



# Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial

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## Summary

**Background** Rotavirus is the most common cause of severe dehydrating gastroenteritis in developing countries. Safe, effective, and affordable rotavirus vaccines are needed in these countries. We aimed to assess the efficacy and tolerability of a monovalent human-bovine rotavirus vaccine for severe rotavirus gastroenteritis in low-resource urban and rural settings in India.

**Methods** We did a randomised double-blind, placebo-controlled, multicentre trial at three sites in Delhi (urban), Pune (rural), and Vellore (urban and rural) between March 11, 2011, and Nov 5, 2012. Infants aged 6–7 weeks were randomly assigned (2:1), via a central interactive voice or web response system with a block size of 12, to receive either three doses of oral human-bovine natural reassortant vaccine (116E) or placebo at ages 6–7 weeks, 10 weeks, and 14 weeks. Infants' families, study investigators, paediatricians in referral hospitals, laboratory staff, and committee members were all masked to treatment allocation. The primary outcome was incidence of severe rotavirus gastroenteritis ( $\geq 11$  on the Vesikari scale). Efficacy outcomes and adverse events were ascertained through active surveillance. Analysis was by intention to treat and per protocol. The trial is registered with Clinical Trial Registry–India (CTRI/2010/091/000102) and ClinicalTrials.gov (NCT01305109).

**Findings** 4532 infants were assigned to receive the 116E vaccine and 2267 to receive placebo, of whom 4354 (96%) and 2187 (96%) infants, respectively, were included in the primary per-protocol efficacy analysis. 71 events of severe rotavirus gastroenteritis were reported in 4752 person-years in infants in the vaccine group compared with 76 events in 2360 person-years in those in the placebo group; vaccine efficacy against severe rotavirus gastroenteritis was 53·6% (95% CI 35·0–66·9;  $p=0\cdot0013$ ) and 56·4% (36·6–70·1;  $p<0\cdot0001$ ) in the first year of life. The number of infants needed to be immunised to prevent one severe rotavirus gastroenteritis episode was 55 (95% CI 37–97). The incidence of severe rotavirus gastroenteritis per 100 person-years was 1·5 in the vaccine group and 3·2 in the placebo group, with an incidence rate ratio of 0·46 (95% CI 0·33–0·65). Prevalence of immediate, solicited, and serious adverse events was similar in both groups. One case of urticaria in the vaccine group and one each of acute gastroenteritis and suspected sepsis in the placebo group were regarded as related to the study product. We recorded six cases of intussusception in the vaccine group and two in the placebo group, all of which happened after the third dose. 25 (<1%) infants in the vaccine group and 17 (<1%) in the placebo group died; no death was regarded as related to the study product.

**Interpretation** Monovalent human-bovine (116E) rotavirus vaccine is effective and well tolerated in Indian infants.

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## Introduction

Rotavirus is the leading cause of severe gastroenteritis in children in developing countries.<sup>1</sup> Two oral, live, attenuated rotavirus vaccines—RotaTeq (Merck) and Rotarix (GlaxoSmithKline)—are presently available.<sup>2</sup> WHO recommends universal introduction of safe and effective rotavirus vaccines in national immunisation programmes.<sup>2</sup> The protective effectiveness of these vaccines is high in high-income countries, but decreases substantially in middle-income and low-income countries.<sup>3–11</sup> Even with moderate clinical

effectiveness in developing countries, the effect on incidence of moderate to severe disease and hospital admissions for gastroenteritis, and related mortality, is relatively higher and of substantial public health importance.<sup>2,7–9,12</sup>

Many countries including India have not yet introduced rotavirus vaccines in their immunisation programmes and where such programmes are introduced with support from the GAVI Alliance, there are sustainability challenges at present vaccine prices when external support is no longer available. In developing countries,

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the availability of affordable and effective rotavirus vaccines is crucial. The 116E rotavirus strain, developed as part of the Indo-US Vaccine Action Program,<sup>13</sup> is a naturally occurring reassortant strain G9P[11], containing one bovine rotavirus gene P[11] and ten human rotavirus genes. The 116E strain readily infected hospital born neonates in Delhi, India, and was regarded as well adapted to the neonatal gut and naturally attenuated, because the neonatal infection was asymptomatic.<sup>14,15</sup> The candidate strain was adapted to grow in Vero cells and was shown to be safe and immunogenic.<sup>16</sup> In this study, we assessed the efficacy and safety of the 116E rotavirus vaccine against severe rotavirus gastroenteritis in low-resource urban and rural settings in India.

## Methods

### Study design and participants

We did this double-blind placebo-controlled trial between March 11, 2011, and Nov 5, 2012, at three low-resource urban and rural sites in Delhi (urban), Pune (rural), and Vellore (60% urban, 40% rural). On the basis of routine surveillance at the sites, female literacy rates were 74% (Delhi), 61% (Pune), and 75% (Vellore). Infant mortality rates were 39·8 (Delhi), 37·5 (Pune), and 30·4 (Vellore) per thousand livebirths.<sup>17</sup> Infants aged between 6 weeks and 7 weeks were eligible for enrolment, if the parents consented for participation and had no plans to move away from the study area during the next 24 months. Infants were excluded if they had received a rotavirus vaccine, or if they had documented immunodeficiency or chronic gastroenteritis or any other disorder that was deemed necessary for exclusion by the investigator. Infants were temporarily excluded if they had any illness needing hospital referral, or diarrhoea, on the day of enrolment.

Ethics and administrative clearances were obtained from the three sites, the Department of Biotechnology (India), and the Western Institutional Review Board (USA). Parents of enrolled infants provided written informed consent. The study was done in compliance with the protocol, good clinical practices, and national regulatory and ethics guidelines.<sup>18,19</sup> A data and safety monitoring board periodically reviewed study data.

### Randomisation and masking

Infants were randomly assigned in a 2:1 ratio via an interactive voice or web response system with a block size of 12, to receive either three doses of 116E vaccine, or placebo, at ages 6–7 weeks, 10 weeks and older, and 14 weeks and older. Randomisation was stratified by study site. Three letter codes were used to maintain the allocation ratio: two letters (X and O) were assigned to the vaccine and one to the placebo (J). The product handling team was independent and based in a separate room with restricted access; they did not interact with other study teams at the site. Letter codes were masked with unique participant identification numbers used to

identify enrolled infants before vials of vaccine and placebo were sent to the clinical coordinator giving the study product to the enrolled infant. Infants' families, study investigators, paediatricians in referral hospitals, laboratory staff, and committee members were all masked to treatment allocation. The site teams remain masked because the study is ongoing.

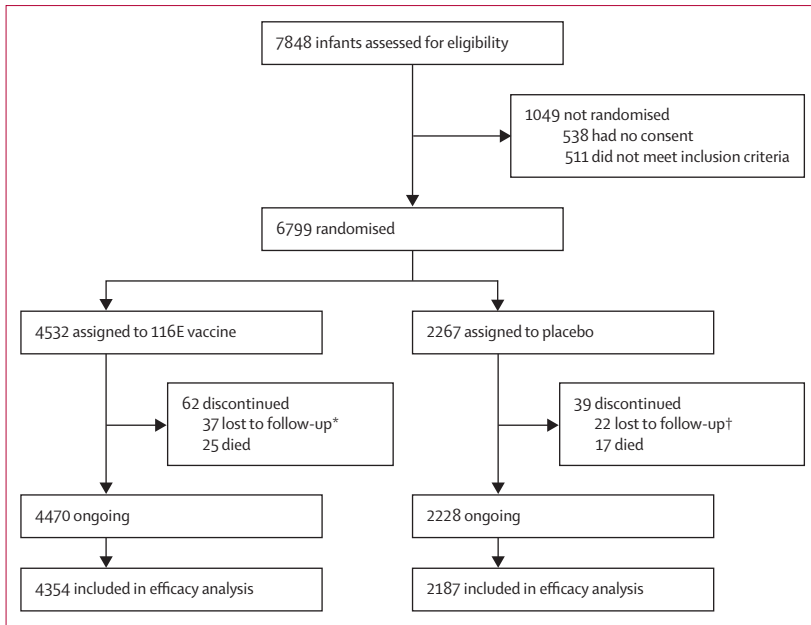
### Procedures

Each 0·5 mL of the 116E vaccine (ROTAVAC, Bharat Biotech International, India) contained no less than 10<sup>5</sup> fluorescent focus units. The placebo was identical in content, packaging, and appearance to the vaccine. Both vaccine and placebo were stored at –20°C (plus or minus 5°C); citrate bicarbonate buffer was stored at room temperature. Vaccine and placebo were given 5–10 min after administration of 2·5 mL of buffer. Other childhood vaccines (combined diphtheria, pertussis, tetanus, *Haemophilus influenzae* type b and hepatitis b, and oral polio vaccine) were given concurrently. Mothers were not given specific instructions about breastfeeding around the time of vaccination.

The primary outcome was severe rotavirus gastroenteritis ( $\geq 11$  on the Vesikari scale). Infants were observed at the study clinic for at least 30 min after vaccine or placebo were given for immediate adverse events. In the first third of enrolled infants, solicited adverse events (fever, vomiting, diarrhoea, cough, runny nose, irritability, or rash) and any other adverse events reported by families were documented daily for 14 days after each dose. Parents of all infants were contacted weekly at home by trained fieldworkers to identify the presence of gastroenteritis, signs and symptoms of suspected intussusception, hospital admissions, and other illnesses. We defined gastroenteritis as passage of three or more looser-than-normal or watery stools in a 24 h period with or without vomiting. Infants with gastroenteritis were given packets of oral rehydration salts solution and zinc tablets.<sup>20</sup> Those with dehydration or other illnesses needing hospital admission were sent to designated hospitals by study physicians. Characteristics of gastroenteritis episodes were documented for each day with home or hospital visits, and a stool specimen was collected up to 7 days after the last day of gastroenteritis. Mothers were given mobile telephones with the contact numbers of the study team, digital thermometers, and participant booklets. Families were instructed to call, or bring their child to the study clinic for gastroenteritis, other illnesses, or presence of signs and symptoms of suspected intussusception; study physicians were available 24 h a day. Costs of medical care (including transportation) for outpatient visits and hospital admissions were covered by the study. Independent paediatricians served as safety advisers at each site and reviewed safety data periodically.

Infants with one or more signs or symptoms of suspected intussusception (abdominal distension, abdominal lump,  $\geq 3$  vomiting episodes in 1 h, and blood

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**Figure 1: Trial profile**  
 \*12 infants lost to follow-up (families moved from study area), 25 refused further participation. †12 infants lost to follow-up (families moved from study area), ten refused further participation.

	Vaccine (n=4532)	Placebo (n=2267)
Delhi	2532	1267
Pune	1000	500
Vellore	1000	500
Age at dosing (weeks)		
Dose 1	6.8 (0.6)	6.8 (0.6)
Dose 2	11.7 (2.4)	11.7 (2.4)
Dose 3	16.3 (2.8)	16.4 (2.8)
Sex, n (%)		
Male	2330 (51%)	1157 (51%)
Infants who received each dose		
Dose 1	4532 (100%)	2267 (100%)
Dose 2	4409 (97%)	2221 (98%)
Dose 3	4356 (96%)	2190 (97%)

Data are n (%) or mean (SD), unless otherwise indicated.

**Table 1: Baseline characteristics and compliance to vaccine or placebo**

in stools) were examined by a paediatrician, referred to a paediatric surgeon, and admitted to hospital, as necessary. An adjudication committee consisting of a paediatric surgeon, a paediatrician, and a radiologist reviewed all investigator-diagnosed cases of intussusception with Brighton criteria level 1 to provide the final diagnosis.<sup>21</sup>

A subset of 150 infants at each site constituted the immunogenicity and viral shedding subgroup. In these infants, 2 mL blood was drawn at baseline and 28 days after the third dose of vaccine or placebo to estimate serum anti-rotavirus IgA, and stool specimens were obtained before and on days 3 and 7 after each dose for

shedding of vaccine virus. Rotavirus was detected in stools with a commercial enzyme immunoassay (Premier Rotaclone, Meridian Bioscience, USA). Rotaclone-positive stools were analysed for G (VP7) and P (VP4) genotypes by multiplex PCR.<sup>22,23</sup> VP6 gene detection assay by PCR was done for specimens that could not be genotyped.<sup>24</sup> The assay was not designed to differentiate vaccine G9P[11] from wild G9P[11]. Serum anti-rotavirus IgA was identified by ELISA with a standard curve method.<sup>25</sup> Seroconversion was defined as an increase of four times in titre from paired serum samples.

**Statistical analysis**

With an assumed vaccine efficacy of 60%, an attack rate of 2.6% over 1.5 years, a 20% dropout rate, and 89% power, a total of 6800 infants were needed to accrue 85 cases of severe rotavirus gastroenteritis. To conclude that the vaccine was efficacious, the lower bound of the 95% CI had to be 20% or more.

Analyses were done by Quintiles with SAS (version 9.2). Efficacy analyses were done in the per-protocol and intention-to-treat populations. We regarded the per-protocol population as the primary population and included all infants who received the same treatment at all three doses of vaccine or placebo within the prescribed windows, and who had episodes that took place more than 14 days after the third dose. The intention-to-treat population included all infants who received at least one dose of vaccine or placebo and included episodes that took place after the first dose.

Vesikari scores were computed for each episode during analyses.<sup>26</sup> We regarded an episode of gastroenteritis as a new event on the basis of a report of diarrhoea 7 days or more from the time of the end of the previous episode. For each outcome, only the first event was counted for each infant. We calculated the follow-up period for each event as time to occurrence of the event, the date of dropout, or until the data cutoff date.

We used an equation to define vaccine efficacy by person-time incidence rate:

$$100 \times (1 - [nv/Fv] / [np/Fp])$$

where  $n_v$  and  $n_p$  were the number of infants with at least one case of severe rotavirus gastroenteritis, and  $F_v$  and  $F_p$  were the total length of follow up in the vaccine and placebo groups, respectively. The number of cases in both groups were assumed to follow Poisson distributions with respective parameters  $\lambda_v F_v$  and  $\lambda_p F_p$ . In view of the total number of cases ( $n$ ), the number in the vaccine group follows a binomial distribution with  $n$  trials and probability parameter  $\lambda_v F_v / (\lambda_v F_v + \lambda_p F_p)$ . P values and CIs for vaccine efficacy were computed with exact binomial methods.<sup>27</sup>

We compared the proportion of infants with adverse events between groups with Fisher's exact test. We coded all events with the Medical Dictionary for Regulatory

Activities (version 15.0). The results presented are for the per-protocol population, unless otherwise stated.

This trial is registered with Clinical Trial Registry–India (CTRI/2010/091/000102) and ClinicalTrials.gov (NCT01305109).

### Role of the funding source

The funders of the study had no role in undertaking of the study, data collection, or data analysis. The corresponding author and some primary authors had full access to all the data in the study and had final responsibility for the decision to submit for publication, coordinated by the corresponding author.

### Results

Figure 1 shows the trial profile. We enrolled 6799 infants (3799 in Delhi and 1500 each in Pune and Vellore) of whom 4532 were randomly assigned to receive the 116E vaccine and 2267 were assigned to receive placebo. At analysis, the median age of infants was 17·2 months (range 13·4–21·7), all infants had reached 1 year of age, and loss to follow-up was roughly 1% (figure 1). Total follow-up time in the per-protocol population was 4752 years in the vaccine group and 2360 years in the placebo group. Compliance with dosing was high (96% of infants) and administration was close to the recommended age (table 1).

After accumulation of the target number of primary endpoint cases, the independent biostatistics team of Quintiles, South Africa analysed and provided results to the data and safety monitoring board for review. The board concluded that the primary hypothesis had been satisfied and advised unmasking of data and follow-up of infants until all reached 2 years of age to obtain data for safety and efficacy in the second year of life.

Vaccine efficacy for severe rotavirus gastroenteritis was 53·6% (table 2). The lower confidence limit exceeded the prespecified criterion of 20% (table 2). Survival curves in the vaccine group compared with the placebo group showed a significantly increased cumulative proportion of infants without severe rotavirus gastroenteritis (figure 2). The appendix shows a forest plot with vaccine efficacy by site. We noted no statistically significant interaction of treatment group by site for vaccine efficacy ( $p=0\cdot29$ ). Efficacy against severe rotavirus gastroenteritis during the first year of life was 56·4% (table 2). The number of infants needed to be immunised to prevent one episode of severe rotavirus gastroenteritis was 55 (95% CI 37–97) and for rotavirus gastroenteritis of any severity was 31 (21–54).<sup>28</sup> The incidence of severe rotavirus gastroenteritis per 100 person-years was 1·5 in the vaccine group and 3·2 in the placebo group, with an incidence rate ratio of 0·46 (95% CI 0·33–0·65). The absolute rate reduction for severe rotavirus gastroenteritis was 1·7 (2·5–0·9).

Efficacy against severe gastroenteritis of any cause was 18·6% and in the first year of life was 24·1% (table 2).

The efficacy estimates in the intention-to-treat analysis were similar to those for the per-protocol analysis

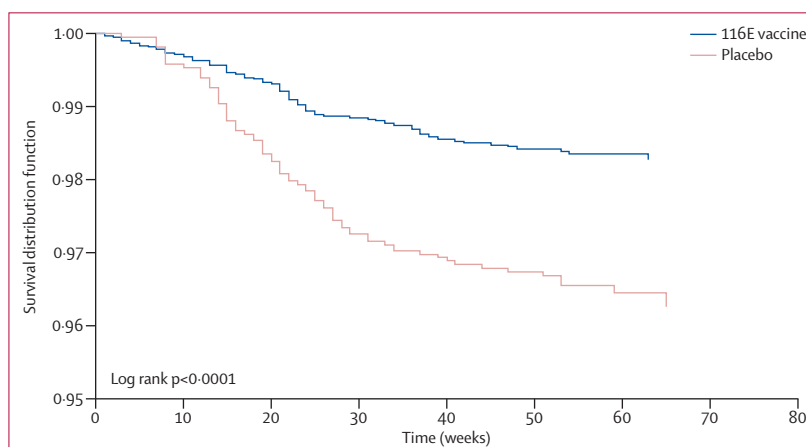
(appendix). The most common (83%) rotavirus genotypes identified in the 147 primary cases of severe gastroenteritis were G2P[4] (n=48 [33%]), G1P[8] (44 [31%]), G12P[6] (21 [14%]), and G12P[8] (8 [5%]). Although the trial was not powered to evaluate efficacy against individual rotavirus genotypes, we did a post-hoc analysis in the per-protocol population. The CIs of the genotype-specific results are consistent with the overall protective efficacy (table 3). The statistical test for interaction between vaccine efficacy and genotype of the

See Online for appendix

	Vaccine (n=4354)	Placebo (n=2187)	Vaccine efficacy (% [95% CI])	p value
<b>Severe rotavirus gastroenteritis</b>				
Overall*	71 (2%)	76 (3%)	53·6% (35·0 to 66·9)	0·0013
At 1 year of age	56 (1%)	64 (3%)	56·4% (36·6 to 70·1)	<0·0001
<b>Severe rotavirus gastroenteritis needing hospital admission† or supervised rehydration therapy‡</b>				
Overall*	71 (2%)	76 (3%)	53·6% (35·0 to 66·9)	<0·0001
At 1 year of age	56 (1%)	64 (3%)	56·4% (36·6 to 70·1)	<0·0001
<b>Very severe rotavirus gastroenteritis</b>				
Overall*	10 (<1%)	11 (<1%)	54·4% (–18·3 to 82·6)	0·1130
At 1 year of age	9 (<1%)	9 (<1%)	49·8% (–42·6 to 82·4)	0·2176
<b>Rotavirus gastroenteritis of any severity</b>				
Overall*	287 (7%)	216 (10%)	34·6% (21·6 to 45·3)	<0·0001
At 1 year of age	226 (5%)	171 (8%)	34·6% (19·7 to 46·6)	<0·0001
<b>Rotavirus gastroenteritis of any severity needing hospital admission† or supervised rehydration‡ therapy</b>				
Overall*	277 (6%)	201 (9%)	32·0% (18·0 to 43·5)	<0·0001
At 1 year of age	218 (5%)	161 (7%)	32·9% (17·2 to 45·5)	0·0002
<b>Severe gastroenteritis of any cause</b>				
Overall*	308 (7%)	188 (9%)	18·6% (1·9 to 32·3)	0·0305
At 1 year of age	221 (5%)	145 (7%)	24·1% (5·8 to 38·7)	0·0123

Data are n (%), unless otherwise indicated. We defined severe gastroenteritis as episodes with a Vesikari score of 11 or greater. Episodes of severe rotavirus gastroenteritis had a Vesikari score of 11 or greater and presence of rotavirus (rotaclone positive and VP6 or VP4 and VP7 positive by RT-PCR) strains; includes all cases except those for which G9P[11] was isolated. Episodes of very severe gastroenteritis had a Vesikari score of 16 or greater. \*Median age was 17·2 months (range 13·4–21·7) at the time of analyses. †Inpatient admission for at least 6 h in a treatment facility or hospital. ‡Administration of oral rehydration salts or intravenous fluids.

**Table 2: Efficacy of the vaccine against gastroenteritis in the per-protocol population**



**Figure 2: Kaplan-Meier survival curves for severe rotavirus gastroenteritis**

Per-protocol population. Time 0 represents 15 days after receipt of the third dose of vaccine or placebo.

	Vaccine (n=4354)	Placebo (n=2187)	Vaccine efficacy (% [95% CI])
G2P[4]	21	27	60.9% (29.1 to 79.2)
G1P[8]	25	19	31.3% (-29.9 to 63.8)
G12P[6]	8	13	69.1% (20.5 to 89.0)
G12P[8]	3	5	69.9% (-53.1 to 95.4)
Others*	14	12	41.4% (37.2 to 67.3)
Total	71 (2%)	76 (3%)	53.6% (35.0 to 66.9)

Data are n or n (%), unless otherwise indicated. Differences in efficacy by genotype were not statistically significant. \*Includes all genotypes causing seven cases or less (G9P[4], G9P[8], G1P[4], G1P[6], G2P[6], G1P[0], G0P[0], and G12P[11]).

**Table 3: Protective efficacy of the vaccine against severe gastroenteritis caused by different RV genotypes**

	Vaccine (n=4531)	Placebo (n=2265)	p value
Children who had a serious adverse event	925 (20%)	499 (22%)	0.13
Infections and infestations	777 (17%)	418 (19%)	0.19
Lower respiratory tract infection	261 (6%)	124 (6%)	0.66
Gastroenteritis	221 (5%)	109 (5%)	0.95
Rotavirus gastroenteritis	77 (2%)	69 (3%)	0.0005
Bronchopneumonia	76 (2%)	38 (2%)	1.00
Pneumonia	60 (1%)	21 (<1%)	0.19
Respiratory, thoracic, and mediastinal disorders	129 (3%)	71 (3%)	0.54
Wheezing	106 (2%)	54 (2%)	0.93
General and administration site disorders	72 (2%)	33 (2%)	0.75
Pyrexia	62 (1%)	29 (1%)	0.82

**Table 4: Serious adverse events coded by the Medical Dictionary for Regulatory Activities system of organ classification and preferred terms**

infecting strains was not significant ( $p_{\text{interaction}}=0.19$ ). In the per-protocol population, G9P[11] was not detected in any cases of rotavirus gastroenteritis. Seroconversion to the vaccine was shown in the immunogenicity subset 4 weeks after the third dose, in 115 (40%) infants in the vaccine group (288 pairs) and 25 (18%) infants in the placebo group (136 pairs; OR 2.95, 95% CI 1.77–5.05), suggesting that-wild type rotavirus infections were common during the immunisation period. In post-hoc analyses, we detected an increase of three times in 135 (47%) of 288 vaccine recipients and 26 (19%) of 136 of placebo recipients (OR 3.73, 95% CI 2.25–6.32). Of the 306 vaccine recipients in the subset, G9P[11] was shed in 37 (12%) infants after dose 1, six (2%) infants after dose 2, and four (1%) infants after dose 3.

19 (<1%) of 4531 infants in the vaccine group and eight (<1%) of 2265 in the placebo group ( $p=0.84$ ) reported an immediate adverse event; these events were vomiting or spitting up of the oral contents, and one infant in the placebo group had a rash. In view of their temporality, most events were labelled as related; all were mild and none resulted in hospital admission or death. In the 14 days after dosing, adverse events were ascertained in 1530 (34%) vaccine recipients and 768 (34%) placebo recipients. The most common adverse events after the

three doses in the vaccine and placebo groups were general disorders and administration-site disorders (1299 [85%] vs 657 [86%] infants;  $p=0.71$ ), respiratory thoracic and mediastinal disorders (844 [55%] vs 431 [56%];  $p=0.69$ ), gastrointestinal disorders (505 [33%] vs 226 [29%];  $p=0.09$ ), skin and subcutaneous tissue disorders (133 [9%] vs 79 [10%];  $p=0.22$ ), infection and infestations (105 [7%] vs 58 [8%];  $p=0.55$ ), and metabolism and nutrition disorders (79 [5%] vs 42 [6%];  $p=0.77$ ). Analyses for solicited adverse events showed a similar prevalence of fever, vomiting, diarrhoea, cough, runny nose, irritability, and rash (data not shown;  $p\geq 0.3$  for all comparisons). G9P[11] genotype was identified in 22 cases of gastroenteritis in the vaccine group, 20 after the first dose and two after the second dose; an approximate rate of one gastroenteritis event in 600 doses for any dose, and roughly one in 200 for the first dose. By Vesikari score, all cases were classified as mild or moderate. We did not examine stools for other enteropathogens.

Table 4 shows findings for serious adverse events. One case of urticaria in the vaccine group and one each of acute gastroenteritis and suspected sepsis in the placebo group were regarded as related to the study product on the basis of temporality of occurrence. Expectedly in this age group, lower respiratory tract infections and gastroenteritis were the most common causes of hospital admission. Of the 25 (<1%) in the vaccine group and 17 (<1%) in the placebo group ( $p=0.33$ ), none was regarded as related to the study product. Six (<1%) cases of intussusception were reported in the vaccine group and two (<1%) were reported in the placebo group. All events took place after administration of dose 3. The minimum interval between dosing and intussusception was 112 days in the vaccine group and 36 days in the placebo group.

## Discussion

Our findings provide good evidence of the efficacy of the 116E rotavirus vaccine and the study satisfied the primary efficacy hypothesis. 116E protected against rotavirus gastroenteritis of varying severity, with protection generally increasing with clinical severity. Importantly, 116E also reduced severe gastroenteritis of any cause, showing the importance of rotavirus as a cause of severe gastroenteritis in infants in India. Findings from intention-to-treat analyses strongly supported those of the per-protocol analyses.

Although comparisons across studies of rotavirus vaccine are difficult to make because of differing populations, protocols, attack rates, and study procedures, our point estimate of efficacy against severe rotavirus gastroenteritis during the first year of life for 116E vaccine is similar to that of RotaTeq and Rotarix when assessed in developing countries. In a combined analysis of two independent, double-blind, placebo-controlled, multi-centre, phase-3 efficacy trials done in Africa (Ghana,

Kenya, Mali)<sup>8</sup> and Asia (Bangladesh, Vietnam),<sup>9</sup> efficacy of RotaTeq against severe rotavirus gastroenteritis in the first year of life was 58·9% (95% CI 40·0–72·3).<sup>29</sup> In a double-blind, placebo-controlled, multicentre, phase-3 efficacy trial done in Africa (South Africa, Malawi), efficacy of Rotarix against severe rotavirus gastroenteritis in the first year of life was 61·2% (95% CI 44·0–73·2).<sup>7</sup> For RotaTeq and Rotarix, efficacy in the second year of life has generally been lower than in the first year of life.<sup>30</sup> Complete data for the efficacy of 116E in the second year of life are not yet available.

Immune responses to vaccination as measured by the prespecified criteria of an increase of four times greater than baseline in serum anti-rotavirus IgA were noted in roughly 40% of vaccine recipients. This rate was lower than the 89·7% noted in the phase Ib/IIa trial. There were several differences in study population and how the study was done between these two studies that might explain the differences in immune responses. In the phase-Ib/IIa trial, the eligibility criteria were more stringent, the study population were healthier and infants with severe malnourishment were excluded, and the rotavirus vaccine was not given concomitantly with childhood vaccines; co-administration of oral polio vaccine can interfere with the immunogenicity of rotavirus vaccines.<sup>31–33</sup> Furthermore, the age at first vaccination was slightly higher in the phase-Ib/IIa (8 weeks) than in the phase-3 trial (6–7 weeks), and maternally derived serum antirotavirus IgG are known to block rotavirus replication. Additionally, breastfeeding was restricted for 30 min before and after dosing in the phase-Ib/IIa trial but not in the phase-3 trial, which might have an effect on the uptake of rotavirus vaccines. Variability in immune response rates to serum anti-rotavirus IgA across different populations have likewise been reported for other rotavirus vaccines.<sup>34,35</sup>

116E was well tolerated when given with other childhood vaccines. Analyses of immediate adverse events, and solicited and unsolicited adverse events in the 14 days after vaccination, serious adverse events, deaths, and cases of intussusception showed no unfavourable imbalances in recipients of 116E. A thorough assessment of risk of intussusception will await phase 4 surveillance studies (panel). 116E might cause gastroenteritis, but if so, only rarely, and mostly of mild severity.

These findings are of interest for several reasons. First, the rotavirus strain (G9P[11]) that forms the basis of the 116E rotavirus vaccine is an unusual strain and rarely causes clinical disease in India or elsewhere.<sup>1,16,36</sup> That 116E provided heterotypic protection across a broad array of commonly circulating rotavirus genotypes in India strongly suggests that 116E will provide protection throughout India and in other regions of the world.

Second, 116E is the first rotavirus vaccine to show protective efficacy in India, a country comprising a quarter of the entire global mortality due to rotavirus gastroenteritis.<sup>1</sup> 116E protected against severe rotavirus gastroenteritis needing hospital admission or supervised

### Panel: Research in context

#### Systematic review

We searched PubMed between January and July, 2013, for English-language publications, with various combinations of the search terms “Infants”, “diarrhea”, “gastroenteritis”, “rotavirus”, “efficacy”. We focused mainly on articles published between 2005 and 2013, but also included other older relevant publications. The reference lists of review articles were also used to search for relevant publications.

#### Interpretation

Our findings showing that 116E vaccine against severe rotavirus gastroenteritis and severe gastroenteritis of any cause was efficacious and well tolerated in Indian infants are consistent with findings for RotaTeq and Rotarix in high-mortality countries. Complete data for efficacy in the second year of life, and post-marketing surveillance to assess the risk of rare side-effects including intussusceptions, are pending. Gastroenteritis is more common and severe in developing than developed countries; therefore even moderately efficacious vaccines would have substantial vaccine-attributable reduction in severe rotavirus gastroenteritis in such low-income populations.

rehydration therapy—an important observation in a country where health care is difficult to access and most expenses are out-of-pocket. In general, live oral vaccines have been less effective when given to infants in developing countries than when given to those in developed regions. An example is oral polio vaccine which requires a large number of doses to be administered to infants in India to achieve immunity.<sup>37</sup> The underlying basis for suboptimum performance of oral live-attenuated vaccines in India and elsewhere in developing countries has not been delineated and is probably multifactorial including factors such as passive transfer of large concentrations of maternal antibody, poor nutritional status, breastfeeding practices, and frequent exposure to several enteric pathogens.

Third, despite the modest efficacy of 116E vaccine in India, the number of cases and deaths due to severe rotavirus gastroenteritis that are averted by vaccine are likely to be higher than in developed countries because of the significantly higher incidence of rotavirus gastroenteritis.<sup>1,2</sup> In fact, despite the modest effectiveness of all rotavirus vaccines in developing countries, WHO recommends introduction of rotavirus vaccination as part of the national immunisation programmes in these populations because of the high disease burden.

Fourth, the development of 116E rotavirus vaccine represents a shift in the basic theory of new vaccine development and serves as an example of how low-income and middle-income countries can develop these powerful techniques and address endogenous infectious diseases of high burden without relying exclusively on multinational pharmaceutical companies. 116E was developed by an Indian company with substantial technical and financial

support from a unique government-led public–private partnership. 116E will first be targeted to Indian infants, but later to infants in other developing countries. Government, bilateral, and non-government organisation push-funding and technical support substantially derisked the project for the manufacturer, resulting in a favourable price commitment for the public sector at the time of product launch (<US\$ 1.00 per dose).

Finally, this successful product development validates the concept that new vaccines and other health commodities can be developed through socially committed collaborative efforts with effective government participation, and engagement of small to medium-size enterprises resulting in substantially lower investment. In this regard, the vaccine is a product of a path-setting model for development of health technologies at prices that ensure increased access in places where these are needed most.

#### Contributors

NB, JB and MKB prepared the manuscript and all authors reviewed and approved the work. TR-C, AB, JJ, NG, AK, GK, SSR, SJ, JM, AA, HS, and VA designed the protocol, trial implementation strategy, and trial conduct. NB, KA, and ST contributed to the design of protocol, trial implementation strategy, oversight of trial conduct, and data analyses. JB, MKB, GT, RG, HBG, GC, TSR contributed to the trial design, data interpretation, and laboratory guidance. KM, GVJAH, and SP are employees of Bharat Biotech International and contributed to preparation of pilot lots, transfer of technology of some assays, and gave intellectual input into trial design. MP and RK contributed to data analyses. SV analysed specimens.

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#### Conflicts of interest

KM, GVJAH, and SP are employees of Bharat Biotech International. All other authors declare that they have no conflicts of interest.

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