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# Immunogenicity and safety of measles-mumps-rubella vaccine delivered by disposable-syringe jet injector in India: A randomized, parallel group, non-inferiority trial

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ABSTRACT

*Background:* We conducted a randomized, non-inferiority, clinical study of MMR vaccine by a disposable-syringe jet injector (DSJI) in toddlers in India in comparison with the conventional administration.
*Methods:* MMR vaccine was administered subcutaneously by DSJI or needle-syringe (N-S) to toddlers (15–18 months) who had received a measles vaccine at 9 months. Seropositivity to measles, mumps, and rubella serum IgG antibodies was assessed 35 days after vaccination. Non-inferiority was concluded if the upper limit of the 95% CI for the difference in the percent of seropositive between groups was less than 10%. Solicited reactions were collected for 14 days after vaccination by using structured diaries.
*Results:* In each study group, 170 subjects received MMR vaccine. On day 35, seropositivity for measles was 97.5% [95% CI (93.8%, 99.3%)] in the DSJI group and 98.7% [95% CI (95.5%, 99.8%)] in the N-S group; for mumps, 98.8% [95% CI (95.6%, 99.8%)] and 98.7% [95% CI (95.5%, 99.8%)]; and for rubella, 98.8% [95% CI (95.6%, 99.8%)] and 100% [95% CI (97.7%, 100.0%)]; none of the differences were significant. The day 35 post-vaccination GMTs in DSJI and N-S groups were measles: 5.48 IU/ml [95% CI (3.71, 8.11)] and 5.94 IU/ml [95% CI (3.92, 9.01)], mumps: 3.83 ISR [95% CI (3.53, 4.14)] and 3.66 ISR [95% CI (3.39, 3.95)] and rubella: 95.27 IU/ml [95% CI (70.39, 128.95)] and 107.06 IU/ml [95% CI (79.02, 145.06)]; none of the differences were significant.
The DSJI group reported 173 solicited local reactions and the N-S group reported 112; most were mild grade. Of the total of 156 solicited systemic adverse events, most were mild, and incidence between the two groups was similar.
*Conclusions:* MMR vaccination via DSJI is as immunogenic as vaccination by N-S. Safety profile of DSJI method is similar to N-S except for injection site reactions which are more with DSJI and are well-tolerated.
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## 1. Introduction

Worldwide, measles caused 89,780 deaths in 2016, mostly among children under age five [1]. Rubella is generally a mild viral infection in children, but in pregnant women it may cause fetal

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death or severe congenital defects [2]. As a result, the World Health Organization (WHO) recommends measles and rubella vaccines for all the children in the world [3]. In 2012, several global agencies led by the WHO set the goal of eliminating measles and rubella in at least five WHO regions by 2020 [4]. Currently, global measles immunization coverage is at 85%, but, to achieve elimination, at least 95% coverage with two doses of vaccine is required [5]. Though measles vaccine is used universally, in many developing countries, vaccines against mumps and rubella are not used in immunization programs.

Measles-mumps-rubella (MMR) vaccine generally is administered as a subcutaneous injection with needle and syringe (N-S). However, vaccine delivery with needles can cause needle-stick injuries and cross-infection, and it also creates dangerous sharps waste in communities. N-S delivery also complicates the logistics of immunization campaigns, since the requirement for proper sharps disposal can limit their reach and coverage. An alternative to N-S for vaccine delivery is the jet injector, a device that creates a fine stream of pressurized liquid that penetrates the skin to deposit vaccine without using a needle [6].

Disposable-syringe jet injectors (DSJIs) that use a sterile, single-dose, disposable syringe for each patient were introduced in the 1990s, and a number of models have been approved in the United States and Europe for different uses, including vaccinations [6].

The risks associated with DSJI use include failure to deliver the correct dose; pain, bleeding, or swelling at the injection site; and user error in positioning the injector to deliver the dose to the correct layer of tissue—however, most of these risks also apply to vaccination by N-S [7].

Vaccination by jet injection has been shown to induce immunity similar to that provided by N-S injection and to have a similar safety profile for a number of vaccines, including typhoid, cholera, smallpox, hepatitis A and B, influenza, whole cell pertussis-diphtheria-tetanus, polio, yellow fever, and tetanus. [6] A previous study comparing a DSJI with N-S for administering MMR vaccine several years ago met the requirement for rubella but failed to demonstrate non-inferiority of the DSJI to N-S for the measles and mumps vaccines [8]. However, that study used a different jet injector than the one used in the present study as well as a vaccine from a different manufacturer.

We conducted a phase IV, randomized, observer-blind, non-inferiority, parallel-group, multicentric clinical study of MMR vaccination in infants in India to compare immunogenicity and safety of the vaccine when administered by a DSJI to administration by conventional N-S method. A result of non-inferiority for the DSJI would support use of vaccination with a jet injector, offering a needle-free alternative for country immunization programs.

## 2. Methods and materials

The study sponsor was the Serum Institute of India Pvt. Ltd. (SIIPL, Pune, India). DiagnoSearch Life Sciences (Mumbai, India) was delegated by the sponsor for site monitoring, project management, clinical data management, and statistical analysis of the data. Approvals were obtained from the Drug Controller General of India, the institutional ethics committees of all study centers, and the Western Institutional Review Board in the United States. The study was carried out in accordance with the Declaration of Helsinki and the ICH Harmonized Tripartite Guideline for GCP (E6) 1996; the GCP Guidelines in India; and the Ethical Guidelines for Biomedical Research on Human Subjects, issued by Indian Council of Medical Research in 2006.

### 2.1. Vaccine

MMR vaccine (SIIPL, India) was used in the study. It is presented as a single-dose of lyophilized vaccine and is provided with a sterile diluent (0.5 ml of water for injection) in a separate container. The vaccine is reconstituted by adding the diluent to the vial containing the lyophilized pellet. A single dose of 0.5 ml contains live attenuated strains of Edmonston-Zagreb measles virus (not less than 1000 CCID50), Leningrad-Zagreb mumps virus (not less than 5000 CCID50), and Wistar RA 27/3 rubella virus (not less than 1000 CCID50). The same batch of the vaccine (MMR batch 013N4017A expiry May2016 and diluent batch 064Q40330Z expiry April 2016) was used throughout the study. It was stored at 2–8 °C. The dose was 0.5 ml by both delivery methods.

### 2.2. Injection devices

The investigational product for this study was the MMR vaccine administered subcutaneously by the Stratis DSJI (PharmaJet, Golden, Colorado, USA) (Fig. 1). This device is licensed for use in the United States and in the European Economic Area; it is also prequalified by WHO [9,10.11]. The Stratis needle-free injection system delivers 0.5 ml fluid volumes either intramuscularly or subcutaneously by means of a precise narrow fluid stream, which penetrates the skin in about a 1/10th of a second and delivers the medicine or vaccine into the body. Energy to propel the fluid is supplied by a hand-held, spring-powered injector, designed to be reused a minimum of 20,000 times. A disposable syringe containing medicine or vaccine is attached to the injector and placed in contact with the patient's skin. The fluid is then expelled through a very small orifice in the face of the syringe.[10] The batch numbers for the Stratis devices used in the study were 25854275 and 23436455. The reference product was the same MMR vaccine administered subcutaneously via N-S.

### 2.3. Study populations and settings

The study was conducted at six sites across India from September 2014 through December 2015. Eligible participants were healthy children aged 15–18 months who had received a measles vaccine at 9 months of age. Children with a past history of measles, mumps, or rubella infection; significant abnormality; any neoplasm or blood disorder; or a history of allergy to any of the vaccine components and those who had previously received the MMR vaccine were not eligible. After written informed consent from their parents, 5 ml blood was drawn for immunogenicity testing from eligible subjects, and the MMR vaccine was administered


**Fig. 1.** Stratis SC/IM (0.5 ml fixed dose).

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