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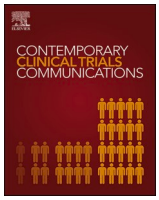

A phase II/III randomised, comparative study evaluating the safety and immunogenicity of Biological E's live, attenuated Measles-Rubella vaccine in 9–12 month old healthy infants

Subhash Thuluva *, SubbaReddy Gunneri, Kishore Turaga, Rammohan Reddy Mogulla, Vijay Yerroju, Kalyankumar Peta, Pothakamuri Venkata Suneetha, Ramesh V. Matur

Biological E Limited, 18/1&3, Azamabad, Hyderabad, 500 020, Telangana, India

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ABSTRACT

Background: Measles is a major cause of childhood mortality and one-third of the world's Measles deaths occur in India. Rubella causes lifelong birth defects (Congenital Rubella Syndrome). Although neither condition has a cure, the MR vaccination can successfully prevent both diseases. The safety of Biological E's live attenuated MR vaccine (BE-MR) was established in 4-5-year-old healthy children. This phase-2/3 study was conducted to assess the safety and immunogenicity of BE-MR in 9–12 month old healthy infants. Overall, 600 subjects were enrolled and equally randomized to receive either BE-MR (n = 300) or the comparator vaccine, SII MR-Vac™ (n = 300). Safety profile of BE-MR vaccine was comparable to SII MR-Vac™ with no severe or serious adverse events (AEs) reported across the study groups. The primary objective of demonstrating non inferiority by BE-MR vaccine compared to SIIL's-MR Vac™ was met. The proportion of subjects with ≥ 2-fold and ≥ 4-fold increase in antibody titre against Measles and Rubella in both the study groups was comparable. Overall, BE-MR vaccine elicited robust and protective immune response as demonstrated by high proportion of sero-protected subjects and a large increase in anti-Measles and anti-Rubella antibodies at day 42 and can be administered safely to infants below one-year of age. This study was prospectively registered with the clinical trial registry of India- CTRI/2016/07/007109.

1. Introduction

Measles and Rubella infections are respectively caused by a single-stranded RNA genome containing Measles and Rubella viruses. They are highly contagious with high rates of morbidity and mortality reported among infants. Both viruses are transmitted by the aerosol borne respiratory droplets and illness begins with fever, cough and conjunctivitis followed by a characteristic rash. Complications of Measles affect most organ systems, with pneumonia accounting for most Measles-associated morbidity and mortality [1,2]. Measles was responsible for more than 207,500 deaths worldwide reported in 2019 most of which were in infants less than 5 years of age [3]. Reportedly, over 2.5 million infants acquire and nearly 49,000 infants die due to the Measles infection each year in India [4].

Rubella virus is the causative agent of Rubella disease (German Measles), and has a public health importance because of the teratogenic potential of infections developed during pregnancy. Due to Rubella, an estimated 100000 infants born with congenital Rubella syndrome (CRS) each year worldwide [5]. No specific treatment for CRS available so far. However, it can be prevented by immunization. Between Jan 2007 and Dec 2018, from data reported to WHO as of January 2020, 139486 Rubella cases were reported to WHO with annual incidence ranged from 13.9 cases and 1.7 cases per million in 2007 and 2018 respectively [6]. In 2019, the Indian government reported 10, 430 Measles cases and 3404 Rubella cases to WHO [7].

High population immunity and high-quality surveillance are the cornerstones to eliminate Measles and Rubella. Both Measles and Rubella are preventable, and can be effectively eliminated by vaccination. WHO published a strategic frame work in 2020, to achieve and sustain the regional measles and rubella elimination goals by 2023 [8]. However, it was not achieved due to COVID-19 pandemic and low vaccination rates, inadequate mechanisms for catch-up vaccination, increasing vaccine hesitancy in several countries and inadequate monitoring and surveillance. So, the core strategies identified remain

* Corresponding author. Biological E Limited, 18/1&3, Azamabad, Hyderabad, 500 020, Telangana, India.
E-mail address: subhash.thuluva@biologicale.com (S. Thuluva).

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relevant post 2020 period and extended the goal for 2021–2030 to "achieve and sustain the regional measles and rubella elimination" [9]. Mortality due to Measles was reduced by 98% in the South-East Asia Region (SEAR) by 2020 compared to 2000. However, COVID-19 pandemic had a significant impact on efforts of eliminating Measles and Rubella [3,10]. As a part of routine immunization, countries in SEAR are administering two-doses of Measles containing vaccine and the coverage of first and second dose of vaccination declined significantly from 94% to 88% and 83%–78% in 2019–2020 respectively. Similar to Measles vaccine, Rubella vaccination coverage was also declined from 93% in 2019 to 87% in 2020 [8]. In India, around 11–20% of children aged between 9 months and 15years are not vaccinated with available MR vaccine, posing a potential threat and urgent need to improve the vaccine coverage [11].

India introduced Measles-Rubella (MR) vaccine in 2017, for infants aged 9 months to 14 years and has seen a reduction in Measles and Rubella cases in states, that have conducted the Measles and Rubella (MR) vaccine campaign. However, there are pockets of low immunization coverage particularly in high-risk areas such as urban slums and migrant populations [12]. Biological E. initiated MR vaccine development by importing Measles finished bulk from PT Bio Pharma of Indonesia and the Rubella component was manufacturedin-country. Biological E. has successfully completed the preclinical toxicity studies and the Phase-I safety study of the live attenuated MR vaccine (BE-MR) in 4-5-year-old healthy subjects (CTRI/2015/11/006375). The objective of this randomized, comparative, multicentre phase-2/3 study is to assess the overall safety and immunogenicity of Biological E's live attenuated MR vaccine in 9–12 month old infants in comparison with a licensed MR vaccine, developed by Serum Institute of India (SII).

2. Methods

2.1. Study population

Overall, 600 subjects were enrolled in this Phase- 2/3 study. Healthy subjects of either gender between 9 and 12 months of age were included in the study. All the 600 subjects were randomized equally to receive either Biological E's Measles and Rubella (BE-MR) vaccine (n = 300) or MR-Vac from Serum Institute of India (SII MR-Vac™ n = 300). Demographic characteristics of study subjects are shown in Table 1.

Infants with exposure to Measles and Rubella ≤30 days before study start, family history of any hypersensitivity reactions to Measles (M), MR (Measles and Rubella) or MMR (Measles, Mumps and Rubella) vaccination(s) or allergy to any of their components, severe hypersensitivity reaction to vaccinations, acute or chronic illness or major congenital defects, history of neurologic disorders or seizures, any confirmed or suspected infection with HIV, HCV and Hepatitis B (HBsAg) or any other medical condition that would make subcutaneous (SC) injection unsafe, were excluded from the study. Complete list of eligibility criteria in both the studies was provided as supplementary information.

Table 1
Demographic characteristics of study participants.

		BE's MR Vaccine (N = 300)	SIIL's MR-Vac (N = 300)	Total (N = 600)
Age at vaccination (months)	Mean (SD)	9.87 (0.756)	9.76 (0.650)	9.81 (0.707)
	Median	9.60	9.60	9.60
Gender, n (%)	Male	145 (48.33)	157 (52.33)	302 (50.33)
	Female	155 (51.67)	143 (47.67)	298 (49.67)
Weight (kg)	Mean (SD)	8.54 (0.857)	8.48 (0.923)	8.51 (0.890)
	Median	8.50	8.50	8.50
Height (cms)	Mean (SD)	71.1 (3.03)	71.1 (3.15)	71.1 (3.09)
	Median	71.0	71.0	71.0

Abbreviations: N = number of subjects in the specified treatment group n = number of subjects in the specified category.

Institutional ethics committee or institutional review board approved the study protocol at all the study sites. The study was conducted in accordance with the ethical principles defined in the Declaration of Helsinki, International Council for Harmonization Good Clinical Practices (ICH-GCP) guidelines, and applicable local regulatory requirements. Written informed consent was obtained from parents/legally acceptable representatives of the all subjects included in the study before the screening for enrolment.

2.1.1. Study design

Phase- 2/3 study was a multicentre, open label, randomized, actively compared design to evaluate the immunogenicity and safety of BE's bivalent live attenuated Measles-Rubella (MR) vaccine, conducted in 6 study centres across India, in comparison with a licensed MR-Vac™ vaccine from Serum Institute of India Limited (SIIL). Site wise enrolment status of the study participants is provided as Supplementary Table 1. Authors do not have access to information that could identify individual participants during or after data collection.

The total duration of the study was 42 Days, an additional window period of 7 days per subject was provided to avoid schedule visit deviation. Informed consent from parents and/or legally acceptable representative/guardian, health assessment, and blood samples were collected for analysis and single dose of the vaccination was given during Visit-1. Visit-2 (Day-7) constituted the day of safety review for both groups. Visit-3 (Day-42) after the single dose of vaccination scheduled for collecting the blood sample for immunogenicity analysis.

2.2. Outcomes

The primary outcome of the study was to evaluate the immunogenic non-inferiority of BE's bivalent live attenuated Measles-Rubella vaccine (BE-MR) vaccine with the licensed MR-Vac™ vaccine manufactured by Serum Institute of India in terms of sero-protection rates at Day 42. Secondary outcome was to demonstrate the safety of BE-MR in comparison with SII MR-Vac™ vaccine.

2.2.1. Safety assessments

Each subject was observed for any immediate local and systemic adverse reactions, up to 60 min' post-vaccination, by the investigator. In addition, subject's parents or legally acceptable representative or guardian were provided with a subject diary and trained to observe and capture adverse symptoms post-vaccination for the next seven consecutive calendar days to report any solicited local and systemic AEs. Only the principal investigator or co-investigator assessed the causality of the reported symptoms. Solicited AEs were assessed as local tolerability that included pain, redness, swelling, tenderness at the injection site, itching, induration; and systemic tolerability that included fever, lymphadenopathy, irritability, feeding problems, acute arthralgia, rash, urticaria and unusual crying. Any other unsolicited AEs reported during the study period were also recorded. The AEs were recorded and followed up for the entire duration of the study starting immediately following vaccine administration until Day-42.

The number and percentage of subjects with adverse events (AEs), Medically attended AEs (MAAEs) and serious adverse events (SAEs) were presented overall by system organ class (SOC) & preferred term (PT). The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one systemic AE (solicited and unsolicited) and with any AE during the solicited follow-up period were tabulated with an exact 95% confidence interval (CI). The same calculations were performed for symptoms rated as Grade 3 and above. Systemic and local tolerability, recorded in subject diaries, were summarized in a frequency table with percentages based on the number of observed values.

Summary of clinically significant vital signs across study visits were tabulated and each parameter was summarized descriptively.

2.2.2. Immunological assays/analyses

Both anti-Measles and anti-Rubella specific antibodies were measured using Siemens Enzygnost® anti-Measles virus and anti-Rubella-Virus IgG ELISA kits, respectively. The quantitative cut-off value defined for Measles sero-protection was an anti-Measles antibody titre of ≥120 mIU/mL and the quantitative cut-off value defined for Rubella sero-protection was an anti-Rubella antibody titre of ≥10 IU/mL. Geometric Mean concentration/titre (GMC/GMT) was defined as the average value (by multiplying all values) of a set of n integers, terms, or quantities expressed as the nth root of their product, where n is the number of subjects.

2.3. Statistics

2.3.1. Sample size

The study was designed to have a power of 90%. Based on available study data, SIIL's combination Measles-Rubella vaccine is known to offer a mean sero-protection level of 96.43% and 91.67% for Measles and Rubella, respectively. The BE-MR-vaccine was also expected to offer no less than 90% of the sero-protection rate. For an alpha value of 0.05, and a two-sided 95% CI, a sample size of 482 subjects (n = 241 in MR group and n = 241 in SIIL's licensed MR- Vac™ group) would enable the study to have a power of 90%. Around 15% of the subjects were expected to drop out during the entire study period'. The total sample size, compensating for 15% attrition (n = 59), was 600 subjects (n = 300 in the MR group and n = 300 in the SIIL's licensed MR-Vac™ group).

2.3.2. Analysis sets

The intent-to-treat (ITT) population included all subjects randomized to one of the study treatment groups. The per-protocol (PP) population included all evaluable subjects who met all the eligibility criteria and complied with the procedures defined in the protocol for whom data concerning immunogenicity endpoint measures were available. Safety analyses were based on the safety population that included all subjects who entered the study and received the vaccination.

2.3.3. Statistical analyses

Demographics and baseline characteristics were summarized descriptively. For continuous variables n, mean, standard deviation, median and range (minimum and maximum) were presented. For categorical data, frequency and percentages were computed.

The primary objective of Phase- 2/3 study was to demonstrate the non-inferiority of BE-MR-vaccine in comparison with SIIL's licensed MR-Vac™ in terms of the difference in the proportion of subjects achieving the antibody titre levels above the kit specified protection threshold levels against each antigen. A two-sided 95% CI for the difference in the proportion of subjects' seroconverted between treatment groups was calculated. Non-inferiority was demonstrated if the lower bound of the 95% CI for the difference in proportions was ≥ −10%.

Differences in the proportion of subjects who achieved a ≥4-fold rise from baseline in antibody titres at Day-42 between treatment groups were also calculated. Fisher's exact test or chi-square test (as appropriate) was to be used to compare the difference in proportions of subjects who achieved a ≥4-fold increase in titres at Day-42 from baseline.

The secondary objective of the study was to assess the safety and tolerability of the BE's MR-vaccine in comparison to SII MR-Vac™ vaccine. The number and percentage of subjects with AEs (solicited and unsolicited), treatment-emergent adverse events (TEAE), and serious adverse events (SAE) were presented for each treatment group overall and by system organ class/preferred term, severity, relatedness, and separately by seriousness. All safety laboratory parameters were assessed for any possible clinically significant changes from baseline. All clinically significant abnormal laboratory parameters were summarized for both treatment groups. All TEAE, including SAEs related to laboratory parameters, were listed. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 and concomitant medications were coded using WHO drug dictionary (WHO-DD 2016).

2.3.4. Randomization

Equal randomization of subjects into two groups (BE-MR and SII MR-Vac™) was performed using interactive web response system, containing the randomization number and intended allocation. The randomization numbers were assigned as e.g., EA001 (E-enrolment; A-site code; 001-number of the enrolled subject) and this number continued in the same serial order until all the subjects were randomly assigned.

3. Results

3.1. Subject disposition

This phase- 2/3 study was carried out at 6 centres in India between September 2016 and March 2017. In total, 600 subjects were enrolled into the study, equally randomized into BE-MR group (n = 300) and SII MR-Vac™ group (n = 300). All study subjects received the single dose of the study vaccine as per the group allocation. Of the 600 subjects, 592 (98.67%) subjects completed the study and 8 (1.33%) subjects discontinued the study. Reason for study dropout is listed in Fig. 1. Immunogenicity data was available in 590 subjects out of 592 subjects who completed the study. Details of study participants disposition is shown in Fig. 1.

Demographic characteristics of study subjects were analysed in the intention to treat (ITT) population. Overall, the demographic and baseline characteristics were comparable between the subjects in BE's MR Vaccine and SIIL's MR-Vac™ groups (Table 1).

3.1.1. Immunogenicity findings

Immunogenicity assessments were primarily based on the PP population that consisted of 590/600 (91.6%) subjects, with 297 in the BE-MR group and 293 in the SIIL's-MR- Vac™ group. The proportion of

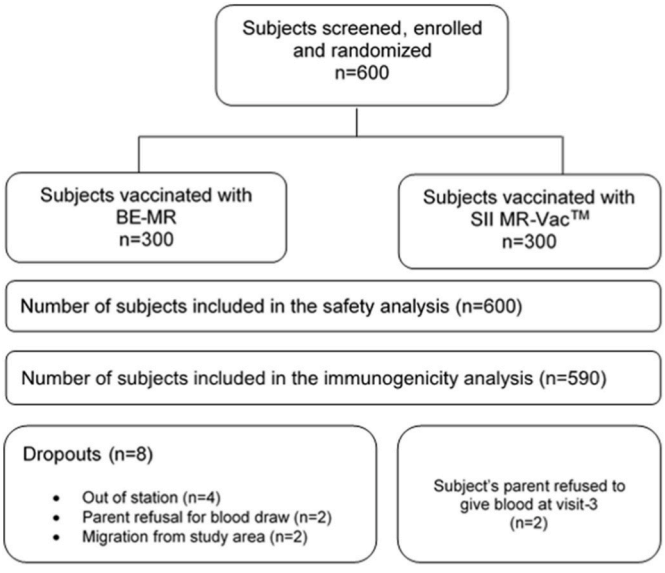


Fig. 1. Subject Disposition
In total, 600 subjects were enrolled into this study. All study subjects received the single dose of either BE-MR vaccine (n = 300) and SII MR-Vac™ vaccine (n = 300). Of the 600 subjects, 592 (98.67%) subjects completed the study and 8 (1.33%) subjects discontinued the study. Immunogenicity data was available in 590 subjects. All 600 subjects were included for safety analysis.
n, number; MR, Measles-Rubella; BE, Biological E; SII, Serum Institute of India.

subjects sero-protected at visit 3 (day 42) were 82.83% (246/297) and 86.01% (252/293) against Measles vaccine and 94.28% (280/297) and 96.25% (282/293) against Rubella vaccine in both BE's MR vaccine group and in SIIL's MR-Vac™ group respectively (Fig. 2a and b). The difference in seroconversion rates between the groups at visit 3 (day 42) was −3.18%, with the lower limit of 95% CI -9.09 for Measles and the difference in seroconversion rates between the groups at visit 3 (day 42) for Rubella was −1.97%, with the lower limit of 95% CI -5.65. The primary objective of demonstrating non inferiority by BE-MR vaccine was met compared to SIIL's-MR Vac™ as the lower confidence limit of the group difference was not below −10.0% for both Measles and Rubella vaccines. Reverse cumulative distribution curves for proportion of subjects sero-protected is depicted as Supplementary Figure 1a and Supplementary Figure 1b.

Anti-Measles and anti-Rubella antibody titre GMT values in the BE-MR group and the SIIL's MR-Vac™ group at Day-42 in the PP population were presented in Table 2. The primary analysis of anti-Measles antibody titres at Day 42 showed GMT of 372.64 and 337.73 in BE's MR vaccine group and SIIL's MR-Vac™ group respectively. The primary analysis of anti-Rubella antibody titres at Day 42 showed GMT of 72.89 and 74.82 in BE's MR vaccine group and SIIL's MR-Vac™ group respectively. The proportion of subjects with ≥ 2-fold and ≥ 4-fold increase in antibody titre against Measles and Rubella in both the study groups was comparable (Table 3).

Overall, seroconversion rates and GMT values against Measles and Rubella vaccines in both the study groups were comparable. Both the vaccines elicited strong immune response as demonstrated by high proportion of sero-protected subjects and a large increase in anti-Measles and anti-Rubella antibodies at Day-42 compared to baseline.

Table 2
GMT ratio for anti-measles and anti-rubella neutralizing antibodies at Day 42 between Treatment Groups.

Antigen	BE's MR Vaccine (N = 297)		SIIL's MR-Vac (N = 293)		Estimated Ratio	(95% CI)
	GMT	(95% CI)	GMT	(95% CI)		
Measles	372.64	(321.83, 431.47)	337.73	(299.46, 380.89)	1.10	(0.91, 1.33)
Rubella	72.89	(64.56, 82.30)	74.82	(67.50, 82.95)	0.97	(0.83, 1.14)

Abbreviations: C.I. = confidence interval; GMT = geometric mean titre; N = number of subjects in the specified treatment group; n = number of subjects with a valid and determinate titre for the specified antigen at Day 42.

Table 3
Fold increase in anti-Measles and anti-Rubella Antibody Titers at Day 42 by Treatment Group.

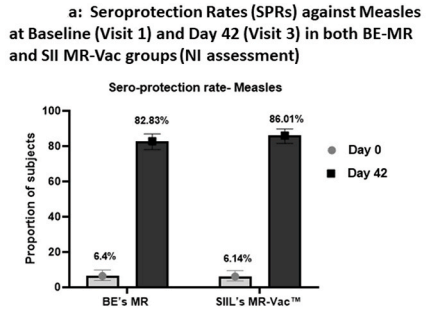
Antigen	Fold Rise	BE's MR Vaccine (N = 297) N1, n (%)	SIIL's MR-Vac (N = 293) N1, n (%)
Measles	≥2-fold rise	273 (91.92)	274 (93.52)
	≥4-fold rise	259 (87.21)	268 (91.47)
Rubella	≥2-fold rise	274 (92.26)	274 (93.52)
	≥4-fold rise	260 (87.54)	269 (91.81)

Abbreviations: N = number of subjects in the specified treatment group; N1 = number of subjects with a valid and determinate titre for the specified antigen at both, Day 0 and Day 42; n = number of subjects achieving the specified fold rise at Day 42.
Note: Percentage has been calculated as (n/N1)*100.

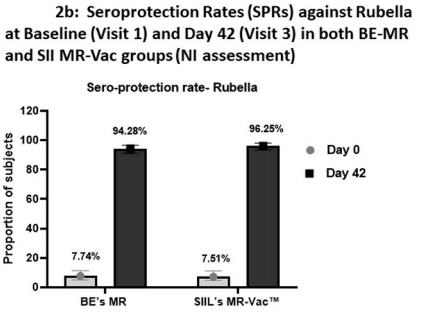
3.1.2. Safety findings

Among all vaccinated subjects (n = 600), 137 subjects (22.83%) subjects reported at least one adverse event. Out of which, 64 (21.33%) subjects were from BE's MR vaccine group and 73 (24.33%) subjects were from SIIL's MR-Vac™ group. Summary of AEs reported in this study is listed in Table 4. The total number of subjects reported with at least one systemic AE were 11% and 9% from BE's MR vaccine group and SIIL's MR-Vac™ group respectively. The most commonly involved system organ class (SOC) for AEs in both groups were general disorders and administration site conditions, reported by 20% of subjects in both the groups. All AEs by SOC, PT and severity is listed in Table 5. Overview of severity and causality of AEs are presented in Table 6. Injection site pain and swelling was the most frequently reported local AE in both groups. All local AEs were considered vaccination-related by definition. Pyrexia was the most frequently reported systemic AE and the most common reason for medically attended AE in both the groups. Summary of local, systemic AEs reported in the study were presented in Supplementary Figs. 2 and 3.

Majority of reported AEs were mild in nature and related to the study vaccine. No severe or serious AEs were reported in either of the vaccine groups. No clinically significant changes overtime was noted in the vital signs. The physical examination results and AEs observed did not indicate any safety issues of concern. Overall, the safety profile of BE-MR was comparable to the control vaccine SII MR-Vac™ in terms of AE rates, related AE rates and medically attended AEs and found to be safe and well tolerated.



Seroprotection at day 42 (Anti-Measles)	BE's MR (N=297)	SIIL's MR-Vac™ (N=293)	95% CI for the Difference in Proportions	p-value*
Seroprotected (≥ 120 mIU/mL)	82.83%	86.01%	(-9.09, 2.71)	0.2873



Seroprotection at day 42 (Anti-Rubella)	BE's MR (N=297)	SIIL's MR-Vac™ (N=293)	95% CI for the Difference in Proportions	p-value*
Seroprotected (≥ 10 IU/mL)	94.28%	96.25%	(-5.65, 1.55)	0.2606

Fig. 2. Seroprotection rates and non-inferiority assessment of Measles and Rubella vaccines
Seroprotection Rates (SPRs) against Measles at baseline (Visit 1) and day 42 (Visit 3) in both BE-MR and SII MR-Vac™ vaccinated groups was shown in 2a and seroprotection rates against Rubella vaccine in both the groups was shown in 2b. Pre-defined non-inferiority criteria was met for both Measles and Rubella, shown in the tables below Fig. 2a and b respectively.

Table 4
Overview of adverse events (safety population).

Parameter	BE's MR Vaccine (N = 300) n (%)	SIIL's MR-Vac (N = 300) n (%)
Number of AEs	99	97
Number of subjects with at least one AE	64 (21.33)	73 (24.33)
Number of MAAEs	20	19
Number of subjects with at least one MAAE	13 (4.33)	15 (5.00)
Number of subjects with at least one SAE	0	0
Number of related AEs	83	80
Number of subjects with at least one related AE	56 (18.67)	61 (20.33)
Number of subjects discontinued due to AE/MAAE/SAE	0	0
Number of deaths	0	0

Abbreviations: AE = adverse event; MAAE = medically attended adverse event; N = number of subjects in the specified treatment group; n = number of subjects in the specified category; SAE = serious adverse event.
Note: AEs with causality recorded as "Certain", "Probable" or "Possible" are categorized as "related AEs".

Table 5
Summary of AEs by SOC and PT.

System Organ Class Preferred Term	BE's MR Vaccine (N = 300) n (%)	SIIL's MR-Vac (N = 300) n (%)
Number of subjects with at least one AE	64 (21.33)	73 (24.33)
Gastrointestinal disorders	2 (0.67)	4 (1.33)
Diarrhoea	1 (0.33)	1 (0.33)
Vomiting	1 (0.33)	3 (1.00)
General disorders and administration site conditions	59 (19.67)	61 (20.33)
Crying	9 (3.00)	8 (2.67)
Injection site erythema	10 (3.33)	7 (2.33)
Injection site induration	1 (0.33)	2 (0.67)
Injection site pain	15 (5.00)	18 (6.00)
Injection site tenderness (pain)*	3 (1.00)	5 (1.67)
Injection site pruritus	1 (0.33)	0
Injection site swelling	10 (3.33)	12 (4.00)
Irritability	11 (3.67)	9 (3.00)
Pyrexia	19 (6.33)	13 (4.33)
Infections and infestations	4 (1.33)	9 (3.00)
Gastroenteritis	0	2 (0.67)
Nasopharyngitis	4 (1.33)	6 (2.00)
Respiratory tract infection	0	1 (0.33)
Metabolism and nutrition disorders	3 (1.00)	4 (1.33)
Decreased appetite	3 (1.00)	4 (1.33)
Respiratory, thoracic and mediastinal disorders	6 (2.00)	3 (1.00)
Cough	6 (2.00)	3 (1.00)
Skin and subcutaneous tissue disorders	3 (1.00)	1 (0.33)
Rash	3 (1.00)	1 (0.33)
Urticaria	1 (0.33)	0

Abbreviations: AE = adverse event; N = number of subjects in the specified treatment group n = number of subjects in the specified category; PT = preferred term; SOC = system organ class.

4. Discussion

In this phase-2/3 trial, we demonstrated immunogenic non-inferiority and safety of BE-MR vaccine in comparison to SII MR-Vac™ in 9–12 months old healthy subjects. The Biological E's MR vaccine contains live, attenuated CAM-70 strain of Measles virus, whereas SII MR-Vac™ vaccine contains Edmonston-Zagreb measles virus strain. Both the strains are licensed and are proven to be highly immunogenic and clinically safe for human use. There is no difference in Rubella virus strain (Wistar RA 27/3) used in both the vaccine. SII MR-Vac™ vaccine was used as a comparator in this study as it was WHO prequalified and available in India.

Table 6
Overview AEs by severity & causality.

Parameter	BE's MR Vaccine (N = 300) n (%)	SIIL's MR-Vac (N = 300) n (%)
	n (%)	n (%)
Number of subjects with at least one AE	64 (21.33)	73 (24.33)
Number of subjects with at least one SAE	0	0
Number of subjects with at least one MAAE	13 (4.33)	15 (5.00)
Severity		
Mild	48 (16.00)	64 (21.33)
Moderate	15 (5.00)	9 (3.00)
Severe	1 (0.33)	0
Life-threatening	0	0
Causality		
Certain	19 (6.33)	19 (6.33)
Probable	30 (10.00)	24 (8.00)
Possible	7 (2.33)	18 (6.00)
Unlikely	5 (1.67)	6 (2.00)
Unrelated	3 (1.00)	6 (2.00)
Unclassifiable	0	0
Certain/Probable/Possible	56 (18.67)	61 (20.33)
Unlikely/Unrelated/ Unclassifiable	8 (2.67)	12 (4.00)
Number of subjects discontinued due to AE/SAE	0	0

Abbreviations: AE = adverse event; C.I. = confidence interval; MAAE = medically attended adverse event N = number of subjects in the specified treatment group; n = number of subjects in the specified category.
SAE = serious adverse event.

Sero-protection rates for Measles and Rubella was 82.83% and 94.28% respectively in BE-MR vaccinated subjects and 86.01% and 96.25% against Measles and Rubella respectively in SII MR-Vac™ vaccinated subjects. Sero-protection rates were similar in both the vaccinated groups and predefined NI criteria was met in terms of the lower bound of 95% CI for the difference in proportions of subjects sero-protected was above the minus 10% points for both Measles and Rubella.

Safety profile of BE-MR vaccine and SII MR-Vac™ were comparable with majority of AEs reported were mild in nature and associated with study vaccine. No serious AEs were reported in both vaccinated groups. Most commonly reported MAAE was pyrexia. Safety profile of BE-MR was further established in a large phase-4 study in 9 months–12 months old healthy infants (N = 1000). Similar to the current study observations, adverse event data, vital signs, and physical examination findings did not indicate any clinically significant safety concerns. Phase-4 study was prospectively registered with the clinical trial registry of India- CTRI/2019/04/018683]. Overall, BE-MR vaccine was found to be safe and well tolerated in 9–12 months old infants when administered as a single dose, subcutaneously.

In the current study, 82.83% of subjects who received MR vaccine were sero-protected against Measles. This data is in line with earlier studies reporting sero-protection rate against Measles, ranging from 87.4% to 92.5% in below one year of age infants after single dose [12–15]. Another study showed high rate (99%) of sero-protection rate against Measles six weeks after a first dose of MMR vaccine [16]. This may be attributable to seronegative status of Chinese infants at baseline compared to Indian infants and the interference of persistent maternal antibodies with vaccine induced antibodies [14,16]. We found that, compared to Measles, sero-protection rate was high (94.3%) against Rubella in this BE-MR combination vaccine. Similar trend (96% sero-protection rate) was observed in comparator vaccine (SII MR-Vac™). This indicates that there may be limited interference by maternal antibodies before one year of age in the uptake of Rubella

vaccine. It was evident from several studies that, after first dose of combination vaccine (MR or MMR), more than 90% of infants were sero-protected against Rubella [14,15,17–19]. Our study, along with others studies have reported effective sero-protection against Rubella with only single dose vaccine administration. This may have greater impact on eliminating Rubella, provided high coverage is achieved.

Despite the availability of a safe and cost effective MR vaccine, global immunization coverage remains suboptimal, notably in high risk settings. In 2021, there were an estimated 128,000 measles deaths worldwide, mostly among under vaccinated or unvaccinated children [20]. The vaccination coverage for MR vaccine reduced by approximately by 10% in 2020 when compared to 2019 [8]. As per the WHO report, in 2022, around 22 million infants missed to receive at least one dose of the Measles vaccine through routine immunization. Bridging this gap can be achieved by introducing additional safe and effective vaccines, akin to those already in use, thus enhancing vaccine coverage and mitigate supply chain disruptions which in turn will help to prevent immunity gaps particularly among children under the age of 5.

In countries where incidence and mortality from Measles are high in the first year of life, manufacturers recommend that vaccination be initiated at 9 months or shortly thereafter. In this study, data was reported after single dose of MR vaccine for infants between 9 and 12 months of age. Studies have reported that after second dose of MR vaccine, Measles sero-protection achieved in almost all infants [12,21]. However, long-term sero-protection, studied at 9–12 years of age, declined even after administration of two doses of MR vaccine [16,22]. It is important to note that although the levels of anti-Measles-virus antibodies may diminish over time, the ability to rapidly mount secondary humoral and cellular immune responses ensures protection from infection. So, continuous and careful monitoring and strategy on deciding dosing schedule may play an important role in offering protection and eliminating Measles and Rubella.

Overall, in this study, we demonstrated that BE-MR vaccine administered as a single dose in infants below one year of age offers sero-protection against both Measles and Rubella in large majority of vaccinated subjects and the vaccine is safe and tolerable. Additional studies will further clarify, whether vaccine can induce sero-protection in immunocompromised infants and if sero-protection can be sustained in the long-term.

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Authors' contribution

All authors met the ICMJE criteria for authorship and were responsible for conception and design of the research, acquisition of data, and its analysis. All the authors were involved in revising the manuscript critically for important intellectual content, and approved the final manuscript.

Data sharing agreement

Study data presented in the manuscript can be made available upon request and addressed to the corresponding author Dr. Subhash Thuluva at his email: subhash.thuluva@biologicale.com.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Employees of Biological E Limited do not have any stock options or incentives.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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