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Evolution of the *Bacillus Calmette-Guérin* scar *Russia* and *Moreau* strains in newborns: A brazilian cohort

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ABSTRACT

Background: In Brazil, in 1925, the *Moreau* strain was introduced, and since its implementation, it has been the routine vaccine for health services. Since 2013, many countries, including Brazil, have been experiencing problems with the production of vaccines. As of January 2018, the country started to use the BCG vaccine with *Russia* strain, developed by the Serum Institute India.
Objective: To describe the evolution of the vaccine scar in neonates vaccinated by BCG-*Russia* compared to BCG-*Moreau*.
Methods: This was a cohort study was conducted in Salvador city, northeast Brazil. The study population consisted of newborns from the reference maternity hospital, who were vaccinated with BCG-ID strains *Moreau* or *Russia*, followed up to assess vaccine lesion evolution.
Results: It was observed that regardless of the vaccine strains, the evolution of the lesion was the same: wheal, reddish macula, induration, pustule, ulcer, and scar. The proportion of vaccine scar in the group vaccinated with BCG *Russia* was lower than that of BCG *Moreau*, 62.5 % and 90.9 %, respectively, with a statistically significant difference.
Conclusion: The evolution of the scar by BCG-*Russia* was similar to the Moreau scar, however different proportions were observed in different stages of lesion between the groups.

Background

Bacillus Calmette-Guérin (BCG) is derived from the *Mycobacterium bovis* strain and has been used since 1924 [1]. It is one of the priority strategies in several countries to control morbidity and mortality from severe forms of Tuberculosis in children [2–4]. In Brazil, BCG is part of the routine of the National Immunization Program, it became mandatory in 1973, it is recommended at birth, applied intradermally, before the age of 5 years.

The number of children (less than15 years) who became infected with tuberculosis in 2019 is estimated at 1.2 million [5]. In the same year, in Brazil, 1.646 new cases were reported in children under 10 years of age, with 39 cases of miliary and meningitis TB in children under 5 years of age. Annual trends in the epidemiological indicators in Brazil showed an increasing incidence rate of TB from 4.2 per 100.000 inhabitants in 2010 to 5.7 per 100.000 inhabitants in 2019, in children under 10 years of age [6]. Despite the increase, the high Neonatal BCG vaccine coverage has contributed with the control of severe forms of the disease in the target public.

Several strains of BCG are used around the world. In Brazil, in 1925, the *Moreau* strain was introduced, and since its implementation, it has been the routine vaccine for health services [7]. It is already known in the literature that the BCG-*Moreau* vaccine has the ability to induce a local reaction, with ulcer formation and permanent scarring in the region of vaccination [8]. Although not all newborns develop scars, the Brazilian strain has a high scar prevalence

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around 83–84% [9], and is considered an acceptable indicator of past vaccination by BCG [10,11].

Since 2013, many countries, including Brazil, have been experiencing problems with the production of vaccines and limited options for supplier laboratories, making it a challenge to supply states and municipalities [12–15]. As of January 2018, the country started to use the *Russia* strain, developed by the Serum Institute India, in the routine of health services.

Although the BCG *Moreau* and *Russia* vaccine strains come from the same genetic grouping (“early group”) [16], they have different characteristics regarding the number of viable bacilli per milliliter, dosage, and administration technology [8,11]. The evolution of the vaccine scar of BCG-*Russia* and comparison with BCG-*Moreau* has not yet been demonstrated. The objective of the present study was to describe the evolution of the vaccine scar in neonates vaccinated by BCG-*Russia* compared to BCG-*Moreau*.

Methods

Design and study population

This study was conducted in Brazil, in the state of Bahia. The study population consisted of newborns from the reference maternity hospital in Salvador, who were vaccinated with BCG-ID strains *Moreau* or *Russia*, and followed up to assess the evolution of the vaccine lesion.

The cohort comprised 542 newborns. Those vaccinated by BCG-*Moreau* were allocated to group 1 and by BCG-*Russia* to group 2. The administration of vaccines was alternated during the week, one day *BCG-Russia* was applied and the next day *BCG-Moreau*, considering the time of validity of the vaccine, and the routine established by the health service. The preparation and application of the immunobiological were performed by the same nursing technician at the health service. All vaccinations were administered via the intradermal route in the left upper arm with 0.1 mL containing $2x10^5$ CFU/mL of BCG-*Moreau* or 0.05 mL containing $2x10^5$ to $8x10^5$ CFU/mL of BCG-*Russia*.

The evolution of the post-vaccination lesion was performed weekly by nursing technicians, based on home visits between 19 November 2018 and 12 August 2020. They were selected to fieldwork-based on their experience with vaccination and were trained by the project team.

The study included newborns: full-term (live births between the 38th and 41st week of gestation), without genetic or other pathologies, complying with the contraindication criteria, and vaccinated up to the first eight days of life.

Data collection and variables

The newborns were evaluated at the time of vaccine application (week 0) and followed from the first to the twenty-fourth week after vaccination. Follow-up was suspended when vaccine scar was formed, regardless of the week. A standardized questionnaire containing the individual identification block, maternal, immunobiological administration, and child data was used.

The following variables were collected at week 0 In the children’s data block: name, date of birth, age, date of vaccine application, application site, vaccine batch, type and size of lesion presented at the time of vaccination, validity, sex, race/color, weight, length, use of medication. Subsequent weeks: signs and symptoms of adverse reaction, type, and size of the post-vaccination lesion, inspection and palpation of the application site and axillary regions. In the evolution of the lesion, the presence of erythema, induration, pustule, crust, and scar was observed over time for both vaccine strains.

The evaluation was carried out by identifying the stage and measurement of the lesion. Cohen's Kappa coefficient (K) was used as a measure of inter-rater agreement. Disagreements were resolved by consulting a third reviewer (trained nurse) for judgment.

Sample size

To estimate the sample size, the number of live births born in hospitals in Salvador was surveyed, through the Information System on Live Births (SINASC), excluding those born at home or other health establishments. About 35.000 children per year were registered. Differences in scar prevalence were considered for each vaccine strain, 52% for BCG-*Russia* and 85% for BCG-*Moreau*, according to the literature, 99% power, 95% significance, requiring 520 children to be recruited.

Statistical analysis

First, descriptive analysis was performed using absolute and relative frequencies, means, and standard deviations of the study variables (characteristics of the vaccinated children and stage of the vaccine lesion) between the BCG-*Moreau* and BCG-*Russia* groups. Hypothesis testing to compare proportions was calculated and the Student *t*-test was used to compare means between groups. The association between the vaccine strain and the occurrence of scarring was verified using Pearson’s statistics. The data were stored and analyzed using the Stata software program, version 13.0.

Ethics statement

The study was approved by the Health Research Ethical Committee, Institute Research for Collective Health of the Federal University of Bahia, Salvador, Brazil (number 2.662.971). The parents or children’s guardians were informed verbally about the research objectives, risks, and benefits, procedures to be followed in these cases, the monitoring of the evolution of the vaccine scar, and contact with the study team. They were asked to attest to their agreement with the study by signing the Informed Consent Term. The participation was completely voluntary and confidential, ensuring the possibility of refusing to participate in the project, without prejudice to the assistance of the newborn or his/her companions.

Results

A total of 542 newborns were recruited, 154 (29%) vaccinated by BGG-*Moreau* and 374 (71%) with BCG-*Russia*, 14 (2.5%) were lost to follow-up. No statistical differences were found for the variables sex, race/color, age, length, weight at birth, post-vaccination reaction (Tables 1 and 2). It was observed that the groups are homogeneous ($p > 0.05$).

In the *Moreau* group, 55.2% were female, 44.8% male; the average age of 3 days and 47.5 cm in length; 3.116 kg; 87% afro descent (declared by the mother as black or brown); 86.4% had a wheal (post-vaccination reaction) with an average size of 5 mm. In the Russia group, 53.1 % were female, 49.4% male; the average age of 3 days and 47.9 cm in length; 3.237 kg; 94.1% of afro descent (declared by the mother as black or brown); 88.5% had a wheal (post-vaccination reaction) with an average size of 5.3 mm (Tables 1 and 2).

In both groups, the following evolution of the post-vaccination lesion was observed: wheal, reddish macula, induration, nodule, ulcer, and scar (Figs. 1 and 2). Nonetheless, there were statistical differences in the proportions of some lesion status when com-

Table 1
Characterization of the study population (categorical variables).

Variables	Strains (N = 528)				*P*
	Moreau (n = 154)		*Russia* (n = 374)		
	n	%	n	%	
Sex					
Female	85	55.1	188	53.1	0.317
Male	69	44.8	185	49.4	
Race/color					
Yellow	2	1.3	0	0	0.027
White	18	11.7	21	5.6	0.016
Indigenous	–	–	–	–	–
Brown	99	64.3	253	67.8	0.432
Black	35	22.7	98	26.3	0.394
Others	0	0	1	0.3	0.520
Post vaccine reaction (week 0)					
Wheal	133	86.4	331	88.5	0.494
Surface nodule (palpable and not visible)	1	0.6	1	0.3	0.516
No reaction	20	13.0	42	11.2	0.569

*hypothesis test for comparing proportions.

Table 2
Characterization of the study population (continuous variables).

Variables	Strains (N = 528) (X ± S)		*p*
	Moreau (n = 154)	*Russia* (n = 374)	
Age (days)	3 ± 1	3 ± 1	0.376
Length (cm)	47.5 ± 5	47.9 ± 3	0.379
Birth weight (g)	3116 ± 627	3237 ± 492	0.068
Reaction mensure (wheal - mm)**	5 ± 2.2	5.3 ± 2.2	0.074

*Student *t* test for independent sample means.
**Kappa = 0,677.

pared between groups. The proportion of vaccine scar in the group vaccinated with BCG-*Russia* was lower than that of BCG-*Moreau*, 62.5% and 90.9%, respectively, with a statistically significant difference. These differences were also observed in the reddish macula, nodule, and ulcer stages. However, for the wheal and induration stages, there were no statistically significant differences between the strains (Table 3).

As for the average size of the scar lesion, there was a difference between the strains, BCG-*Russia* had a smaller scar than BCG-*Moreau*, 4.2 mm (95% CI: 3.8–4.5) and 6.7 mm (95% CI:6.3–7.0), respectively. Differences in mean size were observed at all stages of the lesion, except for the wheel (Table 4).

During the follow-up period, 10 suspected cases of post-vaccination adverse events were reported. Among these, 5 (0.9%) adverse events were confirmed, only 1 (0.2%) case related to BCG-*Russia* and 4 (2.5%) cases related to BCG-*Moreau*. Reactions were classified as local lesions, granuloma was identified in the *Russia* strain, and abscess occurred in the *Moreau* strain. The children were assisted at the special immunobiological reference center of the Federal University of Bahia by pediatricians and an infectious disease specialist and there was no need for tuberculostatic therapy.

Discussion

This is the first study to describe the evolution of the vaccine scar in neonates vaccinated by BCG-*Russia* in Brazilian population. It was observed that regardless of the vaccine strains, the evolution of the lesion was the same: wheal, reddish macula, induration, pustule, ulcer, and scar. The BCG vaccine strains *Russia* and *Moreau* have similar genetic characteristics, an antigenic profile closer to the original strain [16,17]. However, not all children developed a

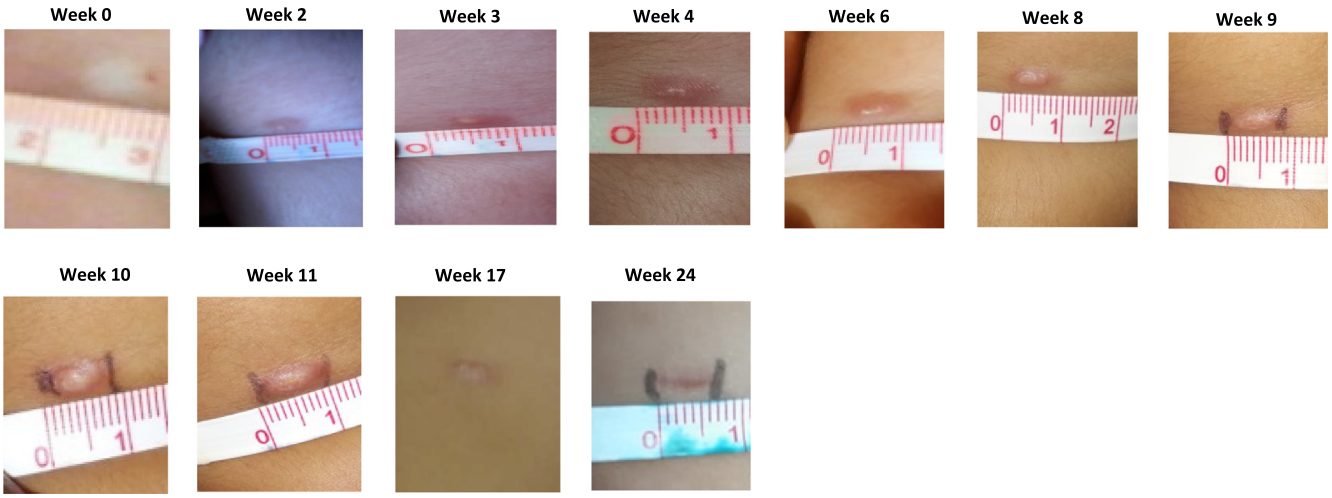

Fig. 1. Description of the evolution of the vaccine scar in newborns by BCG *Moreau* (NB08). NB = newborns.

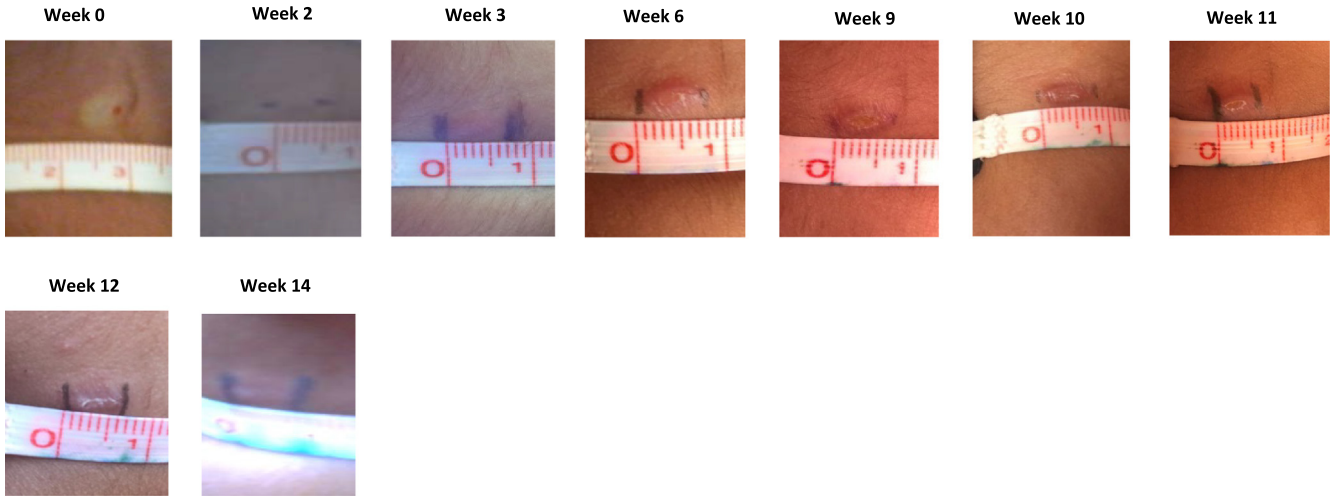

Fig. 2. Description of the evolution of the vaccine scar in newborns by BCG *Russia* (NB03). NB = newborns.

Table 3
Evolution of scar lesion in newborns vaccinated with BCG strains *Russia* and *Moreau*.

Strains	Stages of injury											
	Wheal		Reddish macula		Induration		Nodule		Ulcer		Scar	
	%	X ± S (mm)	%	X ± S (mm)	%	X ± S (mm)	%	X ± S (mm)	%	X ± S (mm)	%	X ± S (mm)
Russia (n = 374)	88.5	5.3 ± 2.2	81.2	4.1 ± 2.1	97.5	6.3 ± 1.7	62.8	4.2 ± 3.4	62.5	4.2 ± 3.4	62.5	4.2 ± 3.4
Moreau (n = 154)	86.4	5 ± 2.2	94.8	5.3 ± 1.5	99.3	7.1 ± 1.1	90.9	6.7 ± 2.3	90.9	6.7 ± 2.3	90.9	6.7 ± 2.3

*t Student test for means of independent samples – papule (t = -1.44); reddish macula (t = 6.33); induration (t = 4.81); nodule (t = 8.33); ulcer (t = 8.36); scar (t = 8.14), p = 0.0000.
**Hypothesis test to compare proportions – reddish macula, nodule, ulcer, scar (p = 0.000); papule (p > 0.494), induration (p > 0.178).

Table 4
Evolution of the BCG vaccine scar from the *Moreau* and *Russia* strains in newborns, according to the mean size of the lesion.

Stages of injury	*Moreau*	*Russia*
	Mean (95% CI)	Mean (95% CI)
Wheal	5.0 (4.6 – 5.3)	5.3 (5.0 – 5.5)
Reddish macula	5.3 (5.0 – 5.5)	4.1 (3.9 – 4.3)
Induration	7.1 (6.9 – 7.2)	6.3 (6.2 – 6.5)
Nodule	6.7 (6.3 – 7.1)	4.2 (3.8 – 4.5)
Ulcer	6.7 (6.3 – 7.1)	4.2 (3.8 – 4.5)
Scar	6.7 (6.3 – 7.0)	4.2 (3.8 – 4.5)

scar. This is a phenomenon known in the literature, with a variation in the prevalence of scarring between 50% and >90% [18,19].

Some factors described that can influence the appearance of the scar: age at vaccination period, technique of immunobiological administration, dose applied, route of administration, vaccine strain, presence of wheal in the first minutes after vaccination, nutritional status, age and gestational maturity at childbirth [20–25].

Despite that BCG-*Russia* vaccine was associated with the scar, the proportion of scars in this group was 62.5%. In Guinea Bissau, a recent study pointed out to a scar prevalence of 52%, observed in BCG-*Russia* vaccinated children in rural areas of the country, and 87% in urban children. This prevalence varied according to sex, place of birth, health region, and maternal ethnicity, among others.

In that study, the difference was attributed to the fact that, in rural areas, the BCG vaccine used was the *Russia* strain. The cohort study of children in urban areas with a higher prevalence of scarring received other strains (BCG-*Merieux*, BCG-*Connaugh,* or BCG-*Danish*) [21,26].

In Uganda, a low prevalence of vaccine scars, around 52.2%, was also observed in children who used the *Russia* strain, and when another strain was used, such as BCG-*Bulgaria* and BCG-*Denmark*, these values rose to 64.1% and 92.6%, respectively. Also induced a significantly less extensive local reaction with a median 2 mm (IQR:1–4 mm) [27].

The BCG-*Moreau* vaccine has a high prevalence of vaccine scarring. In a community trial to evaluate the second dose of BCG vaccine, the prevalence of vaccine scarring found among schoolchildren previously vaccinated at birth with the 1st dose of BCG-*Moreau* vaccine was 83 and 84% in the intervention and control groups [9,28].

Regarding the size of the lesion, BCG-*Russia* induced a smaller local reaction, from the reddish macula to the scar, when compared to BCG-*Moreau.* There was an average scar extension of 4.2 mm and 6.7 mm, respectively.

In the present study, it was identified that the proportion of scars and their extension is influenced by the strain used in the vaccination. Studies mentioned above have also demonstrated this variability between the different strains [29,30].

In another study, a prospective cohort in Guinea Bissau, that assessed factors determining scar, children vaccinated by BCG-*Russia* had a higher risk of non-scarring when compared to BCG-*Danish*. The absence of post-vaccination wheal or wheal size of less than 3 mm was associated with absence of scarring when compared to children with the greater extension of the post-vaccination lesion. When evaluating children's nutritional and socioeconomic factors, no association with the absence of scar was observed [22].

In Denmark, a randomized study conducted to assess the impact of the BCG-*Danish* vaccination technique on scar development in a high-income environment, observed that 87% had a wheal

after vaccination, 11% had a bulge, and 2% had no reaction. The mean wheal size was 3.8 mm. In infants with a wheel, the probability of developing a scar was 96%, declining to 87% in the case of a bulge, and to 56 % in the case of no reaction. Wheal size was positively correlated with the probability of getting a scar and scar size [23]. These results are similar to those found in our study regarding the proportion of papules and lesion size between the *Russia* and *Moreau* strains.

The presence of a scar is no guarantee of immunity, however, some studies that compared children with and without scars and their association with general, specifics (respiratory symptoms) and infant mortality and morbidity pointed out to a reduction in hospitalization, deaths, and better child survival with a positive scar in the first years of life [19–21,29].

Stoogard et al., suggests that the association between scarring and mortality indicators may reflect the host's immunological characteristics before BCG vaccination, that is, infants with impaired or immature immune systems may fail to form a scar after BCG vaccination and also fail to fight the infection [21]. It is also highlighted that formation of a scar, results from a short period of BCG replication at the injection site and represents the accompanying inflammatory process [19].

One of the limitations of the present study may have been the technique of applying the vaccine. There were two vaccinating techniques, however, to reduce bias, we performed training with both and validated the correct vaccination under the supervision of a nurse who has been experienced with BCG for many years. The evaluation of the lesion evolution and measurement was verified by pairs (independents) of evaluators under frequent supervision of the project team, to minimize errors in the classification and measurement of the local reaction.

Conclusion

The evolution of the scar by BCG-*Russia* was similar to the *Moreau* scar, however with different proportions to the stages of the lesion between the groups. The *Russia* strain had less severe skin lesions, a lower incidence of adverse events when compared to the *Moreau* group. This finding is an important analyzer regarding the efficacy and safety of the vaccine in the Brazilian population. Other studies need to be carried out to increase knowledge about the mechanisms involved in scarring and whether this indicator has an influence on vaccine efficacy, and consequently, on tuberculosis morbidity and mortality.

Contributors:

R.A. Souza participated in conceptualization, data curation, investigation, methodology, formal analysis, project administration, supervision and wrote original draft, review and editing. F.R. Barreto contributed to the project administration, formal analysis and reviewed the manuscript. M. Natividade and J.S. Nery reviewed the manuscript. C.A.S. Teles supported the writing of the methodology, formal analysis and reviewed the manuscript. C.C.O.J. Lima contributed to project administration. I.S. Castelo performed data curation. J.A.F. de Andrade performed to training the field team, assisting children,qualifying the project and reviewed the manuscript. M.L. Barreto contributed to the writing of the project and review the manuscript. S.M. Pereira conceptualised the study, performed formal analysis, project administration, supervision and review the manuscript.

Data availability

Data will be made available on request.

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.

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