A phase III randomized, open-label, non-inferiority clinical trial comparing liquid and lyophilized formulations of oral live attenuated human rotavirus vaccine (HRV) in Indian infants

Catherine Cohet, Brigitte Cheuvart, Leentje Moerman, Dan Bi, Adrian Caplanusi, Mallesh Kariyappa, Sanjay Lalwani, Monjori Mitra, Amita Sapru, Shruti Saha, P.V. Varughese, Rajeev Zachariah Kompithra, and Sanjay Gandhi

ABSTRACT
The human rotavirus vaccine (HRV; Rotarix, GSK) is available as liquid (Liq) and lyophilized (Lyo) formulations, but only Lyo HRV is licensed in India. In this phase III, randomized, open-label trial (NCT02141204), healthy Indian infants aged 6–10 weeks received 2 doses (1 month apart) of either Liq HRV or Lyo HRV. Non-inferiority of Liq HRV compared to Lyo HRV was assessed in terms of geometric mean concentrations (GMCs) of anti-RV immunoglobulin A (IgA), 1-month post-second dose (primary objective). Reactogenicity/safety were also evaluated. Seroconversion was defined as anti-RV IgA antibody concentration ≥20 units (U)/ml in initially seronegative infants (anti-RV IgA antibody concentration <20 U/mL) or ≥2-fold increase compared with pre-vaccination concentration in initially seropositive infants. Of the 451 enrolled infants, 381 (189 in Liq HRV and 192 in Lyo HRV group) were included in the per-protocol set. The GMC ratio (Liq HRV/Lyo HRV) was 0.93 (95% confidence interval [CI]: 0.65–1.34), with the lower limit of the 95% CI reaching ≥0.5, the pre-specified statistical margin for non-inferiority. In the Liq HRV and Lyo HRV groups, 42.9% and 44.3% (baseline) and 71.4% and 73.4% (1-month post-second dose) of infants had anti-RV IgA antibody concentration ≥20 U/mL, and overall seroconversion rates were 54.5% and 50.0%. Incidences of solicited and unsolicited adverse events were similar between groups and no vaccine-related serious adverse events were reported. Lyo HRV was non-inferior to Lyo HRV in terms of antibody GMCs and showed similar reactogenicity/safety profiles, supporting the use of Liq HRV in Indian infants.

PLAIN LANGUAGE SUMMARY
What is the context?
- Rotavirus is the most common cause of acute gastroenteritis and contributes to the high number of hospitalizations and deaths in young children worldwide.
- Vaccination against rotavirus has led to a significant decrease in rotavirus-related infections.
- The human rotavirus vaccine Rotarix (GSK) is currently used as a liquid or lyophilized formulation.
- In clinical trials conducted in European and North American infants, the liquid vaccine showed ability to induce immune response and safety comparable to the lyophilized formulation.
- Only the lyophilized vaccine is currently marketed in India.

What is new?
- We compared the 2-dose liquid and lyophilized human rotavirus vaccines in Indian infants in a phase III clinical trial.
- The ability to induce immune response for the liquid formulation was not inferior to that observed for the lyophilized vaccine.
- The safety profiles of the 2 formulations were comparable.

Why is this important?
- This study shows that the liquid human rotavirus vaccine can be administrated to infants from India.
Introduction

Rotavirus (RV) is a prominent cause of acute gastroenteritis, which accounts for substantial morbidity worldwide and persistently high mortality rates in low-income settings. Despite the significant reduction in the burden of RV disease following worldwide implementation of mass vaccination and further prevention measures, RV continues to disproportionately affect children <5 years of age. In 2016, RV-gastroenteritis resulted in an estimated number of 128,515 deaths worldwide in this age group. In India, RV morbidity and mortality remain considerable, with around 8% of global RV deaths occurring in this country in 2016. The Indian Rotavirus Surveillance Network reported that between 2012 and 2014, 35.7–43.0% of children hospitalized with acute gastroenteritis across different regions were RV positive. More recent etiological studies identified RV as the cause of up to 42.5% of diarrheal disease cases in India and highlighted a great genotypic variety of circulating strains from one region to another and over time.

In 2016, India became the first country in the World Health Organization (WHO)'s South Asian region to introduce RV vaccination as part of the national immunization program. The program was first launched in 9 states, and reached nationwide implementation in 2019. Two domestically produced vaccines, the live-attenuated human (nHRV; Rotavac liquid, Bharat Biotech International Limited India) and the human-bovine reassortant (BRV-PV; Rotasiil lyophilized, Serum Institute of India) vaccines are used in the country's Universal expanded Immunization Programme (UIP). The oral live-attenuated human rotavirus vaccine (HRV, Rotarix lyophilized, GSK) and the live-attenuated human-bovine reassortant vaccine (HBRV; RotaTeq liquid, Merck, United States), the 2 vaccines recommended by the WHO for global use against RV, are also marketed in India.

HRV is a two-dose vaccine, starting as early as 6 weeks of age and has shown an acceptable safety profile and broad protective efficacy against different RV genotypes, sustained up to the third year of life. The liquid HRV formulation (Liq HRV) is now the most widely licensed, including in the European Union countries, Canada and Japan. In India, only the lyophilized formulation of the vaccine (Lyo HRV) is licensed, since 2008. Liq HRV was shown to have similar immunogenicity and safety profiles to Lyo HRV and has the advantage of facilitating storage, handling and administration. The aim of this study was to assess the immunogenicity, reactogenicity and safety of Liq HRV in Indian infants as compared to the licensed Lyo HRV (Figure 1).

Methods

Study design and participants

This phase III randomized, open-label, non-inferiority clinical trial was conducted in 8 centers across India from February to December 2019. Healthy infants 6–10 weeks of age at the time of the first vaccination were eligible for enrollment if they had a birth weight >2000 g, and if their parents/legal acceptable representatives were willing and able to comply with protocol requirements, and signed an informed consent form prior to enrollment in the study. Exclusion criteria included planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first dose and ending 30 days after the second dose, with the exception of licensed routine childhood vaccinations as part of local immunization practices and inactivated influenza vaccine, history of confirmed RV-gastroenteritis, history of intussusception, and previous vaccination against RV. A complete list of inclusion and exclusion criteria is available at http://www.gsk-studyregister.com/study/116566.

Infants were randomized (1:1) into 2 groups to receive 2 doses of either Liq HRV or Lyo HRV, administered 1 month apart (Figure 2). Randomization was performed with a web-
based randomization system, using a minimization procedure accounting for center and the study as factors with equal weight. The study was open label, but laboratory staff responsible for testing were blinded to the intervention.

The vaccines were administered orally. An additional dose was allowed in case of regurgitation after vaccination. The vaccines’ compositions have been previously described.\textsuperscript{12}

The study was conducted in compliance with the Declaration of Helsinki, the principles of Good Clinical Practice and all applicable regulatory requirements. The study protocol and subsequent amendments were reviewed and approved by the National Regulatory Authority and Institutional Review Boards/Institutional Ethics Committees at each site. The study is registered at www.clinicaltrials.gov (NCT02141204) and www.ctri.nic.in (CTRI/2014/06/004654).

**Study objectives**

The primary objective was to demonstrate the non-inferiority of Liq HRV compared to Lyo HRV, in terms of geometric mean concentrations (GMCs) of anti-RV immunoglobulin A (IgA), measured 1-month post-second dose. Non-inferiority was demonstrated if the lower limit (LL) of the 2-sided 95% confidence interval (CI) for the ratio of anti-RV IgA antibody GMCs (Liq HRV over Lyo HRV) was ≥0.5.

Secondary objectives included the assessment of immunogenicity at 1-month post-second dose in terms of seroconversion rates, and evaluation of reactogenicity and safety.

**Immunogenicity assessment**

Blood samples (approximately 2 mL) were collected prior to the administration of the first dose and 1-month post-second HRV dose for the determination of anti-RV IgA antibody concentration. Antibody GMCs were calculated pre-vaccination and 1-month post-second HRV dose. Seroconversion rates were calculated post-second dose.

Laboratory testing of the pre-vaccination blood samples from the first 141 infants enrolled in the study indicated that 47.5% of them were seropositive (having anti-RV IgA antibody concentration ≥20 units [U]/mL) prior to vaccination, suggesting an overall high seropositivity rate in the population targeted for enrollment. Therefore, the definition for seroconversion was changed after the study start to allow inclusion of initially seropositive infants in the pre-protocol set (PPS). Seroconversion was defined as an anti-RV IgA antibody concentration ≥20 U/mL in initially seronegative infants (anti-RV IgA antibody concentration <20 U/mL) or a ≥2-fold increase compared with pre-vaccination values in initially seropositive infants. This definition has been previously used in another HRV clinical trial in Indian infants.\textsuperscript{13} A post-vaccination anti-RV IgA antibody concentration ≥20 U/mL has been previously established as an appropriate correlate of efficacy in HRV clinical trials.\textsuperscript{14,15}

Sera were tested at GSK Clinical Laboratories Sciences (Belgium) by a modified enzyme-linked immunosorbent assay used in the clinical development of HRV, as previously described.\textsuperscript{16,17}

**Safety and reactogenicity assessment**

Adverse events (AEs) were recorded by parents on diary cards. Solicited (cough/runny nose, diarrhea, fever, irritability/fussiness, loss of appetite, and vomiting) and unsolicited AEs were recorded for 8 days (day 1–day 8) and 31 days (day 1–day 31), respectively, following each HRV dose. All AEs were graded on a scale of 1 (mild) to 3 (severe).

Serious AEs (SAEs), as well as AEs/SAEs leading to withdrawal from the study, were assessed throughout the study (starting from dose 1 up to 1-month post-second dose). The causality between each AE/SAE and the study vaccines was assessed by the investigators.

**Statistical analyses**

A total number of 450 infants (225 in each study group) was planned for enrollment in order to achieve a target size of at least 292 evaluable infants, assuming that 35% of infants would be non-evaluable/withdrawn (based on a study with Lyo HRV in India).\textsuperscript{18} Assuming identical GMCs in the 2 groups and a 0.79 standard deviation for the log\textsubscript{10}-transformed concentration, the power to reach the primary objective was 90%.
Table 1. Characteristics of infants (per-protocol set).

|                  | Liq HRV | Lyo HRV |
|------------------|---------|---------|
| N                | 189     | 192     |
| Mean age at first HRV dose (SD); weeks 6.8 (1.1) | 6.8 (1.1) |
| Mean age at second HRV dose (SD); weeks 11.6 (1.3) | 11.5 (1.2) |
| Male, n (%)      | 106 (56.1%) | 91 (47.4%) |
| Asian ancestry, n (%) | 189 (100%) | 192 (100%) |
| Mean height at first HRV dose (SD), cm 55.0 (2.6) | 54.8 (2.7) |
| Mean weight at first HRV dose (SD), cm 4.3 (0.7) | 4.3 (0.7) |

Liq HRV, human rotavirus vaccine (liquid formulation); Lyo HRV, human rotavirus vaccine (lyophilized formulation); N, number of infants in each group; SD, standard deviation, n (%), number (percentage) of infants in each category.

Primary immunogenicity analyses were conducted on the PPS, comprising all eligible infants from the exposed set (ES) who received both doses as per protocol (e.g., compliance to vaccination schedule, no prohibited medication/vaccination administered), complied with the blood sample schedule, and had available immunogenicity data at both sampling timepoints. A supplementary analysis based on the ES was also performed.

Safety analyses were performed on the ES, including all infants that received at least one HRV dose.

GMC calculations were performed by taking the antilog of the mean of the log concentrations transformations; antibody concentrations below the technical cut-off of the assay (13 U/mL) were given a value of half the cut-off. CIs for GMCs were calculated assuming that log-transformed values were normally distributed with unknown variance, by exponential-transformation of the CI for the mean of log-transformed concentration.

The 95% CI for the between-groups anti-RV IgA antibody GMC ratio (primary objective) was estimated using an ANCOVA model on the log-transformed concentrations, including the group and the logarithm of pre-vaccination concentration as covariates. The GMC ratio and 95% 2-sided CI were derived by exponential transformation of the corresponding group contrast in the model. All other comparative analyses were descriptive/exploratory.

Seroconversion rates and the proportion of infants with (S) AEs were calculated with exact 95% CIs. The between-group difference in seroconversion rates was calculated with Miettinen and Manning 95% CIs. All analyses were performed with the SAS software.

Results

Demographics

A total of 449 infants (224 in the Liq HRV group and 225 in the Lyo HRV group) were included in the ES. Two hundred and nine and 210 infants in the Liq HRV and Lyo HRV group, respectively, completed the study. Reasons for not completing are shown in Figure 2. The PPS included 189 infants in the Liq HRV group and 192 in the Lyo HRV group (Figure 2).

The mean age at first dose was 6.8 ± 1.1 weeks in both groups in the PPS and all infants were Asian. The proportion of male infants was slightly higher in the Liq HRV compared to the Lyo HRV group (Table 1). Demographic characteristics in the ES (Supplemental Material, Table S1) were similar to those in the PPS.

In total, 85.1% and 82.4% of infants also received routine vaccines at dose 1 and dose 2 of HRV, respectively.

Immunogenicity

At 1-month post-second dose of HRV, the between-group GMC ratio (Liq HRV/Lyo HRV) was 0.93 (95% CI: 0.65–1.34). As the LL of the 95% CI was above the pre-specified statistical margin, non-inferiority of the immunogenicity of Liq HRV compared with Lyo HRV was demonstrated. Similarly, in a supportive analysis conducted only in infants seronegative before vaccination, the LL of the 95% CI for the between-group GMC ratio was 0.52 (Table 2). Anti-RV IgA GMCs were 90.25 U/mL in the Liq HRV group and 94.16 U/mL in the Lyo HRV group (Figure 3A).

Table 2. Results of between-group comparison of immunogenicity at 1-month post-dose 2, overall and in infants seronegative at pre-vaccination (per-protocol set).

| Group                      | N   | GMC*, U/mL | GMC ratio (Liq HRV over Lyo HRV) |
|----------------------------|-----|------------|----------------------------------|
| Non-inferiority of Liq HRV compared to Lyo HRV in terms of GMCs (primary confirmatory objective) |     |            |                                   |
| Liq HRV                    | 189 | 88.8       | 0.93 (95% CI: 0.65–1.34)          |
| Lyo HRV                    | 192 | 95.6       |                                   |
| Between group ratio in infants seronegative at pre-vaccination (secondary, supportive data) |     |            |                                   |
| Liq HRV                    | 108 | 43.05      | 0.88 (95% CI: 0.52–1.49)          |
| Lyo HRV                    | 107 | 48.97      |                                   |

| Group                      | N   | SC, % | Difference in SC rates (Liq HRV minus Lyo HRV) |
|----------------------------|-----|-------|-----------------------------------------------|
| Between-group difference (exploratory analysis) |     |       |                                               |
| Liq HRV                    | 189 | 54.5% | 4.50 (95% CI: −5.53–14.44)                     |
| Lyo HRV                    | 192 | 50.0% |                                               |
| Between-group difference in infants seronegative at pre-vaccination (secondary, supportive data) |     |       |                                               |
| Liq HRV                    | 108 | 58.3% | 3.19 (95% CI: −10.02–16.30)                    |
| Lyo HRV                    | 107 | 55.1% |                                               |

Liq HRV, human rotavirus vaccine (liquid formulation); Lyo HRV, human rotavirus vaccine (lyophilized formulation); N, number of infants in each group; GMC, geometric mean concentration; U, units; CI, confidence interval; SC, seroconversion.

The bolded value indicates that the statistical criteria to demonstrate the confirmative primary objective was met.

* The GMC was estimated from the ANCOVA model for the confirmatory primary objective and the ANOVA model for the secondary, supportive analysis.
For both groups, immunogenicity results were similar between the ES and the PPS (Table S2).

**Safety and reactogenicity**

The most frequently reported solicited AE was irritability/fussiness, which occurred in 38.4% of infants in the Liq HRV group and 45.3% of infants in the Lyo HRV group. Irritability/fussiness was the most common grade 3 solicited AE, reported in 3.1% and 5.3% of infants in the Liq HRV and Lyo HRV groups, respectively. It was also the most commonly reported related solicited AE, in 16.1% of infants in the Liq HRV group and 19.1% of infants in the Lyo HRV group. The most frequent grade 3 related solicited AEs were irritability/fussiness in the Liq HRV group and vomiting in the Lyo HRV group, reported in 1.8% and 2.2% of infants, respectively. Medically-attended solicited general AE were reported in ≤2.7% of infants in both groups, with cough/runny nose being the most common. Figure 4 presents the incidence of solicited general AEs (any and grade 3) following vaccination, after each dose and overall.

Unsolicited AEs were reported in 24.1% and 25.8% of infants receiving Liq HRV and Lyo HRV, respectively, and grade 3 AEs were infrequent (Table S3). The most commonly reported unsolicited AEs were injection site swelling in 5.8% and 5.3% of infants, injection site pain in 4.5% and 3.1% of infants, and pyrexia in 4.5% and 5.8% of infants in the Liq HRV and Lyo HRV groups, respectively.

In the Liq HRV group, 9 SAEs (intestinal obstruction, pneumonia, urinary tract infection and respiratory distress each in 1 infant, gastroenteritis in 2 infants, and bronchiolitis in 3 infants) were reported in 7 (3.1%) infants. The intestinal obstruction was mild in intensity, with the onset at 20 days post-dose 2 and a duration of 4 days. In the Lyo HRV group, 3 SAEs (thrombocytopenia, hemorrhagic diarrhea, and dengue fever) were reported in 2 infants (0.9% of infants). All SAEs were recovered/resolved by the end of the study and none were considered related to vaccination by the investigator (Table S3).

**Discussion**

This is the first study comparing Liq HRV and Lyo HRV in India. The liquid formulation of HRV was developed in response to recommendations from several organizations (WHO, United Nations Children’s Fund [UNICEF]),

encouraging its use due to simplicity of administration, reduction in shipment and storage costs, and increased manufacturing capacity compared with a lyophilized formulation.

In this study, non-inferiority of immune responses elicited by Liq HRV compared to Lyo HRV was demonstrated in Indian infants, in terms of anti-RV IgA antibody GMCs, at 1 month after completion of the 2-dose schedule. The results are in line with previous reports showing similar immunogenicity and safety profiles for the 2 formulations.

In a previous study in 1274 infants aged 6–12 weeks conducted in Panama, in which HRV was co-administered with routine pediatric vaccines, seroconversion rates and anti-RV IgA antibody GMCs were similar between infants receiving the Liq
and Lyo HRV formulations. In another trial, Liq HRV was co-administered with routine vaccines following the WHO’s Expanded Programme on Immunization (EPI) schedule to 750 infants in Vietnam and the Philippines and showed adequate immune responses 1 month-post-vaccination; the results also indicated some flexibility in the vaccination schedule, with similar immunogenicity and safety observed when Liq HRV was administered 1 or 2 months apart. Moreover, immune responses elicited by both Liq HRV and Lyo HRV in the present study were in the range of those reported for HRV in infants from low- and middle-income countries, including India.

Data in the current study were generated using a more inclusive definition for seroconversion compared to the one used in most clinical trials with HRV, in which seroconversion was defined as anti-RV IgA concentration ≥20 U/mL post-vaccination in infants with a concentration <20 U/mL pre-vaccination. In both groups in the current study, the observed seroconversion rates obtained with the more inclusive definition were ≥50.0% versus ≥55.1% when assessed with the definition considering only infants seronegative at baseline. The latter value is in line with results obtained in a previous study with Lyo HRV administered according to the same schedule in 363 Indian infants (58.3%), using the earlier definition which excluded initially seropositive infants. Anti-RV IgA antibody GMCs are also comparable between the 2 trials when excluding initially seropositive infants (49.2 U/mL versus 43.05 and 48.97 U/mL in the current study, in infants receiving Liq HRV and Lyo HRV, respectively). In the current study, the additional criteria to define seroconversion were used to address high seropositivity levels at baseline, and therefore allowed the evaluation of Liq HRV in a population which seems to better reflect the pre-RV vaccination serostatus of infants in India. Indeed, more than 40% of infants in this study showed anti-RV IgA concentrations ≥20 U/mL before vaccination. In another clinical trial in South Indian infants, conducted between March and December 2012, more than half of the infants showed baseline anti-RV IgA concentrations ≥20 U/mL. The proportion of seropositive infants observed reinforces previous observations of high circulation of RV strains in India, and the mounting of response upon exposure to the pathogen in the first weeks of life.

Safety data generated in this study further support previous evidence that 2 doses of Lyo HRV are well tolerated in infants worldwide, including in India. In this study, no intussusception cases were reported following administration of HRV, but one infant who received Liq HRV experienced intestinal obstruction, which was resolved within 4 days from onset. No safety concern was observed for either Liq or Lyo HRV administration during the current study, in line with the favorable benefit/risk profile established for RV vaccines.

More than 80% of infants in this study received the HRV doses co-administered with other routine vaccines. Co-administration of Liq HRV with routine pediatric vaccines was previously shown not to impact immune responses or the safety profile of the vaccines in infants in Vietnam and the Philippines. These data support the use of Liq HRV within the EPI. Currently, nHRV and to a lesser extent BRV-PV are used in the Indian UIP, while HRV and HBHRV are available on the Indian private market, allowing access of Indian infants to additional RV vaccines. Of note, between 2012 and 2015, private sector vaccination accounted for 3.4% of RV immunizations in India, although this contribution has decreased following the increase in coverage under the UIP.

This study’s main strength was the more inclusive definition used for seroconversion, which allows to reflect more accurately the real-world use of the vaccine in a heterogeneous population in terms of exposure to circulating RV. The study also has some limitations. First, the use of different definitions for seroconversion across clinical trials and RV vaccines hinders comparisons with previously published results, including those with HRV. However, the additional criteria were needed to include the high proportion of baseline-seropositive infants and exploratory analyses were also conducted in seronegative infants only, confirming the overall study outcome. Second, the majority of the infants participating in the study were located in Western and Southern India, potentially hampering representativeness of the study population and interpretation of the results, given that the incidence of RV infection varies between regions. In addition, the difference between the ES and PPS was >15%, although analyses showed comparable immunogenicity results between the 2 sets.

Conclusion

Immune responses induced by Liq HRV were non-inferior to those elicited by Lyo HRV when administered according to a 2-dose schedule in infants from India. The 2 vaccine formulations had a similar reactogenicity and safety profile and no
safety concerns were identified. The results of this study support the use of Liq HRV in Indian infants.

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Authors contribution

All authors participated either in the design (CC, BC, LM, AC, DB, MK, SG), implementation (CC, AC, MK, SL, MM, AS, SS, PVV, RZK, SG) or analysis and interpretation of data (CC, BC, LM, DB, MK, SL, RZK, SG) of the study, as well as in the development of this manuscript. All authors had full access to the data and granted their final approval of the manuscript before submission.

Disclosure of potential conflicts of interest

CC and AC were employees of the GSK group of companies at the time of study conduct. BC, LM, DB and SG are employees of the GSK group of companies, and DB and SG hold shares in the GSK group of companies as part of employee remuneration. MK received grants from the Banglore Medical College and Research Institute during and outside the conduct of the study. MM received grants from the Institute of Child Health during the conduct of the study. AS receives professional fees from the KEM Hospital Research Centre, Pune for her role as investigator in studies funded by pharmaceutical companies including the GSK group of companies. SL, SS, PVV, and RZK have no competing interest to declare.

Data sharing statement

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Trademark statement

Rotarix is a trademark owned by or licensed to the GSK group of companies. RotaqTeq is a trademark of Merck Inc. Rotavec is a trademark of Bharat Biotech International Limited India. Rotasil is a trademark owned by Serum Institute of India Pvt. Ltd.

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ORCID

Catherine Cohet http://orcid.org/0000-0002-0022-7251
Brigitte Cheuvart http://orcid.org/0000-0001-7156-0062
Dan Bi http://orcid.org/0000-0003-0426-4639
Rajeev Zachariah Kompithra http://orcid.org/0000-0002-7678-8426

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