Systematic literature review on the safety and immunogenicity of rotavirus vaccines when co-administered with meningococcal vaccines

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ABSTRACT
This study is aimed to review the published evidence on safety, immunogenicity, and efficacy of rotavirus vaccines when co-administered with meningococcal vaccines in infants. A systematic literature search was performed in four databases containing peer-reviewed articles and conference abstracts. In total, twelve articles were included in the review; 11 provided information on safety and five on the immunogenicity of rotavirus vaccines following co-administration. No paper was found on efficacy. Additional routine vaccines were administered in all studies. The safety analysis was mainly focused on fever, vomiting, diarrhea, intussusception, and changes in eating habits. Overall, safety profiles and immune responses associated with rotavirus vaccination were comparable between infants co-administered with rotavirus and meningococcal vaccines and infants receiving rotavirus vaccines without meningococcal vaccines. Although data are limited, co-administration of rotavirus and meningococcal vaccines does not appear to interfere with the safety or immunogenicity of rotavirus vaccines.

PLAIN LANGUAGE SUMMARY

What is the context?

● Rotavirus is one of the leading causes of acute diarrheal disease in children under the age of 5 years worldwide. It results in a high disease burden in developed countries and a high mortality rate in resource-limited countries.

● Invasive meningococcal disease remains an important health concern. It is disabling in 12-20% and fatal in 5-15% of cases.

● Effective vaccines for the prevention of these two diseases have been introduced in many countries.

● Co-administration of rotavirus and meningococcal vaccines, administered orally and parenterally, respectively, during the same consultation could reduce medical visits and associated costs and increase vaccination coverage.

What is new?

● We reviewed the published evidence on the safety profile, immunogenicity and efficacy of rotavirus vaccines when co-administered with available meningococcal vaccines in infants during their first year of life.

● From the 12 studies comparing administration of rotavirus vaccines with or without meningococcal vaccines, we observed:
  ■ No higher rate of rotavirus vaccine-related adverse events upon co-administration.
  ■ A comparable immune response against rotavirus vaccine between groups.
  ■ No studies assessing efficacy were identified.

What is the impact?

● Though limited, the available data indicate that the co-administration of rotavirus vaccines with meningococcal vaccines does not affect the safety profile and immunogenicity of rotavirus vaccines.

Introduction

Rotavirus (RV) is a common cause of severe and fatal acute diarrhea in young children throughout the world. In the European Union, 300–600 children per 100,000 under the age of 5 years are hospitalized due to RV gastroenteritis (RVGE) annually. Many countries worldwide have already included oral RV vaccines in their National Immunization Programs (NIP) as recommended by the World Health Organization (WHO). Following RV vaccine introduction, significant reduction in infant diarrheal deaths, RVGE-related hospitalization, and cases of RVGE was observed. Currently, there are two globally available oral vaccines for the prevention of RVGE in the first year of life. The human live-attenuated RV vaccine containing G1P[8] strain (HRV, Rotarix) is administered as a two-dose schedule, with a minimum interval of 4 weeks between doses, the first dose...
being administered from 6 weeks of age. The schedule must be completed by 24 weeks of age.5,6 The human-bovine live-attenuated reassortant pentavalent RV vaccine (HBRV, Rotarix) is administered as a three-dose regimen, with an interval of at least 4 weeks between doses, the first dose being administered between 6 and 12 weeks of age. The schedule must be completed by 32 weeks of age.7,8 Additionally, new live-attenuated naturally reassortant monovalent (nHRV, Rotavac) and human-bovine reassortant pentavalent (BRV-PV, Rotasili) RV vaccines have been recently licensed.9,10 All these four vaccines are now WHO prequalified.11

Invasive meningococcal disease (IMD), characterized by high mortality and morbidity, is mainly caused by six (MenA, MenB, MenC, MenW, MenY, and MenX) of the 12 serogroups of Neisseria meningitidis. Epidemiology of IMD varies considerably geographically, with socio-economic setting, and over time.12 Different meningococcal vaccines are available to prevent IMD. Following recommendations of these vaccines in immunization programs, disease incidences decreased significantly in many countries worldwide.13,14 In young children, meningococcal vaccines are generally administered from 2 to 24 months of age: recombinant four-component MenB vaccine (4CMenB, Bexsero), Hib and MenC (Menitorix) and MenC and MenY (Hib-MenCY-TT, MenHibrix, discontinued in 2016) tetanus toxoid conjugated vaccines, tetravalent MenA, MenC, MenW-135, MenY diphtheria toxin (MenACWY-CRM, Menveo, and Menactra) and tetanus toxin conjugated vaccines (Nimenrix), MenA (MenAV, MenAfriVac) and MenC (MenCC, NeisVac-C) tetanus toxoid conjugated vaccines, and MenC diphtheria toxin conjugated vaccines (Men-C, Meningitec, and Menjugate).15

Since the vaccination schedules for RV and some meningococcal vaccines overlap, co-administration of these vaccines as part of the routine immunization is likely.16,17 Given the increased recommendations of meningococcal vaccines worldwide, a summary of data on the safety, immunogenicity, and efficacy of their co-administration with RV vaccines is of interest to demonstrate the compatibility of these vaccines. This evidence could more easily prompt healthcare practitioners to boost parental attitude toward vaccination and to co-administer the vaccines, thus increasing RV and meningococcal vaccine coverage amongst children <5 year-olds, while saving on costs and number of medical visits required to comply with the routine vaccination schedule.18

### Methods

The objectives of this systematic literature search were to identify the published worldwide evidence on the safety profile, immunogenicity, and efficacy of RV vaccines when co-administered (at the same clinical visit) with meningococcal vaccines in infants during the first year of life.

### Identification, selection, and data extraction

The literature search was carried out in PubMed, Embase, Cochrane Library, and LILACS (Latin America) databases for peer-reviewed articles published between 1 January 2000 and 04 January (PubMed), 11 January (Embase), 13 February (Cochrane and LILACS) 2019. In addition, international conference abstracts published between 2014 and 2018, selected from the hits from the Embase search, were searched to identify studies not yet published in peer-reviewed journals. A gray literature search (03 March 2019) was also conducted to identify data for the remaining gaps. The websites of Pan American Health Organization (PAHO), Centers for Disease Control and Prevention (CDC), European Center for Disease Prevention and Control (ECDC), WHO, and regional agencies (National Health Service England and Ministries of Health of Spain, Brazil, and Italy) were searched for relevant data. In addition, an internet search was performed using the terms “rotavirus vaccines,” “meningococcal vaccines,” and “coadministration.” Search strings are provided in Supplementary Table S1.

Relevant studies were selected by a three-step selection procedure checking against a list of inclusion and exclusion criteria (Table 1). In a first step, a screening of titles and abstracts was performed in duplicate by two epidemiologists and relevant papers were selected for full-text screening. In case of doubt, the article was included in the full-text screening step. In a second step, full-text papers were screened in duplicate by two epidemiologists. Critical appraisal of full-text articles was performed only if the article provided information for one of the review objectives. Further scrutiny of articles was carried out during the data-extraction step (third step) to identify any additional information that might be relevant to be included in the current assessment. The reference lists of selected articles, narratives, and systematic reviews were checked manually for potentially relevant studies. Data from the selected articles were summarized using

| Table 1. Systematic literature review: inclusion and exclusion criteria during the selection phases. |
|-----------------------------------------------|-----------------|-----------------|
| Period of publication                        | 2000 onwards    | Conference abstracts published before 2014 |
| Study design/type                            | Studies providing original data | Systematic reviews and meta-analysis* |
| Study population                             | Children <12 months old | Narrative reviews* |
| Study comparison                             | Co-administration of rotavirus vaccine and meningococcal vaccine; Rotarix 2 dose vaccine schedule is from 6–24 weeks with minimum duration of 4 weeks between doses. | Animal studies |
| Study data                                   | Quantitative and qualitative outcomes of all types of Rotavirus vaccination (immunogenicity, efficacy and/or safety data) | Articles that describe non-pertinent publication types (e.g. letters to the editor, editorials or comments) |
| Study population                             | Children <12 months old | Non-pertinent age groups (adolescents, adults) |
| Study comparison                             | Co-administration of rotavirus vaccine and meningococcal vaccine; Rotarix 2 dose vaccine schedule is from 6–24 weeks with minimum duration of 4 weeks between doses. | Clearly no co-administration of rotavirus vaccine and meningococcal vaccine |
| Study data                                   | Quantitative and qualitative outcomes of all types of Rotavirus vaccination (immunogenicity, efficacy and/or safety data) | Data not relevant for the objectives (e.g. data of meningococcal vaccination outcomes) |

*Reference lists were checked on possibly missed relevant articles. If this was the case, the original articles were included and the systematic review or meta-analysis itself was excluded.
a standardized data-extraction spreadsheet in Excel. If needed, percentages of safety and immunogenicity parameters were calculated from the original data. If the article referred to a registration number at clinicaltrials.gov, the website was checked and relevant data were extracted.

**Study quality assessment**

The original research articles eligible for data extraction were assessed using the SIGN checklists; this included criteria of the Cochrane checklists and the most important criteria of PRISMA and STROBE guidelines. The studies were rated as "high" quality if there was little or no risk of bias and the results were not likely to be changed by further research, "acceptable" quality if some flaws in the study were present with an associated medium risk of bias and results may change in the light of further studies, and "low" quality if significant flaws associated with high risk of bias were present. The final decision whether the quality of a study was sufficient or not for inclusion was based on the expertise of one epidemiologist, keeping the results of the checklist and the objectives of the review in mind. In case of doubt, the methodological quality of the study was discussed with the second epidemiologist.

**Results**

In total, 3,098 references (including 342 conference abstracts) were retrieved from the databases and websites or identified by manual searching. Of the 2,815 unique records, twelve articles were finally included in the review (Figure 1). No additional articles were found through the gray literature search. Study design and characteristics are presented in Table 2. Quality of selected studies was

![Selection procedure](image_url)

Figure 1. Selection procedure.

RV: Rotavirus vaccine; MV: meningococcal vaccine.
Table 2. Description of studies included in the literature review.

| Study design | Study period | Study population | Sample size | Related vaccines | Co-administration group | Study quality |
|--------------|--------------|------------------|-------------|------------------|-------------------------|--------------|
| Open-label, randomized | Oct 2010–May 2012 | Healthy infants aged 55–89 days | 733 | RV: NR MV: MenACWY-CRM | RV: part of routine vaccinations: given at 2, 4, and 10 MoA | Acceptable |
| United States | | | | | RV at 2, 4, (and 12) MoA or 2, 4, 6 (and 12) MoA | |
| United States | Oct 2010–May 2012 | Infants aged between 8 weeks and <18 months. | Approx. 1,290,000 | RV: probably HRV MV: 4CMenB | Booster dose of RV and MV + other vaccines | Low |
| United States | Feb 2014–March 2016 | Healthy infants aged 6–12 weeks born ≥37 weeks | 600 | RV: HRV MV: Hib-MenCY-TT | RV and MV combined at 2 and 4 MoA + routine vaccines | Acceptable |
| Mali | Oct 2014–March 2015 | Healthy children aged 9–11 months | 1,364 | RV: HBRV MV: MenACWY-CRM | RV and MV combined at 2, 4, and 6 MoA + routine vaccines | Acceptable |
| United States | March 2007–Nov 2009 | Healthy infants aged 55–89 days, born ≥37 weeks and birth weight ≥2.5 kg, that received at least one vaccine dose | 273 | 4CMenB | Booster dose of RV and MV + other vaccines | Acceptable |
| United States | | | | | | |
| United States | March 2013–March 2014 | Healthy infants aged 46–74 days at enrolment and received 1 dose of HexpB vaccine ≤3 days of birth | 384 | RV: HBRV MV: MenCC | | Acceptable |
| Spain | | | | | | |
| Spain | Jan 2014–Nov 2015 | Healthy infants aged 55–75 days, born ≥37 weeks, birth weight ≥2.5 kg | 263 | RV: HBRV MV: MenCC | RV and MV at 2 MoA, RV at 4 and 6 MoA + routine vaccines | Acceptable |
| Worldwide | NA | Infants, adolescents, and adults | 5,515 (>7,000 including toddler) | RV: HRV or HBRV MV: 4CMenB | According to the corresponding study design. | Low |
| Argentina and Colombia | March 2007–Nov 2019 | Healthy infants aged 55–89 days old, born ≥37 weeks and birth weight ≥2.5 kg, that received at least one vaccine dose | 3,033 | RV: HBRV MV: MenACWY-CRM | RV and MV at 2 and 4 MoA + routine vaccines | Acceptable |
| Finland | Jan 2007–March 2007 | Healthy infants aged 6–7 weeks | 247 | RV: HBRV MV: MenCC | RV and MV combined at 10–11 WoA; RV and MV combined at 20–21 WoA; RV alone at 24–25 WoA + routine vaccines | Acceptable |
| Czech Republic, Finland, France, Germany, Italy, Spain | Sept 2004–Aug 2006 | Healthy infants aged 6–7 weeks and birth weight >2000 g | 1,216 | RV: HRV MV: MenCC-CRM (Spain only) | RV at 2, 4, and 6 MoA and MV at 10–11 WoA and 2 and 4 MoA + routine vaccines | Acceptable |

(Continued)
mostly “acceptable.” After the initial screening, seven conference abstracts were selected for in-depth analysis. Three eligible abstracts referred to data published in full reports; all three reports were added to the full-text screening. The remaining four abstracts were considered not relevant with respect to objectives or did not report data on co-administration of RV and meningococcal vaccines. Eleven studies provided information on the safety profile of co-administration of RV vaccines and meningococcal vaccines.25–30 and five studies reported data on immunogenicity.21,22,24,29,31 No studies presented data on vaccine efficacy.

**Safety**

**Co-administration of RV and meningococcal vaccines compared to sequential administration**

One randomized trial evaluated the co-administration of the HBRV vaccine and a tetanus toxoid conjugate MenCC vaccine (at 10–11 and 20–21 weeks of age, Group 1) compared to their sequential administration at alternating visits, at least four weeks apart (HBRV administered at 6–7 and 15–16 weeks of age, Group 2) in healthy infants aged 6–7 weeks.29 The third dose of HBRV was administered at 24–25 weeks of age in both groups. Both groups received additional routine vaccines (Supplementary Table S2). In the first 6 days after the first co-administered dose, proportion of participants with a solicited systemic adverse events (AEs) in Group 1 was 23.3% (diarrhea), 19.8% (vomiting), and 8.6% (fever), while 44.0% was assessed as related to HBRV (Table 3). In the 13-day period after their second dose, 42.6% of the children in Group 1 experienced at least one systemic AE related to HBRV. In Group 2, none of the systemic AEs were reported by >10% of the participants during the 13-day period following the second and third HBRV doses. Two serious adverse events (SAEs) occurred, one in each group: an episode of epilepsy of moderate intensity, starting 13 days after the second vaccination (Group 1) and a severe viral infection, starting 9 days after the third vaccination (Group 2). These events were considered not related to either study vaccine by the study investigators. One infant in each group experienced non-serious, mild hematocrit that was considered related to HBRV in Group 1 and to MenCC in Group 2.

**Routine vaccination including co-administration of RV and meningococcal vaccines compared to routine vaccines including RV without meningococcal vaccines**

Five phase III clinical studies investigated the co-administration of HRV or HBRV vaccines and conjugated meningococcal vaccines as part of routine immunization compared to vaccination without meningococcal vaccine, but including RV vaccines.23,25–28 The results could not be stratified for the AEs related to RV vaccines as other routine vaccines were also administered in all studies. We focused on diarrhea, vomiting, intussusception, change in eating habits, and fever (Table 4).

One phase 3 study assessed the immunogenicity and safety of 3 + 1 doses of Hib-MenCY-TT vaccine when co-administered with routine vaccines including HRV.29 In the co-administration group, enrolled infants received 2 doses of HRV at 2 and 4 months of age and 3 primary doses of Hib-MenCY-TT at 2, 4, and
6 months of age and a booster dose at 12–15 months of age, along with other routine vaccines. In the control group, infants were administered with 2 HRV doses at 2 and 4 months of age, Hib vaccine without a meningococcal component at 2, 4, and 12–15 months of age, and other routine vaccines. Fever was reported by 41.8% of infants in the co-administration group and 48.5% in the control group; vomiting was reported by 4.7% and 6.6% of participants, diarrhea by 8.8% and 5.9%, change in eating habits by 59.6% and 66.0% of participants, respectively (Table 3). No cases of intussusception were reported. None of the reported SAEs was assessed as vaccination-related by the investigator.22

Three articles were identified on HBRV.25,26,28 Immunogenicity and safety of MenACWY-CRM, Menveo co-administered with routine vaccines including HBRV was assessed in a large phase 3 study conducted in the United States (US)28 and in Colombia and Argentina.26 After three infant doses of MenACWY-CRM and three HBRV doses at 2, 4, and 6 months of age in US infants, fever was reported by 5%, vomiting by 5%, diarrhea by 7%, and change in eating habits by 15% of study participants.28 When the same 3-dose vaccination schedule was evaluated in Colombia and Argentina, the incidence of solicited systemic AEs was 13.3% (fever), 14.2% (vomiting), 15.4% (diarrhea), and 17.1% (change in eating habits) after the first vaccination (at month 2).26 Co-administration of two primary doses of MenACWY-CRM (at 2 and 6 months of age) with 3 HBRV doses was also assessed in the Latin American study population. At month 2, fever, vomiting, diarrhea, and change of eating habits were reported by 5.0%, 8.3%, 14.0%, and 12.3% of participants, respectively.28 In both studies, comparable results were obtained in the control group who received routine vaccines without MenACWY-CRM. In the US population, three SAEs reported in any of the three articles.25,26,28 Additionally to the five aforementioned phase III clinical studies, safety data on the concomitant administration of 4CMenB and HRV were retrieved from a prospective surveillance study conducted among children up to 18 months of age who received 4CMenB as part of the NIP in the United Kingdom (UK).30 The study revealed no significant safety concerns within 20 months following 4CMenB introduction. Evaluation of immunization records for HRV vaccine collected before and after 4CMenB introduction suggested that 4CMenB reactogenicity did not affect compliance with the recommended vaccination schedule, including the administration of HRV.30

### Co-administration of RV and meningococcal vaccines, no comparative group

Four studies examined the co-administration of HRV or HBRV and meningococcal vaccines, however, no comparison was made with the administration of RV vaccines without meningococcal vaccines.20,21,23,24 Additional vaccines were also provided in all four studies as part of the local immunization program.

Two of the four studies were conducted in Spain to assess the immunogenicity and safety of several hexavalent and pentavalent combination vaccines administered in a mixed primary series concomitantly with other recommended vaccines.20,24 In a phase 3, single-arm study, the mixed 2-4-6-month schedule of hexavalent DTaP5-HB-IPV-Hib (Vaxelis) and pentavalent DTaP5-IPV-Hib (Pediace) vaccines was co-administered with three HBRV doses at 2, 4, 6 months of age) and MenCC and PCV13 vaccines (at 2 and 4 months of age). Solicited vaccine-related systemic AEs within 1–5 days following vaccinations at 2, 4, and 6 months of age.

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### Table 3. Systemic adverse events (%) related to co-administration of HBRV and MenCC or their sequential administration

| Systemic AEs (%) | Group 1 (Co-administration) | Group 2 (Sequential administration) |
|------------------|-----------------------------|-------------------------------------|
|                  | Post-dose 1* | Post-dose 2* | Post-dose 3** | Post-dose 1** | Post-dose 2** | Post-dose 3** |
| Any (solicited/unsolicited) related to HBRV | 65.5 | 42.6 | <10 | NR | <10 | <10 |
| Any solicited related to HBRV | 44.0 | 27.0 | NR | NR | NR | NR |
| Diarrhea | 23.3^ | 13.0^ | 6.4 | 13.1 | 8.3 | 5.9 |
| Vomiting | 19.8^ | 10.4^ | NR | 5.7 | NR | NR |
| Fever | 8.6^ | 18.3^ | NR | NR | NR | NR |
| Any unsolicited related to HBRV | 45.7 | 24.3 | NR | NR | NR | NR |

*After co-administration of HBRV and MenCC vaccines. ** After sequential administration. ^ Unclear if related to meningococcal vaccine or HBRV vaccine. AE: Adverse event. NR: Not reported. HBRV: human-bovine live-attenuated reassortant pentavalent rotavirus vaccine. MenCC: MenC tetanus toxoid conjugate vaccine.
The study revealed comparable reactogenicity profiles in infants who did or did not receive RV vaccine. A systemic AE was reported for 23.1% of children, including 17.4% severe (grade 3) systemic AEs. Fever and vomiting were reported in 58.9% and 35.5% of children during the first 7 days after vaccination. There were no SAEs that were considered related to the study vaccines in either studies.

Although HBRV is recommended as a 3-dose primary vaccination series in infants from 6 weeks to 32 weeks of age, an additional HBRV dose co-administered with MenAV, measles, and yellow fever vaccines in 9–11-month-old infants was evaluated in Mali. Gastrointestinal illness was reported in 13.0% of the participants, including vomiting, diarrhea, or gastroenteritis, within 28 days after vaccination. No vaccination-related SAE and no cases of intussusception were reported.

A review of the 4CMenB clinical development program reported results from a pooled sub-group analysis of two pivotal trials (5,515 participants) in which 303 infants had received at least one dose of RV vaccine (HRV or HBRV according to local recommendations) concomitantly with 4CMenB and other recommended vaccines. The study revealed comparable reactogenicity profiles in infants who did or did not receive RV vaccine. A systemic AE was reported for 80.5% of infants in the co-administration group and 75.3% of infants not receiving RV vaccines. Severe systemic reactions were recorded for 19.5% and 12.7%, respectively. Of them, fever was reported in 4.9%, 6.2%, and 3.6%, vomiting in 12.7%, 8.1%, and 6.5%, and changing in eating habits in 36.6%, 22.9%, and 17.7% of participants.

The second Spanish open-label study assessed the co-administration of HBRV (2, 4, 6 months of age), MenCC (2 months of age) and PCV13 (2, 4, 6 months of age) with DTaP-IPV-HB-PRP-T (Hexaxim) and DTaP-IPV//PRP-T (Pentaxim) (2, 4, 6 months of age). Any solicited systemic AE was reported in 97.4% of children, including 17.4% severe (grade 3) systemic AEs. Fever and vomiting were reported in 58.9% and 35.5% of children during the first 7 days after vaccination.

It was observed that in the first 7 days after vaccination, fever was reported in 4.9%, 6.2%, and 3.6%, vomiting in 12.7%, 8.1%, and 6.5%, and changing in eating habits in 36.6%, 22.9%, and 17.7% of participants.

**Immunogenicity**

Immunogenicity results were identified in five studies. Geometric mean concentrations and titers are summarized in Table 5, seroconversion and seroresponse rates are presented in Table 6. Seroconversion rate was defined as the percentage of participants who were reported in 73.5%, 59.0%, and 42.7% of children, respectively.

### Table 4. SAE and a selection of solicited systemic adverse events (AEs) during concomitant administration of rotavirus vaccine and meningococcal vaccines plus other routine vaccines or individual administration of rotavirus vaccine plus other routine vaccines in 5 studies.

| Reference | N | Primary schedule* | Primary RV+ MV+ | RV+ MV+ routine | RV+ MV+ | Routine RV+ | Routine MV+ | Routine routine |
|-----------|---|------------------|----------------|-----------------|--------|-------------|-------------|----------------|
| Block 2016 | 27 | 2, 4, 6** | 4.6 | 5.8 | 6.3 | 8 | 17.2 |
| Klein 2012 | 22 | 2, 4, 6** | 2.4 | 2.4 | 2.4 | 8.5 | 23.4 |
| Klein 2017 | 28 | 2, 4, 6** | 2.4 | 2.4 | 2.4 | 8.5 | 23.4 |
| Tregnaghi | 26 | 2, 4, 6** | 2.4 | 2.4 | 2.4 | 8.5 | 23.4 |
| Vesikari 2017 | 30 | 2, 4, 6** | 2.4 | 2.4 | 2.4 | 8.5 | 23.4 |

*Temporary tables 1 and 2 for definition of vaccines abbreviations.
immunosorbent assay) who had antibody titer below this threshold pre-vaccination. Seroresponse rates were defined as at least threefold increase in IgA response from pre- to post-vaccination. Two studies did not present data for a comparator group with individual RV vaccination.\textsuperscript{21,24}

In a phase 3b, placebo-controlled study conducted across six European countries (the Czech Republic, Finland, France, Germany, Italy, and Spain), HRV or placebo were co-administered with routine vaccines recommended in the respective countries. Immunogenicity results were available from 794 infants in the HRV group and 422 infants in the placebo group. Spain was the only country administering a meningococcal vaccine (MenC-CRM, Meningitec administration group and 80.1% in those receiving HRV with meningococcal vaccine schedule in bold. ^GMC: Geometric mean concentration. *2-dose HRV vaccination, at 2 and 4 months. \textdagger Meningococcal vaccine and rotavirus vaccine provided sequentially. GMT: Geometric mean titer. N: number of participants included in the analysis. M: Month. NA: Not applicable. IgA: immunoglobulin A. SNA: serotype-specific rotavirus neutralizing antibody.

Efficacy

No studies reporting efficacy results of RV vaccination and meningococcal vaccination were identified by this systematic review.

Discussion

This systematic review aimed to retrieve and summarize the currently available evidence on the safety profile, immunogenicity, and efficacy of RV vaccines when co-administered with available meningococcal vaccines in infants. The limited number of studies presenting a comparative evaluation of RV vaccines when administered with or without meningococcal vaccines, as well as the heterogeneity in study designs and local immunization programs led to a descriptive analysis of the data without applying meta-analysis methods. Other routine injectable vaccines were also administered in all studies, thus no direct comparison between RV vaccine alone and RV and meningococcal vaccines together could be made. However, the concomitant administration of other routine vaccines is representative of the current vaccination practice. The quality of studies included was generally acceptable. In most of the studies, investigators were not blinded for the study allocation groups, which could be a limitation in the perspective of the assessment of AEs. Our search identified only one study with immunogenicity data in low- and middle-income countries. This is considered another limitation since the disease burden of both RV and meningitis is high in this setting.\textsuperscript{33}

Safety analysis was mainly focused on AEs that might be associated with RV vaccination, such as fever, diarrhea, vomiting, change in eating habits, and intussusception, and found no new safety concerns upon co-administration with meningococcal vaccines. In the only study comparing directly the co-administration of HRV and MenCC vaccines with their sequential administration, the incidence of gastrointestinal symptoms tended to be lower in the sequential group than in the co-administration group.\textsuperscript{29} Although the difference was not considered clinically significant, the authors point out that the convenience of co-administration of HBRV and MenCC may outweigh the

Table 5. Rotavirus immunogenicity measured as geometric mean titer or geometric mean concentration (n = 4 studies).

| Reference                  | N   | Rotavirus vaccine | Meningococcal vaccine | Schedule*                                    | Measured at day; post-dose | Parameter                  | GMT or GMC (95%CI) |
|----------------------------|-----|-------------------|-----------------------|----------------------------------------------|----------------------------|---------------------------|-------------------|
| Klein 2019\textsuperscript{22} | 316 | HRV               | Hib-MenCY-TT          | 2, 4, 6\textsuperscript{6}                  | 2 M; 2                     | IgA antibody titer       | 138.9 (104.0–185.5)^ | 115.0 (87.5–151.0)^ |
| Vesisari 2011\textsuperscript{29} | 202 | HBRV              | MenCC                 | 2, 4, 6                                      | 42; 3                      | IgA antibody titer       | 290.6 (215.1–392.5)^ | 363.1 (290.3–454.2)^ |
| Haidara 2018\textsuperscript{21} | 292 | HBRV              | MenAV                 | Booster dose at 9 to 11                      | 28                         | SNA response to G1       | 187.2 (148.8–235.5)^ | 211.4 (168.6–264.9)^ |
| Martinon-Torres 2019\textsuperscript{24} | 263 | HBRV              | MenCC                 | 2, 4, 6                                      | 1 M; 3                     | IgG antibody titer       | 118.4 (90.9–154.3)^  | NA                |

All studies provided routine vaccines concomitantly to combined rotavirus vaccine and meningococcal vaccine or rotavirus vaccine individually. *At age in months, meningococcal vaccine schedule in bold. ^GMC: Geometric mean concentration. *2-dose HRV vaccination, at 2 and 4 months. Meningococcal vaccine and rotavirus vaccine provided sequentially. GMT: Geometric mean titer. N: number of participants included in the analysis. M: Month. NA: Not applicable. IgA: immunoglobulin A. SNA: serotype-specific rotavirus neutralizing antibody.
Table 6. Seroconversion and seroresponse rates following rotavirus and meningococcal vaccination (n = 5 studies).

| Reference        | N  | Rotavirus vaccine | Meningococcal vaccine | Schedule* | Measured at day; post-dose | Parameter | Levels                      | Co-administration | Sequential*/individual RV administration |
|------------------|----|-------------------|-----------------------|-----------|----------------------------|-----------|-----------------------------|-------------------|--------------------------------------|
| Klein 2019       | 316| HRV               | Hib-MenCY-TT          | 2, 4, 6*  | IgA ≥20 U/ml (overall)     | 2 M; 2    | 81.3 (74.2–87.1)            | 85.5 (79.6–90.2) | 80.1 (73.1–86.0) | 94.6 (90.0–97.5) |
| Vesikari 2010    | 1,216| HRV               | Men-CRM               | 2, 4      | IgA ≥20 U/ml (and <20 U/ml at baseline) | 1-2 M; 2 | 80.1 (73.1–86.0)            | 92.3 (64.0–99.8) | 82.1 (73.1–87.7) | 84.3 (74.7–91.4) |
| Vesikari 2011    | 202| HBRV              | MenCC                 | 2, 4, 6   | IgA ≥3 fold increase $^5$ | 42; 3     | 96.9 (91.3–99.4)            | 98.1 (93.2–99.8) | 96.6 (95.5–97.7) |                  |
|                  | 202| HBRV              | MenCC                 | 2, 4, 6   | G1** ≥3 fold increase $^5$ | 42; 3     | 57.1 (46.7–67.1)            | 63.5 (53.4–72.7) |                  |                  |
|                  |    |                   |                       |           | G2** ≥3 fold increase $^5$ |           | 33.7 (24.4–43.9)            | 38.5 (29.1–48.5) |                  |                  |
|                  |    |                   |                       |           | G3** ≥3 fold increase $^5$ |           | 33.7 (24.4–43.9)            | 37.5 (28.2–47.5) |                  |                  |
|                  |    |                   |                       |           | G4** ≥3 fold increase $^5$ |           | 44.9 (34.8–55.3)            | 46.2 (36.3–56.2) |                  |                  |
|                  |    |                   |                       |           | P1A[8]** ≥3 fold increase $^5$ |           | 32.7 (23.5–42.9)            | 40.4 (30.9–50.5) |                  |                  |
| Haidara 2018     | 292| HBRV              | MenAV                 | Booster dose at 9 to 11 | IgA ≥20 U/ml (and <20 U/ml at baseline) | 28 | 56.9 (49.2–64.5) | NA |                  |
|                  |    |                   |                       |           | ≥3 fold increase $^5$ |           | 74.7 (69.7–79.6) | NA |                  |
|                  |    |                   |                       |           | ≥3 fold increase $^5$ |           | 44.9 (39.2–50.6) | NA |                  |
|                  |    |                   |                       |           | ≥3 fold increase $^5$ |           | 83.5 (75.9–91.1) | NA |                  |
| Martinon-Torres  | 263| HBRV              | MenCC                 | 2, 4, 6   | IgA ≥20 U/ml (and <20 U/ml at baseline) | 1 M; 3   | 93.9 (91.1–96.6) | NA |                  |
| 2019             |    |                   |                       |           | ≥3 fold increase $^5$ |           | 57.3 (51.7–63.0) | NA |                  |
|                  |    |                   |                       |           | ≥3 fold increase $^5$ |           | 88.4 (82.1–93.1) | NA |                  |
|                  |    |                   |                       |           | ≥3 fold increase $^5$ |           | 90.8 (85.6–94.5) | NA |                  |

NB. All studies provided routine vaccines concomitantly to combined rotavirus vaccine and meningococcal vaccine or rotavirus vaccine individually. Seroconversion rate was defined as percentage of infants with anti-RV immunoglobulin A and G (IgA and IgG) ≥20 U/mL (measured by enzyme-linked immunosorbent assay) post-vaccination who had antibody titer below the threshold pre-vaccination. Seroresponse rates were defined as at least threefold increase in IgA response from pre- to post-vaccination. *At age in months, meningococcal vaccine schedule in bold. ** SNA response to rotavirus genotype. $^3$-dose HRV vaccination, at 2 and 4 months. $^6$ meningococcal vaccine and rotavirus vaccine provided sequentially. $^5$ ≥3 fold increase from pre- (baseline) to postvaccination. $^\wedge$ Co-administration results are for Spain. Results of control group are the results for the countries: Finland, Italy, Germany, France, and Czech Republic, respectively, where no meningococcal vaccine was administered. N: number of participants included in the analysis. M: Month; NA: Not applicable; SNA: serotype-specific rotavirus neutralizing antibody.
slight increase in risk of mild diarrhea and mild vomiting associated with co-administration. In studies comparing routine co-administration of RV and meningococcal vaccines with vaccination schedules without meningococcal vaccines, similar rates of solicited systemic AEs were found. Studies reporting safety data for co-administration of RV and 4CMenB vaccines were mainly focused on 4CMenB-related safety aspects, but reactogenicity of 4CMenB was not impacted by the concomitant administration of RV vaccines, supporting their concomitant use in routine practice. Following the introduction of 4CMenB to the NIP in the UK in 2015, no significant safety concerns were observed.

There is a theoretical concern that the co-administration of multiple antigens may lead to immune interference. The reviewed literature revealed that anti-RV IgA response rates were comparable between groups of children receiving RV and meningococcal vaccines versus those receiving RV vaccines alone or subsequently, regardless of the administration of other routine vaccines. Moreover, serotype-specific rotavirus neutralizing antibody response rates were similar for children receiving HBRV and MenCC either concomitantly or separately. This suggests the absence of immune interference, but might also be explained by the differences in the route of administration (oral for RV vaccines versus intramuscular for meningococcal vaccines) along with vaccine type and composition.

Only one study reported immunogenicity data for 4CMenB when co-administered with RV. Immune responses of 4CMenB did not appear to interfere with the immunogenicity of any of the vaccines tested, including RV. Oral poliovirus vaccine (OPV), the only oral vaccine commonly co-administered with RV vaccine, may slightly reduce the immune response to RV vaccine, but clinical protection against severe RVGE is maintained. Since OPV was not administered in any of the studies included in this review, we could not evaluate the co-administration of RV vaccines, meningococcal vaccines, and OPV.

Worldwide, several national and international agencies recommend the co-administration of RV vaccines with other infant vaccines against diphtheria, tetanus, pertussis, Hib, poliovirus, Hepatitis B, Pneumococcal, and Meningococcal disease. Co-administration of vaccines could contribute to better vaccine coverage and could reduce medical visits and associated costs. It also helps to provide protection for children during the vulnerable early months of their lives.

A summary contextualizing the results and their potential clinical relevance is provided in Figure 2 to assist communications to the parents.
Conclusions
Despite the limited data, co-administration of RV and meningococcal vaccines does not appear to interfere with the safety or immunogenicity of the two globally available RV vaccines.

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PP, BB and LM are employees of the GSK groups of companies. PP and BB hold shares in the GSK group of companies.

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Author contributions
All authors had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. All authors reviewed and commented critically drafts of the manuscript for important intellectual content and gave final approval to submit for publication. The corresponding author had final responsibility to submit for publication. Drafts were developed by a professional publication writer according to the recommendations and documentation. All authors were involved in the study conception and data interpretation. PP managed the collection and generation of the study data and performed the study and PP and BB provided materials.

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