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ORIGINAL RESEARCH

Comparative Immunogenicity and Safety of Measles-Mumps-Rubella Vaccine When Administered Using Needle Free Injection System to That with Conventional Needle-Syringe in India: A Randomized, Parallel Group Study

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Introduction: Pain due to injection and fear of needles is documented barriers to vaccination in children. Needle-Free Injection System ie N-FIS®, is an innovative delivery solution that addresses these limitations. To demonstrate its performance, study was conducted to compare immunogenicity and safety of the MMR vaccine when administered by N-FIS, to that administered using needle-syringe and needle.

Methodology: This was a prospective, randomized, parallel group study (January–September 2024). Eligible participants 9–12 months of age were administered MMR vaccine 0.5 mL, subcutaneously using either N-FIS® or syringe. Immunogenicity and safety were assessed before and 28 days post vaccination.

Results: A total of 60 infants with mean age of 10.5 months were enrolled in the study. At 28 day post dose 1 there was a significant and comparable rise in the MMR GMTs between the two groups. Similarly, at 28 day post vaccination, there was a significant rise in the proportions of seropositive subjects and the rates were comparable between the two groups (Measles: 100% vs 83%, p = 0.046; Mumps: 96.1% vs 95.8%, p = 0.999, Rubella: 92.3% vs 100%, p = 0.491). N-FIS was well tolerated and significantly lower number of subjects experienced pain (12% with N-FIS vs 33% with syringe). No serious or severe adverse events were reported.

Conclusion: Administration of MMR vaccine using N-FIS induced robust and comparable immune responses to that observed with use of Needle-syringe and was well tolerated providing an alternative to paediatrician over conventional delivery system.

Keywords: needle free injection system, immunogenicity, measles, mumps, rubella

Introduction

Immunization is an integral strategy of child's primary healthcare and one of the most cost-effective interventions, averting an estimated 4.4 million deaths yearly. Thus, there is a need to ensure that no child is left behind without the benefits of vaccination.[1] Despite effective vaccines being available, a significant portion of children remain unvaccinated, leaving them vulnerable to preventable diseases, particularly in low- and middle-income countries.[2] For example, effective vaccines are available for measles-mumps-rubella (MMR), still they continue to remain a major cause of morbidity and mortality worldwide. In 2023, there were over 10.3 million measles cases, 20% higher than that reported in 2022; and more than 0.1 million deaths.[3,4] It is one of the most contagious diseases and requires maintaining high population immunity to prevent outbreaks. In 2023, the global mean coverage for two-dose measles vaccination was 65.3. These figures fall short of the 95% coverage needed to prevent outbreaks, reduce deaths, and achieve elimination

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goals.[5] Similarly, congenital rubella syndrome (CRS), clinical manifestations of which include growth retardation, cardiac defects, cataracts, and hearing impairment, is one of the most devastating congenital infections caused by rubella virus. Over 0.1 million babies are born with CRS every year causing a significant burden on the affected individuals and on healthcare systems.[6] Further, the burden of mumps remains high in countries like India which do not offer routine mumps vaccination but is considered as an insignificant public health problem due to lack of data.[7]

MMR is a live-attenuated vaccine that offers protection against these life-threatening diseases and across the globe it is administered to children with needle and syringe (N-S). However, use of injections for vaccine delivery with needles is known to be associated with needle-stick injuries (NSI), needle phobia, pain and distress leading to poor compliance.[8] Injection pain and fear of needles are documented barriers to vaccination in children, prevalence of which ranges from 5–13% in a general paediatric population and 8–28% in an under-vaccinated population.[9] Since concerns about pain and fear are common, there is a need for an alternative delivery system that can help in overcoming these limitations and improve compliance by overcoming vaccine hesitancy.

An important innovation in this direction is the advent of needle free injection system that offers an alternative to N-S for vaccine delivery. Vaccination by this technology has been shown to induce immunity comparable to that provided by N-S injection and have a similar safety profile (eg typhoid, hepatitis A and B, influenza, diphtheria-tetanus-pertussis, polio, yellow fever, etc).[10] Policy makers and healthcare professionals are encouraged to use these data to support integration of evidence-based interventions and remove barrier to vaccination.

IntegriMedical has developed Needle-Free Injection System ie N-FIS®, an innovative drug delivery technology designed to minimize pain during administration and provide a more comfortable, and stress-free experience for individuals, including those with needle phobia. It is designed to administer drugs and biologics through intramuscular and subcutaneous route and delivers up to 0.5 mL of liquid medication under the skin, in less than 1/10th of a second giving precise performance. N-FIS® utilizes high-velocity jet stream using mechanical power to effectively and consistently administer the biologics and drugs. The device is powered by a compressed spring which, when released, propels the plunger forward to deliver the medication at high speed, thus penetrating the skin. N-FIS has received regulatory approval for manufacturing and sale in India as well as CE approval for sale in Europe.[11,12] The authors conducted a randomized, parallel-group study to compare immunogenicity and safety of the MMR vaccine when administered by an N-FIS to administration by conventional N-S method. Results from this will help the use of N-FIS for MMR vaccination.

Materials and Methods

This was a prospective, randomized, single-centre, open label, parallel group study conducted in infants 9–12 months of age at Ruby Hall Clinic, Pune, India, from January 2024 to September 2024 (Clinical Trials Registry India Number CTRI/2024/01/061633). The study protocol was approved by the Institutional Ethics Committee of Ruby Hall Clinic ie Poona Medical Research Foundation, Pune, India. The study was conducted in accordance with the principles of Good Clinical Practice (GCP) and the current version of the Declaration of Helsinki, Indian Council of Medical Research Ethical Guidelines for Biomedical Research on Human patients and applicable regulatory guidelines. An informed consent form was signed by each participant's parents or legally acceptable representatives before enrolment into the study.

Study Population

The study population comprised healthy infants aged 9–12 months of either gender. Subjects were excluded from the study if they had history of previous MMR vaccination or exposed to these diseases, or received systemic immunosuppressive medications or cytotoxic medications within the 4 weeks prior to enrolment or blood products within 16 weeks prior to enrolment. History of allergy likely to be aggravated by any of the vaccine components, neurological disease/seizures, chronic illness or family history of immunodeficiency, or symptoms of acute illness at the time of enrolment were other reasons for exclusion.

Subjects meeting eligibility criteria were randomized in blocks of two to ensure balanced allocation, with the order of vaccine administration determined by a pre-specified randomization schedule and each subject assigned a unique

randomization code. A total of 60 eligible subjects were randomized to receive MMR vaccine subcutaneously in anterolateral aspect of the thigh (Tresivac® manufactured and marketed by Serum Institute of India; prepared from live attenuated strains of Edmonston-Zagreb Measles virus, L-Zagreb Mumps virus and Wistar RA 27/3 Rubella virus) administered with either N-FIS or conventional N-S in 1:1 ratio.

Immunogenicity Assessment

Blood samples were collected at pre-vaccination and 28 days after dose 1. Measles and mumps IgG were measured using indirect sandwich chemiluminescence immunoassay (Liaison, DiaSorin, Saluggia, Italy) with cut-off values of 16.5 AU/mL and 11 AU/mL, respectively. Rubella IgG was measured using chemiluminescent microparticle immunoassay with cut-off values of 10 IU/mL.

Safety Assessment

The investigator assessed the intensity, duration, and relation of each adverse event during the trial. Parents/guardians used diary cards to record the solicited local symptoms (pain, redness and swelling at the injection site) and general symptoms (fever, rash, and any suspected signs of meningeal irritation, including febrile convulsions) on Day 1 and occurring over 28 days post-vaccination and were transcribed into the case report form.

Unsolicited symptoms and the occurrence of serious adverse events (SAEs) were recorded throughout the study. The intensity of symptoms was graded on a scale of 0–3. Grade 3 solicited symptoms were defined as: pain: the child cried when the limb was moved or a spontaneously painful limb; redness and swelling: injection site surface diameter > 20 mm; fever: temperature > 39°C. Unsolicited symptoms (including SAEs) were defined as grade 3 when they prevented normal daily activity.

Statistical Analysis

A sample size of 60 subjects was selected for this study based on feasibility to obtain data on the performance of the IntegriMedical N-FIS® by comparing the immunogenicity and safety to that obtained with conventional N-S. All the analyses were performed on intention-to-treat set using SPSS version 26.0 (IBM Corp. ARMONK USA) software. An intention-to-treat set included all participants who were randomly assigned to receive vaccine either by N-FIS® or conventional needle, regardless of whether they completed the treatment, adhered to the protocol, or dropped out.

The continuous variables were summarized using mean and standard deviation, whereas categorical variables were expressed as frequencies and percentages. Descriptive statistics were used to summarize baseline characteristics and safety outcomes. For antibodies titres, the geometric mean concentration (GMC) calculations were performed by taking the anti-log of the mean of the log transformations and were presented with 95% CI. The GMCs were compared using paired t-tests, and The seroprotection/seropositivity rates were compared using Fisher's exact test;. Statistical significance was set at $p < 0.05$. For safety analysis, the number and percentage of subjects with at least one local or severe reaction were assessed.

Results

Demographics and Baseline Characteristics

A total of 60 infants were enrolled in the study and randomized. Baseline and demographic characteristics are presented in Table 1. The mean age of participants was ~10.5 months (range 10.6–10.9 months). At baseline, no demographic variations were observed between the study groups in terms of age, height and weight. However, there were more males in the N-S group 50.0%. A total of 10 subjects lost to follow up; 6 in N-FIS and 4 in N-S group. The follow-up data for these subjects could not be obtained because they relocated and were unable to participate in subsequent sessions.

Immunogenicity and Seropositivity/Seroprotection

Across the two vaccination groups, post dose 1 there was a significant rise in the observed GMTs to measles, mumps and rubella from baseline to day 28. GMTs were not significantly different between the two groups (Table 2).

Table 1 Baseline and Demographic Characteristics of Children in Treatment Groups

Characteristic	N-FIS (N = 30)	N-S (N = 30)
Age in months	10.6 ± 0.8	10.9 ± 1.1
Male, n (%)	14 (46.7%)	15 (50.0%)
Female, n (%)	16 (53.3%)	15 (50.0%)
Height, cm	70.36 ± 3.6	68.47 ± 5.1
Weight, kg	7.41 ± 1.1	7.36 ± 1.0

Table 2 Antibody Geometric Mean Titres (GMT) of N-FIS and N-S Groups Pre- and Post-Vaccination

	N-FIS (N = 26)		N-S (N = 24)	
Vaccination	Pre (95% CI)	Post (95% CI)*	Pre (95% CI)	Post (95% CI)*
Measles AU/mL	24.78 (12.92, 47.52)	119.10 (82.06, 172.88)	45.60 (20.69, 102.53)	100.48 (58.86, 171.54)
Mumps AU/mL	34.81 (16.92, 71.74)	103.54 (70.22, 152.67)	33.45 (16.64, 67.23)	115.58 (76.53, 174.56)
Rubella IU/mL	6.30 (1.95, 20.35)	45.15 (28.65, 71.16)	5.47 (1.41, 21.23)	60.95 (47.71, 77.86)

Note: *$p < 0.05$.
Abbreviation: CI, Confidence interval.

Table 3 Seropositivity/Seroprotection Rates of the N-FIS and N-S Groups Pre- and Postvaccination

Parameter	Post Vaccination		p-value
	N-FIS (N = 26)	N-S (N = 24)	
Measles	100.0%	83.3%	0.046
Mumps	96.1%	95.8%	0.999
Rubella	92.3%	100.0%	0.491

There was a significant rise in the proportions of seropositive subjects from baseline to day 28 after dose 1, and the rates were comparable between the two groups. The seropositivity/seroprotection rates ranged from 83.3% to 100.0% for measles, 95.8% to 96.1% for mumps and 92.3% to 100% for rubella (Table 3).

Safety

The N-FIS device used for administration of MMR vaccine was well tolerated comparable to that with N-S. There were no reports of meningeal irritation, febrile convulsions or parotid gland swelling during the 28-day period post vaccination. Significantly lower number of subjects experienced pain with N-FIS (12%, 3/26) compared with N-S (33%, 8/24) at 2 mins post vaccination. The intensity was mild and transient in nature. However, pain persisted in one subject who received vaccine with N-S even at day 28 post vaccination. Further, there were no incidence of serious adverse events nor that of tenderness or erythema/redness in any subjects. No subjects withdrew from the study due to an adverse event. None of the adverse events were assessed by the investigator as causally related to the device.

Discussion

Globally, implementation of measles containing vaccine into immunisation scheme has helped in reducing its cases. In order to achieve its elimination, the immunisation coverage should be >95%.[13] However, in recent years, there has been surge in measles cases, alongside a declining vaccination coverage in many countries; vaccine hesitancy being a substantial contributing factor to it.[14] Historically, N-S are used to administer vaccines that are known to be associated with NSI, needle phobia, pain, distress, ultimately leading to vaccine hesitancy and noncompliance. For example, in one of the studies among 2568 school children, 47.7% and 42.6% reported needle fear and anxiety, respectively.[15] Availability of N-FIS, a needle free injection system can overcome this limitation and help improve the compliance as well as immunisation coverage. In this study, the authors evaluated the performance of N-FIS used to administer MMR vaccine by comparing the immunogenicity and safety to that when given with traditional N-S in infants 9–10 months of age.

Administration of MMR vaccine using N-FIS induced robust immune responses and was comparable to that produced using N-S. We observed high antibody GMTs for all vaccine antigens indicating that the first dose elicits a satisfactory immune response. The GMT produced with MMR using N-FIS was comparable to that produced using N-S. Similarly, in a study published earlier, the MMR vaccine administered using disposable-syringe jet injector produced immune response that was comparable to that with N-S. However, this study was conducted in children 15 months of age who had received their first dose at 9 months.[16] It should be noted that this finding is consistent with a study conducted earlier that suggested the persistence of high circulating maternal antibodies at 9 months of age with baseline seropositivity rates of 15% for measles and 20% each for mumps and rubella.[17] At day 28 post vaccination, >100% and 92.3% of infants were seroprotected against measles and rubella, whereas 96.1% of infants were seropositive for mumps. The seroprotection and seropositivity rates obtained with use of N-FIS were numerically greater than those obtained using N-S for measles (83.3%), mumps (95.8%) and lesser to that with rubella (92.3%). The high seropositivity/seroprotection rates observed here for each vaccine antigen are consistent with those observed in previous studies.[16]

Safety is one of the most important aspects of any intervention. Injection-related pain and fear are common in children undergoing vaccination and influence vaccine acceptance.[9] In this study, MMR vaccine when administered with N-FIS was well tolerated. Pain was the most common adverse event observed in only 3 subjects with N-FIS and that too of mild intensity. This was significantly less than 8 subjects observed with N-S. No incidence of other local reactions such as erythema or systemic reactions was reported. Also, no serious adverse events were observed in our subjects during the study.

The limitations of this study include its small number of participants and its open-label design. Nevertheless, as the objective was to validate the immunogenicity, safety, and tolerability of the vaccine when administered using the IntegriMedical's N-FIS® compared with a conventional needle and syringe, the findings provide valuable insights into vaccine delivery and lay the foundation for future studies that may have broader implications. Objective immunogenicity measurements and standardized safety assessments were employed to minimize potential bias, supporting the reliability of the results. Overall, this study highlights the potential utility of the N-FIS® device as an alternative method for vaccine administration, and may offer paediatrician a viable option to conventional delivery Administration of MMR vaccine using N-FIS® induced robust and comparable immune responses to that observed with use of N-S and was well tolerated. As this was a post marketing study, the sample size was adequate to evaluate the comparative performance and support the administration of an MMR vaccine with IntegriMedical's N-FIS®, however, a cost comparison was not included. Although N-FIS® entail higher upfront costs due to advanced technology, they offer substantial long-term economic benefits. Their durable design reduces recurrent expenditures on needles, syringes, and sharps disposal. By preventing needle-stick injuries, these systems reduce healthcare costs associated with injury management and post-exposure prophylaxis. Furthermore, advantages such as improved patient comfort, ease of administration, and greater acceptability—particularly by alleviating needle fear among needle-phobic individuals enhance patient compliance, thereby improving treatment adherence, and resulting in better health outcomes and overall cost efficiency. Moreover, wider adoption and increased acceptability are expected to optimize costs over time. Successful implementation of N-FIS® at a larger scale would require consideration of several factors, including scalability, cost-effectiveness, and provider training. While the device offers advantages in patient comfort and ease of administration, structured training initially for healthcare personnel will ensure consistent and safe administration. In conclusion, the results of our study suggest that

MMR vaccine administration using N-FIS® in infants induces immunogenicity comparable to that achieved with N-S, provides effective protection, and is well tolerated.

Data Sharing Statement

The data are not publicly available due to their containing information that could compromise the privacy of patients. All data supporting this study will be provided by the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The study was conducted in accordance with the principles of Good Clinical Practice (GCP) and the current version of the Declaration of Helsinki, Indian Council of Medical Research Ethical Guidelines for Biomedical Research on Human patients and applicable regulatory guidelines. The study protocol was approved by the Institutional Ethics Committee of Ruby Hall Clinic ie Poona Medical Research Foundation, Pune, India. An informed consent form was signed by each participant's parents or legally acceptable representatives before enrolment into the study.

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Disclosure

Mr Ankur Naik is the Chief Technology Officer of IntegriMedical LLC and reports a patent US20230414876A1 issued to IntegriMedical LLC and a patent US11752269B2 issued to IntegriMedical LLC. The work is conducted as part of activities demonstrating safety and efficacy of the N-FIS device. Sarvesh Mutha is the Chief Business Officer of IntegriMedical LLC. The authors declare no other conflicts of interest in this work.

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