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SHORT COMMUNICATION

Safety of Russian-Backbone Trivalent, Live Attenuated Seasonal Influenza Vaccine in Healthy Subjects: Open-Label, Non-randomized Phase 4 Study

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Abstract

Introduction and Aim A trivalent live attenuated influenza vaccine (Nasovac-S®) was developed and licensed in India. A phase 4 study was conducted to assess safety.

Methodology This non-randomized, open-label, single-arm study among individuals ≥ 2 years of age involved administration of 0.5 mL of Nasovac-S intranasally, with a 1-month follow-up after vaccination. Adverse events (AEs) were collected via structured diaries.

Results Among 500 vaccinated subjects, 160 were between 2 and 17 years of age, 240 were 18–49 years old and 100 were 50 years and older. A total of 533 solicited reactions were reported. The majority of these reactions were mild, and almost all of them resolved without any sequelae. A total of 20% of subjects reported at least one local solicited reaction, and 23% reported at least one systemic solicited reaction. None of the 45 unsolicited AEs reported by 37 subjects (7.4%) were causally related to the study vaccine.

Conclusions The data from the study adds to the existing safety database of Nasovac-S.

Registry Clinical Trials Registry of India (CTRI/2015/08/006074).

Key Points

A phase 4 study systemically assessed the safety of a Russian-backbone trivalent, live attenuated seasonal influenza vaccine (Nasovac-S®) among people ≥ 2 years old.

Systemic and local solicited reactions were seen among ~ 20% of the subjects, and these were mostly mild and transient.

The vaccine did not cause any serious or severe adverse event.

1 Introduction

Annual vaccination is an important intervention to control seasonal influenza infections [1–3]. Two types of safe and effective vaccines—live attenuated influenza vaccine (LAIV) and inactivated influenza vaccine (IIV)—are available [4, 5]. The LAIVs offer the advantage of ease of administration, are easier to scale up, and mimic natural infection [6].

An LAIV with Leningrad-based strains as a backbone was developed and has been in use in Russia for many decades [1, 7]. Another LAIV, with a backbone of Ann Arbor-based strains, was developed and licensed in the USA during 2003, and has subsequently become available in Europe as well (Brand names: FluMist in the USA and Fluenz in Europe) [1, 7]. Russian-backbone LAIV viruses are produced via genetic reassortment by the Institute of

Sponsor Serum Institute of India Pvt. Ltd., Pune (which is also the manufacturer of the vaccine).

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Experimental Medicine (IEM) and are supplied to the Serum Institute of India Pvt. Ltd. (SIIPL) [6, 8, 9].

SIIPL developed a monovalent LAIV against type A H1N1 virus (Nasovac®) during the 2009 pandemic. The vaccine showed excellent safety during clinical development and post-marketing use of millions of doses [10]. The effectiveness of Nasovac against laboratory-confirmed pandemic H1N1 infections was found to be 75.5% [95% confidence interval (CI) 42.1–89.7] [11].

Using the same LAIV platform, a trivalent LAIV (Nasovac-S®) was developed and found to be safe in animal studies (unpublished data). Clinical studies showed safety and immunogenicity of the vaccine among individuals ≥ 2 years of age (unpublished data), leading to Indian licensure in 2013 [12] and World Health Organization (WHO) prequalification in 2015 [13].

Nasovac-S was evaluated in three more clinical studies, among children between 24 and 59 months of age. In two studies in Bangladesh—a phase 2 ($n = 300$) and another phase 3 ($n = 1761$)—adverse events (AEs) were similar among vaccine and placebo groups [14, 15]. Similar findings were seen in a phase 3 study in Senegal ($n = 1761$) [16].

The present phase 4 study was conducted to expand the safety database of Nasovac-S.

The study has been registered in the Clinical Trials Registry of India (CTRI/2015/08/006074).

2 Materials and Methods

2.1 Study Procedures

This open-label, non-randomized, phase 4 study was conducted at three tertiary care hospitals across India, during August 2015 and January 2016. The subjects were screened for eligibility after written informed consent was obtained.

Eligible subjects were given a single dose of 0.5 mL of Nasovac-S intranasally (0.25 mL in each nostril) during the first visit (day 0).

The subjects attended safety follow-ups 7 and 30 days after vaccination. The evaluations included medical history and physical examinations on all visits. Solicited reactions were collected up to day 7, whereas unsolicited AEs, including serious adverse events (SAEs), were collected up to day 30.

Solicited local reactions included nasal discomfort, sneezing, stuffy nose, runny nose. Solicited systemic reactions included fever (≥ 38 °C), headache, chills, sore throat, cough, body ache, wheezing and loss of appetite.

An SAE was defined as any event that was either life threatening or resulted in death or significant disability or required hospitalization or was a congenital anomaly/birth defect in the offspring of a study subject or was an important medical event [17].

A structured diary card was given to the subjects or their parents for capturing solicited reactions (up to day 7), unsolicited AEs, or concomitant medications during the entire study period. The subjects or their parents were trained by site staff on the process of filling in these diary cards. Documentation of this training was maintained at the site. The data in the diaries were transcribed onto the electronic case report form (eCRF) after confirmation by medically qualified site staff.

Any clinically significant recordings of vital signs or physical examinations throughout the study were also reported as AEs.

All cases of fever reported during the study were graded on the basis of the recorded temperature as follows: mild ≥ 38 °C to ≤ 38.9 °C; moderate ≥ 39 °C to ≤ 39.9 °C, and severe ≥ 40 °C. The grading of other AEs was based upon the pre-defined criteria described below, adapted from the definitions presented by Tangrea et al. [18]:

- *Mild* discomfort noted, but no disruption of normal daily activities; slightly bothersome; relieved with or without symptomatic treatment.
- *Moderate* discomfort sufficient to reduce or affect normal daily activity to some degree; bothersome; interferes with activities; only partially relieved with symptomatic treatment.
- *Severe* discomfort sufficient to reduce or affect normal daily activity considerably (prevents regular activities for at least 24 h); not relieved with symptomatic treatment; would cause subject or parent to seek medical advice.

All the solicited local and systemic reactions occurring within 7 days post vaccination were deemed "related to the study vaccine." Causality assessment for unsolicited AEs reported during the study was done by medically qualified investigators (or their designee) at each site. In case of every unsolicited AE, they answered the following question: "In your opinion, is there a reasonable possibility that the AE may have been caused by the study vaccine(s)?" Accordingly, all the unsolicited AEs were classified as follows:

- *Related* suspicion of relationship between vaccine and AE, or a reasonable possibility that the vaccine contributed to the AE.
- *Unrelated* no suspicion that there is a relationship between vaccine and AE; there are other more likely causes; the study vaccine did not contribute to the AE.

The principal investigators of each of the three sites are also the authors of this paper.

2.2 Study Population

Subjects ≥ 2 years of age who were resident in the study area and free of obvious health problems, as established by medical history and physical examination, were eligible to be part of the study.

Subjects were excluded if they had immunodeficiency or immunosuppression, a history of acute febrile illness or ongoing infection, asthma with recurrent wheezing, or a history of severe allergic reaction including egg or other vaccine component allergies, allergic rhinitis or Guillain-Barré syndrome. Subjects were also not eligible if they had a history of fever, infection, antibiotic/antiviral use or aspirin therapy (among 2- to 17-year-olds) in last 7 days.

Women with a positive urine pregnancy test (UPT) within 24 h prior to vaccination or women who were breastfeeding or unwilling to undergo a UPT were excluded from the study.

In addition, investigators were able to exclude the subjects because of any acute or chronic, clinically significant abnormalities or other conditions determined during screening that may have interfered with the study objectives or jeopardized the safety or rights of the subjects.

Subject recruitment was done mainly by publicizing the study through word of mouth in communities in the vicinity of the study sites. Those interested in the study approached the site. They were screened and if found eligible, were enrolled in the study.

2.3 Study Vaccine

Nasovac-S was supplied in a single-dose vial as a freeze-dried powder along with 0.5 mL diluent (water for inhalation) for reconstitution. Nasovac-S contained influenza viral strains that were antigenically similar to A/California/07/2009 [H1N1, $\geq 10^7$ 50% egg infective dose (EID_{50})/dose], A/Switzerland/9715293/2013 (H3N2, $\geq 10^7$ EID_{50}/dose) and B/Phuket/3073/2013 type B ($\geq 10^{6.5}$ EID_{50}/dose), as per the recommendation for the Southern hemisphere, 2015. The concentration of type A strains was not less than that of type B.

A reconstituted vial containing 0.5 mL of vaccine was administered as 0.25 mL per nostril using a syringe and a spray device.

2.4 Statistical Analyses

A sample size of 500 individuals was sufficient to yield a 95% CI with 0.7% precision for detecting AEs occurring at a frequency of 1%. The incidence (number of events, number of subjects, and percentage) of solicited local and systemic reactions, unsolicited AEs and SAEs was calculated for all subjects as well as for each age group. Safety analysis was done on both intention-to-treat (ITT) and per protocol (PP) populations. All eligible subjects who received the study vaccine were included in the ITT analysis. The subset of the ITT population who complied with the study protocol, including completion of three study visits, were part of the PP population. Primary safety analysis was carried out on the ITT population. All statistical analyses were performed using the SAS software version 9.4 and SPSS.

3 Results

A total of 501 subjects were screened, one of whom was a screen failure because of a recent history of measles. The age distribution of the 500 subjects was as follows: 160 (2–17 years), 240 (18–49 years), and 100 (≥ 50 years).

Only five subjects did not complete the study, as they were lost to follow-up. The study population consisted of 69.2% males. The mean age was 29.4 (± 19.72) years (range 2–80.4 years). Other demographic details are in Table 1.

A total of 39 subjects had pre-existing conditions, the commonest among which were a history of sterilization surgery in females ($n = 7$) and diabetes mellitus ($n = 4$). Seventeen subjects were receiving prior medications that were ongoing at the time of enrolment. The commonest medications among these were metformin in three subjects and paracetamol in two subjects. None of these conditions or medications met the exclusion criteria.

There were no vaccine-related clinically significant changes in vital signs or physical examinations throughout the study.

The overall incidence rates of AEs in the ITT population ($n = 500$) occurring during the study are presented in Table 2. A total of 578 AEs were reported, of which 221 were local solicited reactions reported by 100 subjects and 312 were systemic solicited reactions reported by 116 subjects. The remaining 45 were unsolicited AEs.

Among local solicited reactions, sneezing (11.2%) was most common, followed by nasal discomfort (10.4%), stuffy nose (8.2%), and runny nose (7.6%). All local reactions were mild, except one moderate event each of nasal discomfort, runny nose, and stuffy nose. All resolved without sequelae, with the exception of one event of nasal discomfort, where the outcome was unknown as the subject was lost to follow-up (Table 3).

The solicited systemic reactions with reporting frequency of more than 10% included headache, cough, and body ache. Others (< 10%) were sore throat, loss of appetite, chills, and wheezing. There were no reports of vaccine-related fever during the trial. All the systemic reactions were mild, except five (two headaches, two sore

Table 1 Summary of baseline characteristics: demographics (intention-to-treat population)

Age group	Pediatric ($N = 160$)	Adults ($N = 240$)	Elderly ($N = 100$)	Total ($N = 500$)
Height (cm) [mean (SD)]	114.4 (21.5)	165.3 (8.54)	161.2 (7.4)	148.2 (27.12)
Weight (kg) [mean (SD)]	21.9 (11.5)	64.04 (11.6)	62.7 (10.1)	50.3 (22.5)
Sex [male, *n* (%)]	89 (55.6)	188 (78.3)	69 (69.0)	346 (69.2)

SD standard deviation

Table 2 Overall incidence of adverse events (solicited and unsolicited) in each age group (intention-to-treat population)

	Pediatric ($N = 160$)	Adult ($N = 240$)	Elderly ($N = 100$)	Total ($N = 500$)
Number of subjects with at least one solicited local reaction [*n*, % (95% CI)]	16, 10% [6.2–15.6]	70, 29.2% [23.8–35.2]	14, 14.0% [8.5–22.1]	100, 20.0% [16.7–23.7]
Number of subjects with at least one solicited systemic reaction [*n*, % (95% CI)]	18, 11.3% [7.2–17.1]	82, 34.2% [28.5–40.4]	16, 16.0% [10.1–24.4]	116, 23.2% [19.7–27.1]
Number of subjects with at least one unsolicited adverse event [*n*, % (95% CI)]	18, 11.3% [7.2–17.1]	16, 6.7% [4.1–10.6]	3, 3.0% [1.0–8.5]	37, 7.4% [5.4–10]
Number of subjects serious adverse event (*n*, % [95% CI])	–	1, 0.4% [0.1–3.2]	–	1, 0.2% [0.0–1.1]

CI confidence interval

Table 3 Summary of solicited local reactions [E, *n* (%)] (intention-to-treat population)

Age groups	Pediatric ($N = 160$)	Adult ($N = 240$)	Elderly ($N = 100$)	Total ($N = 500$)
Local reactions				
Nasal discomfort	3, 3 (1.9%)	49, 43 (17.9%)	8, 7 (7.0%)	60, 53 (10.6%)
Sneezing	11, 11 (6.9%)	46, 37 (15.4%)	11, 8 (8.0%)	68, 56 (11.2%)
Stuffy nose	6, 6 (3.8%)	40, 32 (13.3%)	4, 4 (4.0%)	50, 42 (8.4%)
Runny nose	5, 5 (3.1%)	36, 32 (13.3%)	2, 2 (2.0%)	43, 39 (7.8%)
Systemic reaction				
Headache	1, 1 (0.6%)	53, 47 (19.6%)	7, 5 (5%)	61, 53 (10.6%)
Chills	3, 3 (1.9%)	21, 18 (7.5%)	1, 1 (1%)	25, 22 (4.4%)
Sore throat	3, 3 (1.9%)	46, 41 (17.1%)	5, 5 (5%)	54, 49 (9.8%)
Cough	14, 14 (8.8%)	41, 37 (15.4%)	7, 7 (7%)	62, 58 (11.6%)
Body ache	3, 3 (1.9%)	45, 41 (17.1%)	9, 8 (8%)	57, 52 (10.4%)
Wheezing	2, 2 (1.3%)	21, 16 (6.7%)	0	24, 18 (3.6%)
Loss of appetite	2, 2 (1.3%)	26, 23 (9.6%)	2, 2 (2%)	30, 27 (5.4%)

$\% = (n/N) \times 100$

E number of reactions, *n* number of subjects with at least one reaction

throats, and one wheezing) that were moderate. One subject with wheezing and sore throat was lost to follow-up, and the outcome remained unknown, whereas all others resolved without sequelae (Table 3).

The proportion of subjects reporting at least one solicited reaction was higher in adults (age 18–49 years), as compared to elderly ($\geq$ 50 years of age) and pediatric subjects.

None of the 45 unsolicited AEs reported in 37 subjects were causally related to Nasovac-S. All the events were of mild severity, except for two events: one was moderate (asthenia) and the other was severe as well as serious (viral fever). All the events resolved without sequelae. For two events (dryness of throat and dryness of nose reported in one subject), the outcome was unknown since the subject was lost to follow-up.

The most commonly reported unsolicited AE during the study was fever (2%). Cough was the second most common AE (1.4%). There were three reports each of diarrhea, body ache and asthenia, two each of sneezing, nasopharyngitis, headache, vomiting and pruritus, and one each of conjunctivitis, nasal discomfort, rhinitis, rhinorrhea, upper abdominal pain, allergic dermatitis, rash, dry throat and dry nose.

There was only one SAE during the study. The event was diagnosed as viral fever, and the subject had to be hospitalized for a period of 3 days for treatment. The event was graded as severe and occurred 25 days post vaccination. It was not related to the study vaccine, and the event resolved completely.

4 Discussion

This phase 4 study has added additional safety data to the existing safety database of Nasovac-S. A few solicited reactions (local as well as systemic) were observed during the trial and were mostly mild and transient, with no vaccine-related serious safety concerns observed.

The 1% drop-out rate during the study indicates meticulous follow-up strategies employed by the sites.

Solicited reactions were reported among 4–12% of subjects, the majority of which were mild. There were no other vaccine-related AEs (including one SAE of viral fever) during the study.

Although there was no formal comparison, it was observed that the nature and reporting frequency of solicited reactions during the present study appear similar to those reported during earlier Nasovac-S studies [14–16] (unpublished data).

Clinical studies involving around 131,000 children between 3 and 15 years of age receiving Russian LAIV (monovalent, bivalent or trivalent) did not show any serious safety concerns associated with vaccine, except a few reports of fever. The reactogenicity index was 4% among these children [19]. Most of these were local nasal reactions, similar to the reports from the present study.

In seven FluMist studies among ~ 16,000 subjects, nasal congestion/runny nose were reported at a frequency of 30–50% [20]. In the present study, nasal discomfort, stuffy nose and runny nose were collected as separate reactions, and cumulatively the reporting frequency was around 25%.

In the FluMist studies, solicited reactions were collected for 10–14 days [20], unlike the present study. However, the reports of nasal symptoms between days 7 and 30 in the present study did not significantly increase the frequency.

The rates of other commonly reported solicited reactions such as cough, sore throat, headache and loss of appetite also appeared similar with FluMist [20].

Mild and transient wheezing was seen in 3.6% of subjects in the present study within 7 days. Wheezing has been reported previously during clinical trials of FluMist among 2.1% of children aged 2–5 years [20]. A few reports (~ 1.5%, within 42 days post vaccination) of wheezing were also seen during the Nasovac-S studies in Bangladesh and Senegal, although at a rate similar to placebo [14–16].

In the studies of FluMist as well as those for Nasovac-S in Bangladesh and Senegal, wheezing was protocol defined and diagnosed by a physician [14–16, 21]. There was no protocol defined wheezing in the present study. Wheezing was self-reported by the subjects/parents, which may explain the slightly higher incidence in the present study.

The higher frequency of solicited reactions among 18- to 49-year-olds as compared to other age groups may be explained by differences in diary-filling training given to subjects by the sites. One of the sites exclusively enrolled subjects above 18 years, whereas another enrolled only pediatric subjects.

Shedding of vaccine virus was observed in children receiving Nasovac-S during the clinical trials in Bangladesh [22]. There is a concern of potential viral transmission from such shedding, especially among unvaccinated close contacts. However, to date there is only one report of horizontal transmission with LAIV, which was reported from Finland. A FluMist recipient transmitted the vaccine virus to a placebo recipient child. Even in that case, the child remained asymptomatic [23]. No such cases have been reported with Russian-backbone LAIVs. As such, no viral shedding was assessed during the present study.

4.1 Limitations of the Study

The present study was a single-arm, open-label, non-randomized study without any control arm. It was not possible to use a control arm as there is no intranasal LAIV available in India. Also, an IIV would not have been an appropriate control as the routes of administration and safety profiles of the two would be different.

Subjects were trained by site staff on how to capture the AEs on the diary cards, and there is a possibility that the understanding of the subjects may have varied across different sites. We do not have any data to confirm this information. Neither do we have data on the literacy rate of enrolled subjects in our database.

The sample size of 500 subjects may not be enough to detect rare events.

5 Conclusions

The present study provides additional weight to the safety database of Nasovac-S. No new AEs related to the use of this vaccine were reported.

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Compliance with Ethical Standards

Funding The study was sponsored by the Serum Institute of India Pvt. Ltd., Pune, which manufactured the vaccine.

Conflict of Interest Amol Chaudhari and Prasad Kulkarni are employed by the Serum Institute of India Pvt. Ltd., which manufactured the vaccine. Prashant Nigwekar, Anuj Kumar, Vikram Padbidri, and Amlan Choudhury have no conflict of interest that is directly relevant to the content of this study.

Ethical Approval The study was initiated only after obtaining written approval from institutional ethics committees (IECs) of the respective sites as well as the Indian regulatory authority (Drugs controller General of India). The Declaration of Helsinki, Good Clinical Practice guidelines, and Indian regulatory and ethical guidelines were complied with.

Consent Written informed consent from subjects ($\geq$ 18 years of age) or parents (for subjects $<$ 18 years of age) and written assent from children (7–17 years) were obtained prior to performing any study procedures. The consent forms and any subsequent amendments were reviewed and approved by respective sites' IECs. The entire process of informed consent was audio-visually recorded only after additional consent for audio visual recording, as per the prevalent regulatory norms.

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