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A post-marketing surveillance study of a human live-virus pandemic influenza A (H1N1) vaccine (Nasovac®) in India

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A live attenuated pandemic H1N1 influenza vaccine was developed in India. A post marketing surveillance was conducted retrospectively in healthy individuals (≥ 3 y) who were vaccinated intranasally around one year before. After consent, the subjects recorded adverse events developing within 42 d. Among 7,565 individuals (3–85 y), a total of 81 solicited adverse reactions (1%) were reported in 49 subjects (0.65%). The reactions included mild to moderate respiratory symptoms. No H1N1 case was encountered during one year post vaccination. The data show the safety of the live attenuated influenza vaccine platform developed in India.

Introduction

In April 2009, an outbreak of H1N1 influenza infection was detected in Mexico, with subsequent cases observed in many other countries.[1,2] On June 11, 2009, the World Health Organization (WHO) raised its pandemic alert level to the highest level, phase 6.[3]

The first H1N1 case in India was reported in Hyderabad city on May 16, 2009.[4] Pune city in state of Maharashtra reported the first case on June 22, 2009. The first death in India, that of a 14 y old girl from Pune was reported on August 3, 2009. Subsequently, widespread transmission was reported in community.[5] From May 2009 till the week ending on January 2, 2011, Maharashtra state alone reported 9,972 laboratory confirmed cases and 937 deaths, which was the maximum in India.[6]

On July 7, 2009, WHO recommended vaccinations in all countries and also recommended that promoting production of vaccines such as live attenuated influenza vaccines was important.[7,8] In May 2009, Serum Institute of India Ltd (SIIL) signed an agreement with WHO to secure a sub-license for the development, manufacture and sale of a LAIV using the backbone of attenuated strain A/Leningrad/134/17/57 from the Institute of Experimental Medicine (IEM), Russian Federation. Subsequently, SIIL developed a human, live, and monovalent A(H1N1) vaccine in 2009. It is administered by intranasal spray.[9]

The vaccine was found safe in animal toxicity studies. It also showed protective response against H1N1 in a Ferret challenge model. A double-blind randomized placebo-controlled Phase I study in 50 healthy adults found the vaccine (Nasovac®) immunogenic and safe, and the same findings applied also to a double-blind randomized placebo-controlled phase II/III study in 330 vaccinees of various age.[9] Based on this data, marketing license was granted to SIIL on June 18th 2010. A single intranasal dose of 0.5 ml was recommended for adults, elderly and children ≥ 3 y of age. To date, > 2.5 million people in India have received the vaccine.

In view of severe outbreak in Pune, SIIL offered to vaccinate all its employees, their relatives and acquaintances. Vaccination camps were also conducted in some schools and hospitals in the surrounding areas of SIIL. As approximately 10,000 easily reachable people were vaccinated close to the manufacturer, we assessed the safety of Nasovac® in this large population. This post-marketing surveillance (PMS) was planned and accomplished post-hoc.

Results

In all, 7,565 vaccinees were assessed. The mean age was 25.4 (SD 15.8) years, median 25 y, while the range was 3 to 85 y. The age distribution grouped by gender is given in **Table 1**.

A total of 81 solicited adverse reactions [1% (95% CI 0.85% to 1.33%)] within 7 d were reported in 49 subjects. The proportion of subjects reporting at least 1 solicited adverse reaction was 0.65% (95% CI 0.48% to 0.86%) after receipt of Nasovac. Runny nose, sneezing, nasal discomfort, fever, headache were the common reactions, with overall incidence of reactions ranging from 0.01% to 0.32% (**Table 2**).

There were no deaths, life threatening events, permanent disability, events requiring hospitalization or prolongation of hospitalization, or events requiring emergency room visits. In terms of severity, no grade 3 (severe) reactions were reported.

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Table 1. Age distribution grouped by gender

Age in Years	Males N (%)	Females N (%)	Total N (%)
≥ 3.0 to ≤ 17.0	1803 (55.26%)	1460 (44.74)	3263 (100%)
≥ 17 to ≤ 50	2603 (69.43%)	1146 (30.57%)	3749 (100%)
> 50	370 (66.91%)	183 (33.09%)	553 (100%)
Total	**4776 (63.13%)**	**2789 (36.87%)**	**7565 (100%)**

Table 2. Solicited reactions (n = 7565)

Adverse reactions	Frequency (N)	%	95% CI		Mean duration in days (SD)*
			Lower	Upper	
Runny nose	24	0.32	0.20%	0.47%	2.17 (1.74)
Stuffy nose	2	0.03	0.00%	0.1%	2.0 (2.41)
Sneezing	8	0.11	0.05%	0.21%	3.75 (3.33)
Nasal discomfort	13	0.17	0.09%	0.29%	2.46 (1.43)
Lacrimation	2	0.03	0.0%	0.1%	2.0 (2.83)
Sore throat	2	0.03	0.0%	0.1%	1.5 (0.71)
Loss of smell	1	0.01	0.0%	0.07%	3
Arthralgia	1	0.01	0.0%	0.07%	1
Chills	1	0.01	0.0%	0.07%	4
Cough	4	0.05	0.01%	0.14%	3.0 (0.82)
Fatigue	1	0.01	0.0%	0.07%	1
Fever	10	0.13	0.06%	0.24%	2.5 (0.92)
Headache	8	0.11	0.05%	0.21%	1.75 (1.16)
Irritability	1	0.01	0.0%	0.07%	1
Myalgia	1	0.01	0.0%	0.07%	1
Wheezing	2	0.03	0.0%	0.1%	1.0 (1.41)

Table 3. Unsolicited adverse events

Adverse reactions	Frequency (N)	% (n = 7565)	95% CI	
			Lower	Upper
Loss of smell	1	0.01%	0.00%	0.07%
Nasal Discomfort	1	0.01%	0.00%	0.07%
Runny nose	5	0.07%	0.02%	0.15%
Sneezing	3	0.04%	0.00%	0.12%
Sore Throat	2	0.03%	0.00%	0.10%
Stuffy Nose	2	0.03%	0.00%	0.10%
Wheezing	1	0.013%	0.00%	0.07%

All events were non-serious, mild (90%) or moderate (10%) in severity, and no reaction lasted more than 4 d. They also resolved with or without symptomatic treatment leaving no sequelae.

The total number of subjects who took concomitant medications for solicited adverse reactions was 22 [0.29% (95% CI 0.19% to 0.44%)]. Total of 25 concomitant medications were used to manage the solicited adverse reactions symptomatically. The medications included paracetamol, ibuprofen, chlorpheniramine maleate, phenylephrine hydrochloride, codeine. One subject received an unknown homeopathic medicine. Names of medications were not available in 14 cases.

Seven vaccinees [0.20% (95% CI 0.12% to 0.33%)] reported of 15 unsolicited adverse events. The proportion of vaccinees reporting at least 1 unsolicited adverse event was 0.09% (95% CI 0.04% to 0.19%) (**Table 3**). Of these, 7 (46.67%) were mild, and 8 were (53.33%) moderate in severity. Except one case of runny nose at 18 d postvaccination, all unsolicited AEs were deemed unrelated to Nasovac. All unsolicited AEs resolved with or without symptomatic treatment and without any sequelae. Also, no serious adverse event or new onset chronic medical conditions like Guillain-Barré syndrome were reported within 42 d of Nasovac® administration.

A 33-y-old male was reported ILI no less than 6.5 mo after receiving Nasovac®. The episode lasted for 5 d and only symptomatic treatment was given. The causative organism was not identified, but nevertheless, the incidence of ILI was 0.01% (95% CI 0.0% to 0.07%). No case of H1N1 has been found in vaccinees till date.

Discussion

Because of raging pandemic in Pune[5] and hectic vaccination schedule, only a retrospective PMS study on the Nasovac® vaccinees in 2010 was possible. We still believe that useful information was obtained. The study showed that this locally produced intranasal vaccine was safe and caused rather commonplace reactions. Among ~7,500 vaccinees, not a single severe or serious reaction was reported. A meta-analysis of randomized controlled trials which compared LAIVs and IIVs from 11 prospective clinical trials found that the incidence of systemic reactions ranged from 0% to 25%, of which 5 studies reported 0%.[10]

One may rightly ask how precisely did the vaccinees in our study remember minor postvaccination events a year later. Of course, even the prospective cohort studies and randomized controlled trials are not free from the recall bias.[11] However, the accuracy of recall in humans significantly depends on the time interval between the event and the time of its assessment: the longer the interval, the higher the probability of incorrect recalls.[12]

However, up to 80% of critical details of an event can be retrieved for one year or more.[13] Therefore, it is unlikely that any serious event would have left unreported in our questionnaires. This an important finding regarding circumstances in which a new pandemic strain hit the area, killed some patients, caused much concern and forced a local manufacturer (SIIL) to develop within months a new vaccine which then was soon administered to more than 2 million people.[9]

Only one case of ILI during 1 y from vaccination was found. Though one cannot conclude about effectiveness, but it is reassuring that there were no confirmed vaccine failure cases, even if we take into account underreporting.

In conclusion, the Indian-made nasal vaccine against the pandemic H1N1 was a safe vaccine at age of 3 y and older. This particular strain is now of minor importance, but our experience

shows safety of the new live attenuated influenza vaccine platform made by an Indian manufacturer. This is of value for the future trivalent seasonal formulations made with the same platform.

Materials and Methods

Study objectives. The study looked at the incidence of solicited local and systemic reactions within 7 d from vaccination, and searched for any unsolicited event within 42 d postvaccination. Another objective was to assess the incidence of influenza-like-illness (ILI) and laboratory-confirmed H1N1 influenza that may have occurred within a time frame that began from 3 weeks post vaccination till the time of the checkup.

Study procedures. The vaccinees had received a single dose of 0.5 ml of Nasovac® intranasally in 2010. In 2011, the vaccinees or parents/legal guardians were contacted. After consent in writing, they were instructed to record any solicited local and systemic reactions within 7 d and all potential unsolicited events within 42 d postvaccination. A diary card was given to improve the reporting. The investigator reviewed and transcribed the information in Case Report Forms (CRFs).

Study vaccine. The Nasovac® virus strain was grown in embryonated eggs and is antigenically similar to A/California/7/2009 and is cold-adapted (ca), temperature-sensitive (ts) and attenuated (att) strain. After reconstitution with 2.5 ml of sterile water for inhalation, a vial of Nasovac® contains 5 doses, each of 0.5 ml, with not less than 10^7 EID_{50} of A/California/7/2009 (H1N1) virus strain, 2.5% of partially hydrolysed gelatin, and 5% of sorbitol.

Outcome measures. The solicited reactions were nasal discomfort, sneezing, stuffy nose, runny nose, loss of smell, red eyes, lacrimation, facial swelling, fever (> 38°C), headache, chills, fatigue, sore throat, cough, myalgia, arthralgia, irritability, wheezing, loss of appetite, nausea and diarrhea. Any other unsolicited events occurring till 42 d were also to be reported. All events were graded for severity with pre-defined criteria. All solicited post-immunization reactions were considered related to vaccination, whereas the causality of all other adverse events (AE) was assessed on a clinical judgement. The information on ILI and laboratory-confirmed H1N1 influenza in vaccinees in the period from 3 weeks after vaccination till the study was evaluated.

Ethics. This protocol was approved by the Ethics Committee of Serum Institute of India Research Foundation. Written informed consent was obtained from subjects ≥ 18 y, whereas for subjects ≥ 3 to 17 y, parents/legal guardians provided a written informed consent. Assent was obtained from subjects aged 13 to 17 y.

Statistical methods. Age was expressed as mean and SD. The age distribution grouped by gender was expressed as number and percentage. The incidence of solicited and unsolicited reactions, of any other event, of ILI and of the cases of confirmed H1N1 influenza were calculated along with 95% confidence intervals.

Disclosure of Potential Conflicts of Interest

P.S.K. and R.M.D are employed by Serum Institute of India Ltd which is the manufacturer of the study vaccine. S.K.R. is a past employee of the same organization.

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