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Head-to-head immunogenicity comparison of Edmonston-Zagreb vs. AIK-C measles vaccine strains in infants aged 8–12 months: A randomized clinical trial

Shahrokh Izadi [a,*], Seyed Mohsen Zahraei [b], Masoud Salehi [c], Mahdi Mohammadi [a], Seyed Mehdi Tabatabaei [a], Talat Mokhtari-Azad [d]

[a] Health Promotion Research Centre, School of Public Health, Zahedan University of Medical Sciences, Zahedan, Iran
[b] Centre for Communicable Diseases Control, Ministry of Health and Medical Education, Tehran, Iran
[c] Research Center for Infectious Disease and Tropical Medicine, Zahedan University of Medical Sciences, Zahedan, Iran
[d] National Reference Laboratory for Measles and Rubella, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Background: A non-inferiority multi-centre parallel randomized double-blind trial was implemented in Zahedan district, Sistan-va-Baluchestan province, Iran, to compare the performance of the two measles vaccines which are in use in the National Immunization Programme of Iran and are of two different measles virus vaccine strains: Edmonston-Zagreb (EZ) strain vs. AIK-C strain. The main outcome measure was appearance of anti-measles antibody in sera.

Methods: 200 infants, 8–12 months old, whose parents consented for their children to be included in the study, were randomized in permutation blocks of size 4–8 in four Urban Health Clinics. Having given a pre-vaccination blood sample, they received measles-rubella vaccine containing one of the vaccine strains mentioned before. After 60 days, the second blood sample was taken. The sera of the pre- and post-vaccination blood samples were tested for anti-measles antibodies in the National Reference Measles Laboratory. Parents, laboratory technicians and statistician were blind to groupings.

Results: Of the 200 children equally randomized in the two arms, 185 who were seronegative before vaccination (88 in the EZ arm and 97 in the AIK-C arm) were entered in the final analysis. The seroconversion rate in the EZ arm was 76.1% (95% CI: 60.2–85.2%), and that in the AIK-C arm was 58.7%; (95% CI: 48.8–68.7%). The absolute rate difference was 17. 4% (4.1–30.9%; P-value: .012), and the relative seroconversion rate of EZ to AIK-C was 1.3 (95% CI: 1.1–1.6; P-value: .012). No adverse events were reported during the study period.

Conclusion: A considerable difference in the seropositivity of different measles containing vaccines could be demonstrated in the first year of life.

Trial Registration: Iranian Registry of Clinical Trials Registration Number: IRCT2016032827144N1; May 10, 2016 (www.who.int/ictrp/network/irct/en/)

1. Introduction

Measles as one of the most contagious viral diseases, with the largest basic reproductive number ever known (about 20) and having a number of different vaccines produced by different laboratories around the world, remains an important preventable childhood disease. Most measles vaccines originate from the Edmonston strain of measles virus, including the EZ[1] strain and the AIK-C[2] strains that are in common use in Iran's immunization program [1,2]. The first one is the product of Serum Institute of India (SII), and the second one is produced domestically in Razi Institute of Serum and Vaccine Production (RIS). AIK-C strain was the first live attenuated measles virus strain whose complete genomic sequence was published and the Edmonston-Zagreb strain is the most

* Corresponding author at: P.O. Box: 98155-759, Zahedan, Iran.
E-mail addresses: izadish@zaums.ac.ir (S. Izadi), zahraeicdc@yahoo.com (S.M. Zahraei), salehishahestan@zaums.ac.ir (M. Salehi), memohammadi@yahoo.com (M. Mohammadi), dr_smt2001@yahoo.com (S.M. Tabatabaei), mokhtari@hotmail.com (T. Mokhtari-Azad).

[1] Edmonston-Zagreb.
[2] A: America, I: Iran, K: The Kitasato Institute, and C: virus adapted to chick-embryo cells.

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commonly used measles vaccine in the immunization programmes of the WHO. Both these virus strains have been developed from the Edmonston strain [3].

Since 2009, measles outbreaks have occurred in a gradually increasing trend in several parts of Iran [4,5]. Within the past decade, the measles elimination campaign in Iran has witnessed different levels of performance. A number of outbreaks were prevalent in the period of 2009–2014, and microcirculations were undermining the faith in the effectiveness of the immunization activities against measles [5–10].

To constrain an outbreak, the health system sometimes uses the imported measles vaccine SII and sometimes the products of RIS. In these activities, the target population is usually composed of a wide age range, from 6 months to 12 years [5,6,9,11].

The main objective of the present study was to compare the effectiveness of both types of vaccines, which are in common use in outbreak response immunization activities in Iran. The effectiveness of these vaccines has been evaluated in infants under 9 months of age in several studies; however, for the older age groups up to 12 months of age, the health authorities are seeking the best choice between the two vaccine types [12–14]. Hence, a randomized clinical trial was implemented in Zahedan, the capital city of Sistan-va-Baluchestan Province of Iran.

2. Methods

2.1. Trial design

A multicentre double blind randomized non inferiority equally balanced parallel controlled trial, comparing measles vaccine strain AIK-C with EZ strain in 8-to-12-month children, was implemented in four Urban Health Clinics in Zahedan, the capital city of Sistan-va-Baluchestan Province of Iran, during spring and summer 2016.

2.2. Participants

All infants aged between 8 and 12 months being brought to the health clinics involved in the study for immunizing purposes were examined; and if eligible, they were invited for participating in the study. The inclusion criteria for the participants were: (a) being in the age range 8–12 months (240 days to 12 months and 30 days); (b) having no contraindication for receiving measles containing vaccines; (c) negative history of receiving any kind of measles containing vaccine; (d) feasibility of blood sampling from the physical and medical points of view; (e) being permanent residents of Zahedan City; (f) being Iranian; Pakistani, Afghan refugees or travellers from other districts were not invited to be included in the study.

2.3. Interventions

After an interview in the local language by a health expert about the study and its objectives, if the infant's parent or guardian consented for their child to be included in the study, they were asked to sign a written consent form. A questionnaire containing questions about participants' demographic characteristics and history of previous vaccinations and exanthematic diseases were filled out for them. Questionnaire comprised participants' birth weight, mother's age, age at the beginning of supplementary food, mother and father's level of education, and anthropometric measurements, as well as their full contact information including phone numbers and addresses. Blood sample was taken before vaccination and 60 days after vaccination. The parents were instructed about the possible adverse effects of the vaccines. They were also advised that upon occurrence of any unexpected events, they should return to the same health centre both for treatment and for the event to be recorded in the study checklists. After blood sampling, each participant's allocation packet was opened, and vaccination with the defined vaccine was done. The packet and the allocation paper were pinned as attachments to the participant's questionnaire.

2.4. Vaccines characteristics

The participants in both arms of the study were vaccinated with a bivalent measles/rubella vaccine (that is in common use in outbreak containment activities in Iran). The vaccines used in this study had either been produced domestically by Razi Vaccine and Serum Research Institute (Batch Numbers: 01694016 and 01594026) or were the products of Serum Institute of India (Batch Numbers: 012N5011A and 012N5013) imported from India. The measles component of the domestically produced vaccine was an attenuated AIK-C strain of live measles virus propagated in human diploid cells, known as AIC-HDC strain, while the virus strain used in the imported vaccine was the Edmonston-Zagreb (EZ) strain, also produced in human diploid cells. The vaccines were injected subcutaneously in anterolateral aspect of the thigh, using standard needles 16 mm in length.

The imported vaccines were packed in five-dose vials and the domestically produced vaccines in 10-dose vials. The vaccines used in the study were brought from the vaccine depot of the Ministry of Health from Tehran with the same vaccine carrier vehicle, and they were stored in the same vaccine storage system in the Province Health Centre. The vaccines were distributed to the four cooperating health centres using the same vaccine carriers by the same health staff on the first day of the study. Cold chain in the health clinic were checked by both the study supervisor and the physician in charge of each health clinic.

2.5. Outcomes

The primary outcome measure was the detection of IgG-anti-measles antibody 60 days after vaccine inoculation, using ELISA technique.

2.6. Sample size calculations

Regarding a reported seroconversion rate of 80–95% (effect size equal to 0.15) and considering type-one error equal to 0.05 and type-two error equal to 0.20, the sample size for each arm of the study was calculated as 76 persons. Considering an estimated lost to follow-up rate of about 25%, the sample size for each arm was increased to 100, which was equally distributed among the four Urban Health Clinics involved in the study.

2.7. Randomization

After obtaining the informed consent (as described above), filling the questionnaire and doing the first blood sampling, the participants were randomly assigned, in a 1:1 ratio in order to receive either the AIK-C vaccine or the one containing EZ strain. Randomization was balanced with stratification according to the four health clinics. The names of the vaccine producers had been printed on small papers, placed in opaque packets and arranged based on computer generated permutation blocks of 8, 6 and 4 (produced by the first author). In order to prevent any disarrangement of the packets, in addition to printing the row number of the packets on them, they were threaded using a strong string; and in order to prevent reading the contents of the packets by keeping them against a strong light source, a layer of aluminium foil was placed inside each packet. On the participants' blood and sera tubes, only the row number and the participants' names had been

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