 |                                      |              |
|                     |                        |                         |                               |                 |                                      |              |
| Yung CF, et al.     | Singapore              | Rotarix                 | D1: 50%                       | 85%             | D1(17): 8.4 [2.4;19.0]               |              |
|                     |                        |                         | D2: 80%                       |                 | D2(17): 3.1 [0.4;23.4]               |              |
|                     |                        |                         | D2(8-21): 6.3 [0.2;11.7]      |                 |                                      |              |
| Lamrani A, et al.   | France                 | Rotarix/RotaTeq         | D1>6m: 96% [90.2;98.8]        | 95%             | D1(17): 8.1 [2.4;19.0]               |              |
|                     |                        |                         | D1>12m: 90.7% [85.6;94.3]     |                 |                                      |              |
|                     |                        |                         | D2>4m: 100% [81.8;100]        |                 |                                      |              |
|                     |                        |                         | D2>10m: 92.2% [65.6;99.1]     |                 |                                      |              |
| Lamrani A, et al.   | France                 | Rotarix                 | D1: 50%                       | 85%             |                                      |              |
|                     |                        |                         | D2: 80%                       |                 |                                      |              |
|                     |                        |                         | D2(8-21): 6.3 [0.2;11.7]      |                 |                                      |              |
| Ledent E, et al.    | Japan                  | Rotarix                 | D1: 73.9% [50.1;83.7]         | 72%             | D1(17): 8.1 [2.4;19.0]               |              |
|                     |                        |                         | D2: 91.6% [62.4;99.1]         |                 |                                      |              |
| Ledent E, et al.    | France                 | Rotarix                 | D1: 75% [55.88]               | 85%             |                                      |              |
|                     |                        |                         | D2: 80%                       |                 |                                      |              |
|                     |                        |                         | D2(8-21): 6.3 [0.2;11.7]      |                 |                                      |              |

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| Year | Country | Vaccine(s) | Dose 1 (86%) | Dose 2 (90%) | Dose 3 (92%) | Mean (95% CI) Dose 1 & 2 (88%) | Dose 2 (94.8%) | NR | N |
|------|---------|------------|--------------|--------------|--------------|---------------------------------|---------------|----|---|
| 2018 | Netherlands | RotaTeq | D1 & 2: 88% | D2: 90% [81;95] | D3: 94.8% | 86% | D2: 92% [72;100] | | | |
| 2018 | Norway | Rotarix | D1 & 2: 93% [87;98] | D1: 91% | D2: 86% | D1 (1-21): 2.4 [1.5;3.8] | D2 (1-21): 1.8 [1.3;2.4] | | 171,387 |
| 2019 | Norway | Rotarix | D1 & 2: 93% [87;98] | D1: 91% | D2: 86% | D1 (1-21): 2.4 [1.5;3.8] | D2 (1-21): 1.8 [1.3;2.4] | | | |
| 2019 | LMIC (135) | Rotarix/RotaTeq/ ROTAVAC/ROTASIIL/ RV3-BB | 79% [75;82] to 100% [99;100] | Country-specific | D1(1-7): 6.3 [4.3;9.2] | D1(8-21): 1.7 [1.1;2.7] | D2(1-7): 1.8 [1.4;2.3] | | | |

LMIC, Low-middle-income countries; D1, Dose 1; D2, Dose 2; D3, Dose 3; Mean [95% Confidence Interval (CI)]; m, months; w, weeks; 'Hosp', Hospitalisation; NR, Not reported; N, Number; *calculated using data from original publications; †median values; ‡baseline incidence RVGE <15 years.
Table 3. Benefit-risk estimates of rotavirus vaccination in analysed studies.

| Source               | Location       | Vaccine(s)          | Events | Baseline incidence RVGE<5y (N) | Prevented RVGE<5y (N) | Prevented RVGE<5y (%) | Baseline incidence IS <1y (N) | Caused IS <1y (N) | Caused IS <1y (%) | Caused IS <1y (%) | BRR (RVGE/IS) |
|----------------------|----------------|---------------------|--------|-------------------------------|-----------------------|-----------------------|-------------------------------|-------------------|------------------|------------------|-----------------|
| Patel MM, et al. 2009 | LMIC (117)     | Rotarix/RotaTeq     | Hosp   | 117,959                       | 0                     | 194,564               | NR                            | 517,959           | NR               | NR               | NR              |
| Patel MM, et al. 2011 | Brazil         | Rotarix             | Hosp   | 92,453                        | 69,572                | 75.3*                 | 1,214                        | 55                | 2.6*             | 1,265*           | NR              |
|                      | Mexico         | Rotarix             | Hosp   | 16,086                        | 11,551                | 71.8*                 | 1,214                        | 41                | 3.4*             | 282*             | NR              |
|                      |                |                     | Death  | 923                           | 663                   | 71.8*                 | 1,214                        | 61                | 2.3*             | 332*             | NR              |
| Desai R, et al. 2012 | Latin America  | Rotarix/RotaTeq     | Hosp   | 229,856                       | 144,746               | 63.0*                 | 5,556                        | 172               | 3.1*             | 841 [479;1,142]  | NR              |
|                      |                |                     | Death  | 6,302                         | 4,124 [3,740;4,239]   | 65.4*                 | 10 [6;17]                    | 3.1*             | 395 [207;526]    | NR               | NR              |
| Patel MM, et al. 2012 | LMIC (158)     | Rotarix/RotaTeq     | Hosp   | 452,800 [386,600;519,900]b, a | 155,800 [83,300;217,700]b | 34.4*                 | 253 [76,689]                | 615*             | NR               | NR               | NR              |
| Carlin JB, et al. 2013 | Australia      | Rotarix/RotaTeq     | Hosp   | 11,073                        | 6,528                 | 59.0*                 | 144                           | 14                | 9.7*             | 466*             | NR              |
| Desai R, et al. 2013 | US              | RotaTeq             | Hosp   | 71,175 [50,131;96,802]b        | 53,444 [37,622;72,882]b | 75.1*                 | 45 [21.86]                   | 1,093             | [688;1902]       | NR               | NR              |
| Clark A, et al. 2014 | England        | Rotarix             | Hosp   | 14,770 [14,113;15,427]b        | 13,276 [12,255;14,181]b | 89.9*                 | 248                           | 35.4              | [7;97.6]         | 14.3*            | NR              |
| Yung CF, et al. 2015 | Singapore      | Rotarix             | Hosp   | 808                           | 570                   | 70.5*                 | 22                            | 3                 | 13.6*            | 190*             | NR              |
| Ledent E, et al. 2016 | Japan           | Rotarix             | Hosp   | 20,829 [16,301;26,129]b        | 17,925 [11,715;23,276]b | 86.1*                 | 1,571                        | 50 [7;227]        | 3.2*             | 350 [69,2510]    | NR              |
| Lamrani A, et al. 2017 | France          | Rotarix/RotaTeq     | Hosp   | 11,866                        | 10,375 [7,802;13,293]  | 87.4*                 | 214                           | 47 [25;81]        | 21.9*            | 214 [128;362]    | NR              |
| Ledent E, et al. 2018 | France          | Rotarix             | Hosp   | 15,059 [12,100;18,476]b        | 11,132 [7,841;14,409]b | 73.9*                 | 323 [257,400]                | 6.9 [2.3;38.4]    | 2.1*             | 1,624 [240;5,424] | NR              |
| Bruijnings-Verhagen P, et al. 2018 | Netherlands | RotaTeq         | Hosp   | 2,700 [2,400;3,000]b, a, e     | 2,000 [1,800;2,200]b, a | 74.1*                 | NR                           | 2.9*             | NR               | 685 [603;767]    | NR              |
| Bruun T, et al. 2009 | Norway          | Rotarix             | Hosp   | 1,768 [1,761;1774]b, a, e      | 5.2 [2.8;8.3]b, a, e  | 93.6*                 | NR                           | 1 [1;2]          | NR               | NR               | NR              |

NR = not reported, RVGE<5y = rotavirus gastroenteritis <5 years, IS = intestinal symptoms, Hosp = hospitalisation, BRR = benefit-risk ratio.
| Study          | Group                  | Death     | BRR (95% CI) | FVIRIS (95% CI) | IS (95% CI) | IS (0-2 yrs) | Death     | BRR (95% CI) | FVIRIS (95% CI) | IS (95% CI) | IS (0-2 yrs) |
|----------------|------------------------|-----------|--------------|----------------|-------------|--------------|-----------|--------------|----------------|-------------|--------------|
| Clark A, et al. 2019 | Rotarix/RotaTeq/ROTAVAC/ROTA SIIL/RV3-BB | Death 194,471 [158,603;257,080] | 32.1 \(^a\) | NR | 122 [44;322] | NR | 512 [218;1,338] |

LMIC, Low-middle-income countries; ‘Hosp’, Hospitalisation; RVGE, Rotavirus Gastroenteritis; IS, Intussusception; Mean [95% Confidence Interval (CI)]; yrs, years; NR, Not reported; BRR, Benefit-risk ratio; N, Number; \(^a\) calculated using data from original publications; \(^b\) median values; \(^c\) 90% CI; \(^d\) IS risk period (0-2 years); \(^e\) baseline incidence RVGE <15 years.
Figure 1. PRISMA flow diagram.
Figure 2. Forest plot of benefit-risk ratios associated with rotavirus vaccination from selected studies. (a) Hospitalisations (b) Deaths. Confidence intervals were not reported for all modelling studies.
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