Human rotavirus vaccine (RIX4414) efficacy in the first two years of life
A randomized, placebo-controlled trial in China

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Abbreviations: ATP, according-to-protocol; CCID50, median cell culture infectious dose; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; EPI, expanded program on immunization; GE, gastroenteritis; LLR, Lanzhou lamb rotavirus; RV, rotavirus; SAE, serious adverse event; SAS, statistical analysis system; SD, standard deviation; VE, vaccine efficacy

Introduction

Rotaviruses (RV) are a major cause of severe gastroenteritis (GE) in children aged <5 y. For the first time in China, we assessed the efficacy of two oral doses of the human rotavirus vaccine (RIX4414) in infants during the first two years of life (113808/NCT01171963). Healthy infants aged 6–16 weeks were randomized (1:1) to receive two oral doses of either the RIX4414 vaccine/placebo according to a 0, 1 month schedule. Vaccine efficacy (VE) against severe RVGE was assessed from two weeks post-Dose 2 up until the end of the second RV season and calculated with its 95% confidence intervals (CI). The primary efficacy objective was met if the lower limit of the 95% CI on VE was ≥10%. Unsolicited symptoms reported during the 31-d post-vaccination follow-up period and serious adverse events (SAEs) reported throughout the study were assessed. Of 3333 enrolled infants, 3148 were included in the according-to-protocol efficacy cohort. Over two consecutive RV seasons, fewer severe RVGE episodes were reported in the RIX4414 group (n = 21) vs. the placebo group (n = 75). VE against severe RVGE was 72% (95% CI: 54.1–83.6); the lower limit of the 95% CI on VE was >10%. The number of unsolicited symptoms and SAEs reported was similar between both groups. Thirteen deaths (RIX4414 = 6; placebo = 7) occurred during the study. All SAEs and deaths in the RIX4414 group were considered unrelated to vaccination. Two oral doses of RIX4414 vaccine provided a substantial level of protection against severe RVGE in Chinese children during the first two years of life.
countries: a monovalent human rotavirus vaccine (RIX4414; Rotarix®, GlaxoSmithKline Vaccines) and a pentavalent human-bovine rotavirus vaccine (Rotatret®, Merck and Co.).11,12 Phase III studies conducted in Europe, Latin America, Africa, and Asia have demonstrated that the RIX4414 vaccine is efficacious in the first two years of life of infants and well-tolerated.13-17 Other available rotavirus vaccines include Rotavin-M1™ in Vietnam (Center for Research and Production of Vaccines and Biologicals [POLYVAC]),18,19 and the Lanzhou lamb RV vaccine in China (LLR; Lanzhou Institute of Biomedical Products).20 RV vaccination is currently not mandatory in China and is not included in the expanded program of immunization (EPI).21,22 The LLR vaccine was licensed in China in 2001 and while more than 26 million doses of the vaccine have been administered in the private market, the schedule of one dose between 6 and 12 mo of age followed by one dose every year until three years of age, is considered too complex for a national immunization program.7

The aim of this phase-3, multi-center study was to evaluate the efficacy, immunogenicity, reactogenicity, and safety of RIX4414 in Chinese infants during the first two years of life. This paper describes the efficacy and safety of RIX4414, and a subsequent paper will present the reactogenicity and immunogenicity results.

Results

Demography
A total of 3333 infants (RIX4414 = 1666; placebo = 1667) were enrolled between Aug 2010 and Dec 2010; and were followed until the end of the second RV season (May 2012). The according-to-protocol (ATP) cohort for efficacy over two consecutive RV seasons included 3148 infants (RIX4414 =

Figure 1. Participant flowchart.
1575; placebo = 1573). The ATP efficacy cohort for the second RV season included 2979 infants (RIX4414 = 1500; placebo = 1479). The reasons for exclusion from the analyses are shown in Figure 1. The demographic characteristics were similar between the two groups with respect to age, gender, and ethnic origin. The mean age of infants was 9.6 weeks (standard deviation [SD] = 2.62) at Dose 1 and 14.1 weeks (SD = 2.72) at Dose 2; 51.1% of infants were male and all were of Chinese origin.

Vaccine efficacy (VE)—ATP efficacy cohort

From two weeks post-Dose 2 up until the end of the second RV season, 1.3% (n = 21) of infants in the RIX4414 group and 4.8% (n = 75) of infants in the placebo group recorded severe RVGE caused by circulating wild-type RV (P < 0.001). The resulting VE against severe RVGE was 72% (95% confidence interval [CI]: 54.1–83.6) (Table 1); the primary objective was achieved since the lower limit of the 95% CI on VE was >10%. VE against severe RVGE caused by G1 and non-G1 RV types was 64% (95% CI: 20.4–85.2) and 77.8% (95% CI: 58.0–89.2), respectively. G1P[8] (RIX4414 = 8; placebo = 20) and G2P[4] (RIX4414 = 11; placebo = 40) were the most frequent G1 and non-G1 RV types isolated from infants with severe RVGE episodes, respectively (Table 1). Circulation of G3P[8] and G9P[8] was low in the study population; each RV type was detected in three RVGE episodes, all in infants from the placebo group.

From two weeks post-Dose 2 up until the end of the second RV season, significantly fewer RVGE episodes of any severity were recorded in the RIX4414 group (4.4%; n = 70) as compared with the placebo group (10.6%; n = 167), resulting in a VE of 58.1% (95% CI: 44.3–68.8) (P < 0.001) against RVGE of any severity. The most frequent G1 and non-G1 RV types isolated from RVGE episodes of any severity were G1P[8] (RIX4414 = 20; placebo = 38) and G2P[4] (RIX4414 = 42; placebo = 102), respectively (Table 1). G3P[8] was detected in 11 episodes from infants in the placebo group; G9P[8] was detected in one episode from an infant in the RIX4414 group and five episodes from infants who received placebo (Table 1).

The percentage of infants hospitalized for RVGE was lower in the RIX4414 group (0.3%; n = 4) than in the placebo group (1.3%; n = 21) (P < 0.001); VE against RVGE hospitalizations was 81% (95% CI: 43.6–95.3) from two weeks post-Dose 2 until the end of the second RV season (Table 1). VE results for severe RVGE, RVGE of any severity and RVGE hospitalizations observed in the first and second year of life are shown in Table 1. Similar incidences were observed for GE and severe GE due to any cause in the RIX4414 and placebo groups (Table 1). The percentage of infants hospitalized for GE due to any cause was 2.7% (n = 43) in the RIX4414 group and 4.6% (n = 73) in the placebo group.

VE—Total vaccinated cohort (TVC)

From Dose 1 up until the end of the second RV season, the percentage of infants recording severe RVGE caused by circulating wild-type RV was lower in the RIX4414 group (1.5% [95% CI: 1.0–2.2]) than in the placebo group (4.6% [95% CI: 3.6–5.7]) (P < 0.001), resulting in a VE of 67.1% (95% CI: 47.7–79.9).

Seasonality

The highest number of RVGE episodes was observed in January 2012 followed by December 2011 in the RIX4414 and placebo groups.

Safety

During the 31-d post-vaccination follow-up period, at least one unsolicited adverse event was recorded in 310 infants in the RIX4414 group (18.6%) and 368 infants in the placebo group (22.1%). Upper respiratory tract infection was the most common unsolicited adverse event recorded in both groups (RIX4414 = 119; placebo = 124) followed by nasopharyngitis (RIX4414 = 103; placebo = 123). From Dose 1 until the end of the second RV season, at least one serious adverse event (SAE) was recorded in 183 infants (11.0%) in the RIX4414 group and 246 infants (14.8%) in the placebo group. The most frequently reported SAE was bronchitis in the RIX4414 (n = 80) and placebo groups (n = 103). Two cases of intussusception were reported (RIX4414 = 1; placebo = 1), 142 and 65 d after the second dose, respectively. Both cases resolved and were considered as not being related to vaccination by the investigators. All SAEs in the RIX4414 group were considered unrelated to vaccination. Diarrhea, reported as an SAE, in one infant in the placebo group was considered related to vaccination by the investigator.

There were 13 deaths (RIX4414 = 6; placebo = 7) during the study. The causes of death in each group are listed in Table 2. All deaths were considered unrelated to vaccination by the investigators. Eighteen infants withdrew from the study due to unsolicited symptoms and SAEs (RIX4414 = 8; placebo = 10).

Discussion

The disease burden of RV in China is highest in children younger than two years with approximately 42% of RV infections occurring between 7 and 12 mo of age. This was the first clinical trial in China to evaluate the efficacy of the RIX4414 vaccine during the first two years of life. Children in this study were enrolled from rural areas in the Guangxi Province located in southern China where several levels of medical facilities are available including village physicians, township hospitals, and county and city hospitals. Part of the study population resided in remote and/or mountainous areas. While basic medical treatment is offered at the village level; treatment for severe disease may be accessed at the township level and higher.

Our study confirmed that two doses of the RIX4414 vaccine provided a substantial level of protection against severe RVGE (VE = 72% [95% CI: 54.1–83.6]) over two consecutive RV seasons. This result was comparable to the VE observed in similarly-designed two year efficacy studies conducted in Latin America (80.5% [95% CI: 71.3–87.1]) lower than that observed in Europe (90.4% [95% CI: 85.1–94.1]) and high-income Asian countries: Hong Kong, Singapore, and Taiwan (96.1% [95% CI: 85.1–99.5]), and Malawi (38.1% [95% CI: 9.8–57.3]). While the VE in Japan (91.6% [95% CI: 62.4–99.1]) appears to be higher than the VE in China; it must be highlighted that the 95% CIs overlapped. Furthermore, the VE observed in the first year of
life in this study was well conserved into the second year of life ($P < 0.001$) indicative of the persistence of protective efficacy through the second year of life. Additionally, as previously reported, we noted a significant level of protection against RVGE hospitalizations with the RIX4414 vaccine (81%; $P < 0.001$) over two consecutive RV seasons in the present study.13,14 Another finding was the comparable incidence of GE and severe GE due to any cause between the RIX4414 and placebo groups; suggesting that other bacterial and viral enteropathogens could be contributing to GE related illness.

G2P[4] was documented as the predominant strain in episodes of severe RVGE and RVGE of any severity in the current study. This observation is inconsistent with previously observed predominant strain, G3P[8] in China, suggesting that the

| Table 1. Efficacy of RIX4414 over two consecutive RV seasons—from two weeks post-Dose 2 up until the end of the second RV season (ATP cohort for efficacy) |
| Gastroenteritis type | RIX4414 | Placebo | Vaccine efficacy % (95% CI) | $P$ value |
|---------------------|--------|--------|-----------------------------|----------|
| Severe RVGE over two consecutive RV seasons | 1575 21 | 13 (0.8–2.0) | 1573 75 | 4.8 (3.8–5.9) | 72.0 (54.1–83.6) | <0.001 |
| Severe RVGE during the first RV season | 1575 8 | 0.5 (0.2–1.0) | 1573 32 | 2.0 (1.4–2.9) | 75.0 (44.7–90.1) | <0.001 |
| Severe RVGE during the second RV season | 1500 13 | 0.9 (0.5–1.5) | 1479 43 | 2.9 (2.1–3.9) | 70.2 (43.5–85.3) | <0.001 |
| Severe RVGE over two consecutive RV seasons by RV type | | | | |
| G1WT | 1575 9 | 0.6 (0.3–1.1) | 1573 25 | 1.6 (1.0–2.3) | 64.0 (20.4–85.2) | 0.009 |
| Pooled non-G1WT | 1575 12 | 0.8 (0.4–1.3) | 1573 54 | 3.4 (2.6–4.5) | 77.8 (58.0–89.2) | <0.001 |
| G1WT + P8WT | 1575 8 | 0.5 (0.2–1.0) | 1573 20 | 1.3 (0.8–2.0) | 60.1 (5.3–84.8) | 0.035 |
| G1WT + P4 | 1575 1 | 0.10 (0.0–0.4) | 1573 5 | 0.3 (0.1–0.7) | 80.0 (78.5–99.6) | 0.218 |
| G2 + P4 | 1575 11 | 0.7 (0.3–1.2) | 1573 40 | 2.5 (1.8–3.4) | 72.5 (45.5–87.3) | <0.001 |
| G3 + P8WT | 1575 0 | 0.0 (0.0–0.2) | 1573 3 | 0.2 (0.0–0.6) | 100 (141.7–100) | 0.250 |
| G9 + P8WT | 1575 0 | 0.0 (0.0–0.2) | 1573 3 | 0.2 (0.0–0.6) | 100 (141.7–100) | 0.250 |
| RVGE of any severity over two consecutive RV seasons | 1575 70 | 4.4 (3.5–5.6) | 1573 167 | 10.6 (9.1–12.2) | 58.1 (44.3–68.8) | <0.001 |
| RVGE of any severity during the first RV season | 1575 27 | 1.7 (1.1–2.5) | 1573 90 | 5.7 (4.6–7.0) | 70.0 (53.5–81.3) | <0.001 |
| RVGE of any severity during the second RV season | 1500 43 | 2.9 (2.1–3.8) | 1479 78 | 5.3 (4.2–6.5) | 45.6 (20.1–63.4) | 0.001 |
| RVGE of any severity over two consecutive RV seasons by RV type | | | | |
| G1WT | 1575 22 | 1.4 (0.9–2.1) | 1573 46 | 2.9 (2.1–3.9) | 52.2 (19.0–72.6) | 0.005 |
| Pooled non-G1 WT | 1575 49 | 3.1 (2.3–4.1) | 1573 129 | 8.2 (6.9–9.7) | 62.1 (46.9–73.3) | <0.001 |
| G1WT + P8WT | 1575 20 | 1.3 (0.8–2.0) | 1573 38 | 2.4 (1.7–3.3) | 47.4 (7.4–71.0) | 0.024 |
| G1WT + P4 | 1575 2 | 0.1 (0.0–0.5) | 1573 9 | 0.6 (0.3–1.1) | 77.8 (7.2–97.7) | 0.065 |
| G2 + P4 | 1575 42 | 2.7 (1.9–3.6) | 1573 102 | 6.5 (5.3–7.8) | 58.9 (40.5–72.0) | <0.001 |
| G3 + P8WT | 1575 0 | 0.0 (0.0–0.2) | 1573 11 | 0.7 (0.3–1.2) | 100 (60.2–100) | <0.001 |
| G9 + P8WT | 1575 1 | 0.1 (0.0–0.4) | 1573 5 | 0.3 (0.1–0.7) | 80.0 (78.5–99.6) | 0.218 |
| Hospitalization due to RVGE over two consecutive RV seasons | 1575 4 | 0.3 (0.1–0.6) | 1573 21 | 1.3 (0.8–2.0) | 81.0 (43.6–95.3) | <0.001 |
| Hospitalization due to RVGE during the first RV season | 1575 2 | 0.1 (0.0–0.5) | 1573 14 | 0.9 (0.5–1.5) | 85.7 (37.9–98.4) | 0.004 |
| Hospitalization due to RVGE during the second RV season | 1500 2 | 0.1 (0.0–0.5) | 1479 7 | 0.5 (0.2–1.0) | 71.8 (48.0–97.1) | 0.173 |
| All cause GE over two consecutive RV seasons | 1575 728 | 46.2 (43.7–48.7) | 1573 759 | 48.3 (45.8–50.8) | 4.2 (6.2–13.6) | 0.422 |
| All cause severe GE over two consecutive RV seasons | 1575 187 | 11.9 (10.3–13.6) | 1573 206 | 13.1 (11.5–14.9) | 9.3 (11.1–26.0) | 0.357 |

GE, gastroenteritis; RVGE, rotavirus gastroenteritis; N, number of infants included in each group; n (%), number (percentage) of infants recording at least one episode; 95% CI, Exact 95% confidence interval; $P$ value, two-sided Fisher exact test (significant level of $\alpha = 0.05$).
distribution of RV strains differ from year-to-year. Given this interesting aspect of rotaviruses, it is important to assess the ability of the RV vaccine to protect against circulating RV types that may help in controlling the disease burden. In accordance with previous studies, RIX4414 afforded significant protection against severe RVGE and RVGE of any severity caused by G1 and non-G1 RV types. Significant VE was observed against G2P[4] in episodes of severe RVGE (72.5%) and RVGE of any severity RVGE (58.9%) in this study. This is of particular interest as this strain is heterotypic to the RIX4414 vaccine strain for both G and P types, suggesting that in China the RIX4414 vaccine can provide broad protection against non-G1 and non P[8] types. Notably, in some earlier studies, VE against G2 could not be satisfactorily assessed due to the low circulation of G2 type. However, significant protection against severe RVGE due to G2P[4] (P = 0.0086) has been observed in Europe over two consecutive RV seasons. In addition, an integrated analysis on VE against severe RVGE by RV types indicated good clinical protection against G2P[4].

With respect to seasonality, the highest number of RVGE episodes in this study was recorded in January 2012 and December 2011; these findings are consistent with a previous study in China that indicated RV peaks in winter. In terms of safety, there was no evidence of a clinically significant difference between the RIX4414 and placebo groups with respect to unsolicited symptoms reported 31 d post-vaccination and SAEs reported from Dose 1 up until the end of the second RV season. The safety data in this study are consistent with an integrated safety summary report. This integrated safety analysis noted that all SAEs were assessed as unrelated to vaccination and that there was no imbalance between the RIX4414 and placebo groups with respect to the number of deaths. Two cases of intussusception were recorded during the current study (one in each group), both of which resolved. While recent studies have shown some evidence of a temporal increase in the risk of intussusception following the first vaccine dose, it is still uncertain whether RV vaccination has any impact on the overall incidence of intussusception. Our study results provide comparable safety profiles between the RIX4414 vaccine and placebo in Chinese infants.

We conclude from our study that two oral doses of RIX4414 coadministered with routine childhood vaccines is efficacious against severe RVGE caused by circulating RV strains in China during the first two years of life. These data may help public health officials in making an informed decision regarding the adoption of RV vaccination in their country.

### Methodology

**Study design and participants**

We conducted a phase III, randomized, double-blind (i.e., concealed from parents/guardians, study personnel, and

### Table 2. Cause of death from Dose 1 up until the end of the second RV season

| Group   | Dose | Day since last dose | Day since dose 1 | Cause of death                  |
|---------|------|---------------------|------------------|---------------------------------|
| RIX4414 (n = 6) | 2    | 496                 | 526              | Asphyxia                        |
|         | 2    | 538                 | 568              | Drowning                        |
|         | 2    | 118                 | 148              | Central nervous system infection |
|         | 121  | 151                 |                  | Cortical dysplasia              |
|         | 2    | 2                   |                  | Intracranial Hemorrhage         |
|         | 2    | 95                  | 125              | Asphyxia                        |
|         | 2    | 218                 | 248              | Meningitis                      |
|         | 2    | 221                 | 251              | Multi-organ failure             |
|         | 2    | 271                 | 301              | Hemotrophic histiocytosis       |
|         | 2    | 356                 | 386              | Acute lymphocytic leukemia      |
|         | 2    | 341                 | 371              | Death                           |
|         | 2    | 36                  | 69               | Multi-organ failure             |
|         | 111  | 141                 |                  | Multi-organ failure             |
|         | 2    | 107                 | 137              | Diarrhea                        |
|         | 2    | 18                  | 48               | Congenital heart disease        |
|         | 2    | 530                 | 560              | Respiratory failure, brain contusion, subarachnoid hemorrhage, skull fracture, cerebral hematoma, and brain herniation |

n, number of deaths in each group.
Information from the diary cards was used to assess the severity of each GE episode using the 20-point Vesikari scale, where a score of $<7$ was defined as mild, $7–10$ was moderate, and $\geq11$ was severe.

The collected stool samples were analyzed to identify RV using an enzyme-linked immunosorbent assay (ELISA; RotaClone™ assay, Meridian Biosciences). All RV positive stool samples were further tested using reverse transcriptase polymerase chain reaction followed by reverse hybridization and sequencing to determine the $G$ and $P$ types and differentiate the presence of wild-type G1 RV from the vaccine strain virus. These tests were performed at LabCorp Clinical Trials (formerly, Clearstone Laboratory).

**Assessment of safety**

The safety of the vaccine was assessed in terms of the unsolicited symptoms reported during the 31-d follow-up after either dose of RIX4414 or placebo; and SAEs which were recorded from the administration of Dose 1 and up until the end of the second RV season. An SAE is defined as any life-threatening medical event that may require medical or surgical intervention to prevent hospitalization, disability, or a congenital anomaly/birth defect in the study subject or death.

**Statistical analyses**

A target sample size of 3250 infants (1625 in each group) was required to reach 2600 evaluable subjects (1300 in each group) for the efficacy evaluation. Assuming a 2% rate of RVGE during follow-up in the placebo group and a true VE of 80%, this study had 95.8% power to observe a lower limit of 95% CI for VE $>10\%$.

The primary efficacy endpoint was VE against severe RVGE from two weeks post-Dose 2 up until the end of the second RV season. The primary efficacy objective was met if the lower limit of the 95% CI on VE was $>10\%$. Due to the low number of severe RVGE cases observed during the first RV season, this study was extended up until the end of the second RV season for severe RVGE cases. Infants who completed the first RV season and for whom consent to continue till the end of the second RV season was not provided were considered drop-outs. The ATP efficacy cohort included infants who received two doses of RIX4414/placebo; who had entered the efficacy surveillance period; who had no rotavirus other than the vaccine strain in their GE stool samples collected between Dose 1 and two weeks post-Dose 2 of RIX4414/placebo, and who complied with the protocol throughout. The total vaccinated cohort was used in the safety analysis and included infants who received at least one dose of RIX4414/placebo.

The percentage of subjects reporting any and severe RVGE episodes (overall and by $G$ type), RVGE requiring hospitalization, GE, and severe GE due to any cause were calculated for over two consecutive RV seasons, and for the first and second RV seasons with 95% CI. The seasonality pattern of RVGE cases was also recorded.

All statistical analyses were performed using SAS Drug and Development web portal version 3.5 and SAS version Proc StatXact 8.1.
Disclosure of Potential Conflicts of Interest

Authors Huang T, Li Y, Luo D, Tao J, Fu B, Si G, Nong Y, and Mo Z declare to have received institutional funding/grants from GlaxoSmithKline Biologicals SA for the conduct of Rota trials. GS also declare to have received support for travel to meetings for the study or other purposes from GlaxoSmithKline Biologicals SA. Li RC declares no conflict of interest. Liao X, Luan I, Tang H, Rathi N, Karkada N, Htay Han H are employed by GlaxoSmithKline group of companies; Rathi N and Htay Han H also hold stock ownership/restricted shares from the sponsoring company.

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Trademarks

Rotarix is a registered trademark of the GlaxoSmithKline group of companies. Rotatet is a registered trademark of Merck and Co., USA. Rotavin-M1 is a registered trademark of Center for research and production of vaccines and biologicals [POLYVAC], Vietnam. Lanzhou lamb rotavirus vaccine is a registered trademark of Lanzhou Institute of Biomedical Products, China. RotaClone is a registered trademark of Meridian Biosciences, USA.

References

1. Bernstein DI. Rotavirus overview. Pediatr Infect Dis 2009; 28(Suppl 1):S50-3; http://dx.doi.org/10.1097/Inf.0b013138187980ee; PMID:19252423
2. Chandran A, Fitzwater S, Zhen A, Santosham M. Human rotavirus vaccine. Vaccine 2009; 27(Suppl 5):F127-30; PMID:19066497
3. Duan Z-J, Liu N, Yang S-H, Zhang J, Sun L-W, Tang J-Y, Jin Y, Du ZQ, Xu J, Wu QB, et al. Hospital-based surveillance of rotavirus diarrhea in the People’s Republic of China, August 2003-July 2007. J Infect Dis 2009; 200(Suppl 1):S167-73; http://dx.doi.org/10.1086/605039; PMID:19817597
4. Glass RI. RotaClone is a registered trademark of Meridian Biosciences, USA. RotaClone is a registered trademark of Lanzhou Institute of Biomedical Products, China. RotaClone is a registered trademark of Meridian Biosciences, China.

10. Glass RI, Parashar UD, Breese JS, Turciros R, Fischer TK, Widdowson MA, Jiang B, Gentsch JR. Rotavirus vaccines: current prospects and future challenges. Lancet 2006; 368:323-32; http://dx.doi.org/10.1016/S0140-6736(06)68815-6; PMID:16860702
11. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, Abate H, Breezer T, Clemens SC, Cheuvart B, Espinosa F, Giliard P, Innis BL, et al.; Human Rotavirus Vaccine Study Group. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med 2006; 354:11-22; http://dx.doi.org/10.1056/NEJMoa052434; PMID:16399249
12. Vesikari T, Malinoff D, Onnehey P, Van Damme P, Santosham M, Rodríguez Z, Dallas MJ, Hyse JF, Goveia MG, Black SB, et al.; Rotavirus Efficacy and Safety Trial (REST) Study Team. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med 2006; 354:23-35; http://dx.doi.org/10.1056/NEJMoa052664; PMID:16399249
13. Vesikari T, Kvaronen A, Pymula R, Schuster V, Tejedor JC, Cohen R, Meurice F, Han HH, Damaso S, Bouckenhooge A. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. Lancet 2007; 370:1757-63; http://dx.doi.org/10.1016/S0140-6736(07)61744-9; PMID:18037080
14. Llaneres AC, Velázquez FR, Pérez-Schael I, Sánchez-Lorens X, Abate H, Espinosa F, López P, Macias-Parras M, Ortega-Barría E, Rivera-Medina DM, et al.; Human Rotavirus Vaccine Study Group. Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. Lancet 2008; 371:1181-9; http://dx.doi.org/10.1016/S0140-6736(08)60524-3; PMID:18399579
15. Madhi SA, Kirsten M, Louw C, Bos P, Aspinall S, Bouckenhooge A, Neuzil KM, Steele AD. Efficacy and immunogenicity of two or three dose rotavirus-vaccine regimen in South African children over two consecutive rotavirus-seasons: a randomised, double-blind, placebo-controlled trial. Vaccine 2012; 30(Suppl 1):A44-51; http://dx.doi.org/10.1016/j.vaccine.2011.08.080; PMID:22520136
16. Cunliffe NA, Witte D, Ngwira BM, Todd S, Bostock NJ, Turner AM, Chipempi P, Victor JC, Steele AD, Bouckenhooge A, et al. Efficacy of human rotavirus vaccine against severe gastroenteritis in Malawian children in the first two years of life: a randomized, double-blind, placebo controlled trial. Vaccine 2012; 30(Suppl 1):A36-43; http://dx.doi.org/10.1016/j.vaccine.2011.09.120; PMID:22520135
17. Phua KB, Lim FS, Lau YL, Nelson EA, Huang LM, Quak SL, Wei BW, Teoh YL, Tang H, Boudville I, et al. Safety and efficacy of human rotavirus vaccine during the first 2 years of life in Asian infants: randomised, double-blind, controlled study: Vaccine 2009; 27:5936-41; http://dx.doi.org/10.1016/j.vaccine.2009.07.098; PMID:19679216
18. Luan T, Trang NV, Phuong NM, Nguyen HT, Ngo HT, Nguyen HT, Tran HB, Dang HN, Dang AD, Gentsch JR, et al. Development and characterization of candidate rotavirus vaccine strains derived from children with diarrhea in Vietnam. Vaccine 2009; 27(Suppl 5):F130-8; PMID:19931712; http://dx.doi.org/10.1016/j.vaccine.2009.08.086
19. Anh DD, Trang NV, Thiem VD, Anh NTH, Mao ND, Wang Y, et al. A dose-escalation safety and immunogenicity study of a new live attenuated human rotavirus vaccine (Rotavin-M1) in Vietnamese children. Vaccine 2012; 30S:A114-21; http://dx.doi.org/10.1016/j.vaccine.2011.07.118
20. Fa C, He Q, Xu J, Xie H, Ding P, Hu W, Dong Z, Liu X, Wang M. Effectiveness of the Lanzhou lamb rotavirus vaccine against gastroenteritis among children. Vaccine 2012; 31:154-8; http://dx.doi.org/10.1016/j.vaccine.2012.10.078; PMID:23127516
21. Wang X-Y, Riewpaiboon A, von Seidlein L, Chen X-B, Kilgore PE, Ma J-C, Qi SX, Zhang ZY, Hao ZY, Chen JC, et al. Potential cost-effectiveness of a rotavirus immunization program in rural China. Clin Infect Dis 2009; 49:1202-10; http://dx.doi.org/10.1086/609562; PMID:19739973

22. Ouyang Y, Ma H, Jin M, Wang X, Wang J, Xu L, Lin S, Shen Z, Chen Z, Qiu Z, et al. Etiology and epidemiology of viral diarrhea in children under the age of five hospitalized in Tianjin, China. Arch Virol 2012; 157:881-7; http://dx.doi.org/10.1007/s00705-012-1235-9; PMID:22318672

23. Lou J-T, Xu X-J, Wu Y-D, Tao R, Tong M-Q. Epidemiology and burden of rotavirus infection among children in Hangzhou, China. J Clin Virol 2011; 50:84-7; http://dx.doi.org/10.1016/j.jcv.2010.10.003; PMID:21041114

24. Kawamura N, Tokoeda Y, Oshima M, Okahata H, Tsutsumi H, Van Doorn LJ, Muto H, Smolenov I, Suryakiran PV, Han HH. Efficacy, safety and immunogenicity of RIX4414 in Japanese infants during the first two years of life. Vaccine 2011; 29:6335-41; http://dx.doi.org/10.1016/j.vaccine.2011.05.037; PMID:21640780

25. De Vos B, Han HH, Bouckenooghe A, Debrus S, Gillard P, Ward R, Cheuvart B. Live attenuated human rotavirus vaccine, RIX4414, provides clinical protection in infants against rotavirus strains with and without shared G and P genotypes: integrated analysis of randomized controlled trials. Pediatr Infect Dis J 2009; 28:261-6; http://dx.doi.org/10.1097/INF.0b013e3181907177; PMID:19289978

26. Cheuvart B, Friedland LR, Abu-Elyazeed R, Han HH, Guerra Y, Verstraeten T. The human rotavirus vaccine RIX4414 in infants: a review of safety and tolerability. Pediatr Infect Dis J 2009; 28:225-32; http://dx.doi.org/10.1097/INF.0b013e31819715fa; PMID:19209995

27. Buttery JP, Danchin MH, Lee KJ, Carlin JB, McIntyre PB, Elliott EJ, Booy R, Bines JE; PAEDS/APSU Study Group. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. Vaccine 2011; 29:3061-6; http://dx.doi.org/10.1016/j.vaccine.2011.01.088; PMID:21316503

28. Velázquez FR, Colindres RE, Grajales C, Hernández MT, Mercadillo MG, Torres FJ, Cervantes-Apolinar M, DeAntonio-Suarez R, Ortega-Barria E, Blum M, et al. Postmarketing surveillance of intussusception following mass introduction of the attenuated human rotavirus vaccine in Mexico. Pediatr Infect Dis J 2012; 31:736-44; http://dx.doi.org/10.1097/INF.0b013e318253add3; PMID:22695189

29. Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes. Scand J Infect Dis 1990; 22:259-67; http://dx.doi.org/10.3109/00365549009027046; PMID:2271542