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Safety and immunogenicity of dry powder measles vaccine administered by inhalation: A randomized controlled Phase I clinical trial

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ABSTRACT

Background: Measles is a highly infectious respiratory disease which causes 122,000 deaths annually. Although measles vaccine is extremely safe and effective, vaccine coverage could be improved by a vaccine that is more easily administered and transported. We developed an inhalable dry powder measles vaccine (MVDP) and two delivery devices, and demonstrated safety, immunogenicity, and efficacy of the vaccine in preclinical studies. Here we report the first clinical trial of MVDP delivered by inhalation.
Methodology: Sixty adult males aged 18 to 45 years, seropositive for measles antibody, were enrolled in this controlled Phase I clinical study. Subjects were randomly assigned in 1:1:1 ratio to receive either MVDP by Puffhaler® or by Solovent™ devices or the licensed subcutaneous measles vaccine. Adverse events (AEs) were recorded with diary cards until day 28 post-vaccination and subjects were followed for 180 days post-vaccination to assess potential serious long term adverse events. Measles antibody was measured 7 days before vaccination and at days 21 and 77 after vaccination by ELISA and a plaque reduction neutralization test.
Results: All subjects completed the study according to protocol. Most subjects had high levels of baseline measles antibody. No adverse events were reported. MVDP produced serologic responses similar to subcutaneous vaccination.
Conclusions: MVDP was well tolerated in all subjects. Most subjects had high baseline measles antibody titer which limited ability to measure the serologic responses, and may have limited the adverse events following vaccination. Additional studies in subjects without pre-existing measles antibody are needed to further elucidate the safety and immunogenicity of MVDP.

1. Introduction

Measles is a highly contagious viral respiratory disease. Case fatality rates average 1–2 deaths/1000 cases in the developed world but can exceed 10% in areas with limited access to healthcare [1,2]. Immunization programs have reduced worldwide measles deaths from an estimated 562,400 deaths in 2000 to 122,000 in 2012 [3,4] and most of the current measles morbidity and mortality occurs in countries with inadequate vaccine coverage. Global measles vaccine coverage increased from 73% in 2000 to 84% in 2009, but has remained at 84% through 2012 [3]. Measles vaccine has been included in the national immunization program in India since 1985–1986 [5]. However, in 2012, an estimated 6.4 million infants in India were not vaccinated against measles [3].

Part of the difficulty in achieving high coverage levels with subcutaneous measles vaccine is due to the logistical challenges associated with subcutaneous injections. Safe effective injection requires highly skilled health care workers and a short supply of

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such staff is often a rate limiting factor in vaccine delivery. Other limitations of vaccination by injection include the need for onsite reconstitution and filling, vaccine wastage rates associated with multi-dose vials, and safe disposal of sharps waste. Delivery systems that are needle-free and do not require reconstitution could address some of the logistical barriers to immunization associated with injection and potentially improve coverage.

The first vaccines reported in history were not needle based but consisted of powdered scab material from smallpox patients delivered by intranasal insufflation, reportedly practiced in China as early as the 10th century AD [6]. In more recent vaccine history, multiple clinical trials have been conducted with respiratory delivery of liquid aerosol vaccines. Respiratory delivery of vaccines has typically focused on two separate target tissue areas, the nasal airways or the lower airways. The only licensed vaccines for respiratory delivery have been nasal influenza vaccines, which are delivered directly to the nares as large particle sprays to avoid deposition in the lower airways [7]. In contrast, most of the research on respiratory delivery of measles vaccine has focused on generating small particle aerosols for deposition in the lower airway [8]. Many early studies used a modified jet nebulizer to generate liquid measles vaccine aerosol for inhalation. Liquid aerosol measles vaccine has undergone substantial clinical testing and was successfully used in a mass campaign vaccinating over 3 million children in Mexico [9]. A systematic meta-analysis showed that inhaled liquid aerosol measles vaccine was demonstrated to be safe, immunogenic and well tolerated in general [10]. Most studies in children over 10 months of age found an equivalent or superior immune response with aerosolized measles vaccine [10–13]. However, studies in younger infants have not consistently achieved immune responses equivalent to subcutaneous vaccination [14], though one study in Mexico found that increasing exposure time to aerosol measles vaccine elicits immune responses comparable to those seen with the subcutaneous vaccine in 9-month-old infants [15]. Aerosol measles, mumps, rubella combination vaccines have also been shown to induce immune responses similar or superior to subcutaneous vaccination [16–20].

While sharing the needle-free advantages of liquid aerosol vaccine, dry powder aerosol delivery does not require shipping or storage of water or onsite reconstitution or filling, multidose packaging, or an electromechanical device or energy source. For this clinical trial, a novel spray drying method, carbon dioxide assisted nebulization with a Bubble Dryer® (CAN-BD) was used to generate measles vaccine powders with particles in the 3–5 μm size range desirable for pulmonary delivery without destroying biological activity. The CAN-BD process and formulation was optimized resulting in a high yield process for measles vaccine dry powder (MVDP) which meets the WHO standard for thermostability (<1 log loss of potency at 37 °C for 1 week) and maintains the powder properties necessary for inhalation during storage. CAN-BD manufacturing capability for MVDP was established at the Serum Institute of India Ltd (SIIL), Pune, India, as a modified formulation of the SIIL licensed measles vaccine live [21,22]. Two inexpensive devices for respiratory delivery of MVDP, Puffhaler® and Solovent™, were developed. All components which contact either the vaccine or the vaccinee were designed as inexpensive disposable unit dose formats. MVDP developed satisfactory immune responses in cotton rats [23]. When delivered by mask or nasal prong, MVDP was shown to produce robust immune responses in non-human primates, similar to vaccination by injection and to protect from challenge with wild-type measles virus [24]. MVDP was also found safe in licensure level animal toxicity studies (unpublished data). This Phase I study to assess the safety and immunogenicity of MVDP in adults is the first reported clinical study of a dry powder vaccine for inhalation.

The primary objective of this open label, Phase I study was to demonstrate the safety of the MVDP delivered by the respiratory route using two delivery devices. The secondary objective was to measure immune responses as a result of vaccination.

2. Materials and methods

2.1. Study design

This Phase I, open-label, randomized study was conducted at Padmashree Dr. D. Y. Patil Medical College, Pimpri, Pune, India, from March 2012 to May 2013. There was a screening period of 7 days followed by vaccination on day 0. Subjects were randomly assigned in 1:1:1 ratio to receive in parallel either MVDP by Puffhaler® (Group I), MVDP by Solovent™ (Group II) or the licensed subcutaneous measles vaccine (SMV) (Group III). Subjects were randomized to study groups using randomized complete block design at the study site. The randomization codes were generated by computer using permuted block design. Sealed envelopes containing the random allocation for each subject were provided to the site. Post vaccination, there was a follow-up period of 84 days which included 6 visits. On Day 180, a telephone call was made to enquire about development of any serious adverse event. Thus, the total duration of each subject's participation was approximately 187 days.

2.2. Study subjects

Healthy male adults of age 18–45 years who were measles immune, as determined by IgG antibody levels were enrolled in the study. To avoid potential exposure of women who were unknowingly pregnant, only males were included in the study. Potential subjects were contacted through word of mouth. They were excluded from the study if they had immunodeficiency, chronic immunosuppressive therapy, acute febrile illness, any clinically significant disorder, severe allergic reaction, recent receipt of a licensed vaccine, immune sera and/or any blood products, or any investigational study agent, history of chronic alcohol consumption and/or intravenous drug abuse. In the screening phase, positive serology for human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) antibody, or abnormal clinical biochemistry, hematology and urine parameters were also considered as exclusion criteria.

2.3. Vaccines and devices

All the study vaccines (MVDP and SMV) were manufactured by Serum Institute of India Limited (SIIL). SMV is a licensed formulation containing live attenuated Edmonston–Zagreb (E–Z) virus. The vaccine is prepared in human diploid cells (MRC5), suspended in minimal essential medium (MEM) and stabilized with sorbitol. Each single dose when reconstituted with 0.5 ml of sterile water for injection contains not less than 1000 $CCID_{50}$ of live virus. Batch No. 001N1013A (Expiry August 2013) with a potency of 8912.5 $CCID_{50}$ was used. MVDP is a modified formulation of licensed SMV containing not less than 1000 $CCID_{50}$ of live attenuated measles virus E-Z strain propagated on human diploid cells. MVDP is formulated with myo-inositol as a stabilizer instead of sorbitol and processed into a dry powder for inhalation using CAN-BD [25]. Batch numbers 78B and 78C (Expiry February 2013) with a potency of 12,589.25 and 10,000 $CCID_{50}$, respectively were used.

Puffhaler® (manufactured by AktivDry LLC) is an experimental dry powder inhaler designed to aerosolize powders into a reservoir from which the powders are either directly inhaled through a mouthpiece with adults and adolescents or through a mask placed over the nose and mouth with infants and young children [7]. Powders are stored in unit-dose blister packs, placed in a plastic

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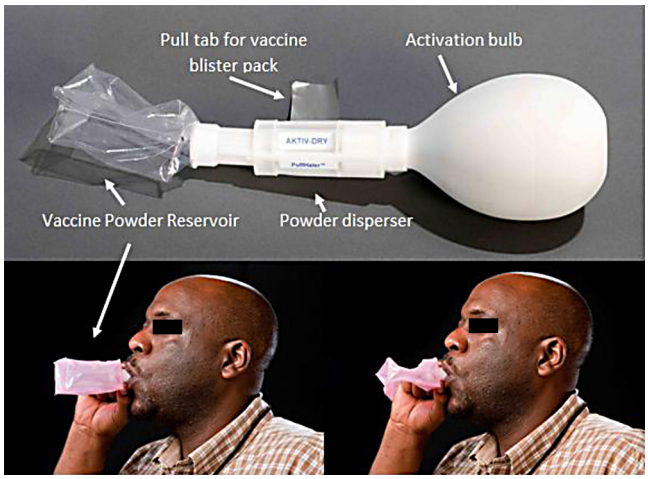

Fig. 1. Caption: PuffHaler Device—the components of the device are labeled above. Below, a model demonstrates mock vaccination by inhaling from the vaccine reservoir.

disperser, opened by removing the pull-tab lid, and aerosolized by squeezing a bulb attached to the disperser. In this study, subjects inhaled MVDP from the reservoir mouthpiece (Fig. 1).

Solovent™ (manufactured by Becton, Dickinson & Company) is an experimental dry powder inhaler designed to aerosolize powders into a spacer from which the powders are either directly inhaled from the spacer with adults and adolescents or through a mask placed over the nose and mouth with infants and young children [7]. Powders are contained between two burstable plastic membranes in a plastic housing which is stored in a foil package to protect the vaccine from light and humidity. At time of use the plastic housing is attached to a 5 ml syringe (without a needle) via a luer fitting. Powders are dispersed into a spacer by depressing the syringe plunger. In this study, subjects inhaled powder directly from the spacer (Fig. 2).

2.4. Serologic testing

Serum Samples were collected from all subjects on screening day (day − 7), day 28 and day 84. The samples were stored and shipped at temperatures between −20 °C and −80 °C. One aliquot was tested for Measles IgG antibodies by ELISA using the Captia™ commercial kit of Trinity Biotech. This testing was performed by Metropolis Laboratory, Mumbai. Seropositivity was defined as titer ≥0.09 IU/ml. One aliquot was tested for measles specific neutralizing antibody titers by the plaque reduction neutralization test (PRNT) at the Centers for Disease Control and Prevention, Atlanta. The standardized PRNT protocol recommended by the WHO was used and the starting dilution for testing the serum samples was 1:4 [26]. Seropositivity was defined as titer ≥120 IU/ml.

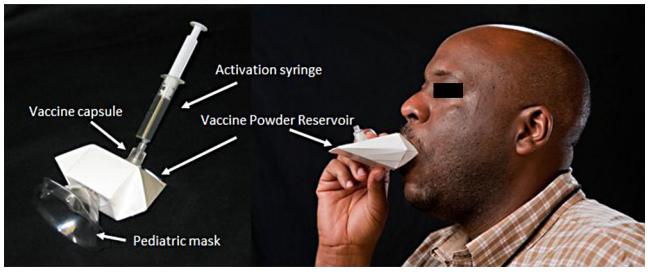

Fig. 2. Caption: Solovent Device—the components of the device are labeled on the left. On the right, a model demonstrates mock vaccination by inhaling from the vaccine reservoir.

2.5. Safety evaluations

All the subjects were followed up for safety evaluations for 180 days after study vaccinations. The evaluations included medical history, vital sign measurements and physical examinations on all visits. Vital signs were measured before and approximately 60 min after vaccination on day of vaccine administration. Clinical laboratory tests for hematology, chemistries and urinalysis were performed on day −7, day 7 and day 14.

Any new clinically significant finding was recorded as an adverse event. Solicited local events such as erythema, induration, swelling and pain and systemic events such as fever, rash, cough, shortness of breath, sneezing, lacrimation, conjunctivitis, fatigue, malaise, sore throat, diarrhea, myalgia, and arthritis were assessed till 14 days after vaccination. Unsolicited AEs were assessed for a period of 84 days post vaccination. Serious adverse events (SAEs) were assessed throughout the entire study period of 180 days post vaccination. Subjects were informed that free treatment was available at the study site for any study related events.

A pre-printed diary card was given to the subject on the vaccination visit (day 0) for capturing adverse events for 14 days after vaccination. The diaries were retrieved on day 14, reviewed and the information was transcribed by the study staff onto the case report form.

2.6. Statistical analyses

The sample size for this study was not determined from power analysis, since this was a Phase I study. Subject age is expressed in mean and standard deviation (SD). The incidence (number and percentage) along with 95% confidence interval (CI) of solicited local and systemic reactions, unsolicited adverse events, SAEs in the study groups were calculated.

For serological assessment on days −7, 28 and 84, the proportion of subjects seropositive for measles IgG antibodies, proportion of subjects having seroprotective PRNT titers (≥120 IU/ml), geometric mean concentrations (GMC) of IgG antibodies and geometric mean titers (GMT) of PRNT were calculated groupwise along with 95% CI. In addition, immunologic response for measles IgG (≥2 fold rise) and PRNT (≥4 fold rise) on days 28 and 84 with respect to baseline were calculated groupwise in percentage alongwith 95% CI. Statistical comparison of post-vaccination seropositivity, seroprotection and seroconversion between groups was done by Chi-square test. GMCs and GMTs between groups were compared by Kruskal–Wallis test. GMCs between each MVDP group and SMV group were also compared by unpaired t test. GMTs within groups were compared by paired t test. A p value less than 0.05 was considered significant.

2.7. Ethical considerations

All the study documents were approved by Institute Ethics Committee (IEC) of Padmashree Dr. D. Y. Patil Medical College, Pimpri, Pune (Federalwide Assurance (FWA) for the Protection of Human Subjects no. FWA00019932) and the Drug Controller General of India (DCGI). The trial was registered at clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT01557699) as well as at Clinical Trials Registry of India (CTRI/2012/02/002447). The study was conducted as per ethical principles of the declaration of Helsinki, good clinical practices guidelines and Indian regulatory and ethical guidelines. Subject information sheet and informed consent form in local languages were used to obtain consent from all the subjects. SIIL, Metropolis laboratories, Aktiv-Dry, Becton, Dickinson & Company and CDC did not have access to identifiable, private subject information at any

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Table 1
Proportion of subjects with four-fold increase in measles plaque reduction neutralization titer at 28 or 84 days post-vaccination.

	Baseline (prevaccination) PRN titer			
	<120	120–1052	>1052	Total
Vaccination Route				
Puffhaler	1/1 (100%)	3/5 (60%)	0/14 (0%)	4/20 (20%)
Solovent	1/1 (100%)	3/7 (43%)	2/12 (17%)	6/20 (30%)
Subcutaneous	0/0	4/6 (67%)	1/14 (7%)	5/20 (25%)
Total	2/2 (100%)	10/18 (56%)	3/40 (8%)	15/60 (25%)

time and the laboratories (CDC and Metropolis) were not engaged in the human subjects aspects of the study.

3. Results

3.1. Demographics

Ninety three subjects were screened of which 60 were found eligible and enrolled. All subjects were Indian males within the ages of 18–45 years. The mean (SD) and the median age in years were 28 (±7) years and 28 years in MVDP Solovent group, 30 (±6) years and 29 years in MVDP Puffhaler group and 28 (±7) years and 29 years in SMV group.

3.2. Safety

No SAE were reported in the study and no solicited reactions were found. One subject had a high respiratory rate on the screening day while another subject had the same on the day of vaccination before receiving the vaccine. These findings were not deemed clinically significant. Both the subjects were from the MVDP Puffhaler® group. Post-vaccination, there were 1, 4, and 3 instances of abnormal respiratory rate measurement in one subject of MVDP Puffhaler®, 4 subjects of MVDP Solovent™ and 2 subjects of SMV groups, respectively. One subject in the SMV group had abnormal respiratory measurements twice at visit 3 and visit 5. However, none of these findings were deemed clinically significant.

There were 165 incidents post vaccination at days 7 and 14, where laboratory parameters were found out of reference range: 47 in MVDP Puffhaler group, 49 in MVDP Solovent group and 69 in SMV group. None of these laboratory parameters were deemed clinically significant by the investigator, and hence, are not reported as adverse events.

3.3. Serologic response to vaccination

All eligible subjects were seropositive for measles by ELISA and PRNT at the baseline sample on day − 7 (data not shown). Only two subjects had a PRNT < 120 mIU at baseline, one each in the Puffhaler and Solovent groups, and both subjects developed protective titers, with at least four fold increases in PRN titer, following vaccination (Table 1). Among subjects with baseline PRN titers 120–1052, 10 of 18 (56%) had at least four fold increases in titer at 28 or 84 days. The proportion of subjects who seroconverted was similar for both MVDP groups and the SMV group (Table 1). Among subjects with PRN titers > 1052 at baseline, only 3 of 40 had at least four fold increases in titer and the proportion of subjects who seroconverted was similar across all groups (Table 1). Also, the proportion of subjects showing seroconversion by ELISA on days 28 or 84 in both of the MVDP groups was similar to those in SMV groups for all baseline titer categories (data not shown).

All subjects remained seropositive by ELISA and PRNT on days 28 and 84. All subjects had protective titers (PRN > 120) after vaccination with the exception of one subject in the SMV group whose

Table 2
Measles plaque reduction neutralization test geometric mean titers.

Statistics	MVDP Puffhaler® (*n* = 20)			MVDP Solovent™ (*n* = 20)			SMV (*n* = 20)		
	Baseline	Day 28	Day 84	Baseline	Day 28	Day 84	Baseline	Day 28	Day 84
GMT	1914.3	2626.5	1789.5	1479.5	1569.1	1526.5	2010.4	1789.7	1152.2
95% CI	(826.95, 4431.6)	(1719.7, 4011.4)	(966.32, 3313.9)	(768.41, 2848.6)	(937.44, 2626.4)	(824.95, 2824.8)	(1033.6, 3910.5)	(1047.8, 3057.0)	(669.71, 1982.2)
p-Value*	–	0.4271	0.4014	–	0.6766	0.6114	–	0.2949	0.0976
p-Value**	–	–	–	–	–	–	0.6976	0.3122	0.6184

* *p*-Value were obtained using paired *t* test (comparing within each treatment group between visits, $\alpha = 0.05$).
** *p*-Value were obtained using Kruskal–Wallis test (between the MVDP and SMV treatment groups, two tailed, $\alpha = 0.05$).

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Table 3
Measles specific IgG antibodies measured by EIA geometric mean concentrations.

Statistics	MVDP Puffhaler® ($n=20$)			MVDP Solovent™ ($n=20$)			SMV ($n=20$)		
	Baseline	Day 28	Day 84	Baseline	Day 28	Day 84	Baseline	Day 28	Day 84
GMC	0.91	1.46	1.71	1.31	1.49	2.14	0.86	1.03	1.45
95% CI	(0.63, 1.33)	(1.06, 2.01)	(1.31, 2.22)	(0.93, 1.84)	(1.13, 1.96)	(1.72, 2.68)	(0.57, 1.32)	(0.86, 1.23)	(1.07, 1.95)
p-Value*	0.9553	0.0569	0.4793	0.2453	0.0369	0.0824	–	–	–
p-Value**	–	–	–	–	–	–	0.2079	0.1231	0.0920

* p-Value were obtained using unpaired test (comparing each MVDP with SMV (between the groups with respect to same time points. i.e. day 28 vs. day 28), two tailed, $\alpha = 0.05$).
** p-Value were obtained using Kruskal–Wallis test (between the MVDP and SMV treatment groups, two tailed, $\alpha = 0.05$).

PRN titers dropped below 120 on day 28 and increased to 150 by day 84 (data not shown). The GMTs calculated from the PRNT titers on days 28 and 84 in all three groups were similar (Table 2).

The GMCs of measles specific IgG antibodies on days −7, 28 and 84 were higher in both MVDP groups as compared to the SMV group on days 28 and 84 (Table 3). The difference between MVDP Solovent™ and SMV on day 28 was statistically significant ($p = 0.0369$).

4. Discussion

In this Phase I study of healthy adult male subjects, use of MVDP delivered by either Puffhaler® or Solovent™ had a safety and immunogenicity profile comparable to that of licensed measles vaccine delivered by the subcutaneous route. There were no reports of clinically significant adverse events, serious adverse events or deaths during the study, despite a close follow up including using subject diaries in all three groups and follow-up for 180 days post vaccination. The most common adverse events following subcutaneous measles vaccination are mild fever and rash, which can occur in up to 5% of vaccinees. These events are much less common following vaccination in immune persons [11]. The absence of adverse events in this study is consistent with the subjects being measles immune at baseline [27].

The standard definition of measles seroconversion is changing from non-protective to protective titers, which is the primary objective of vaccination. The PRNT assay is considered the gold standard for assessing measles immunity because PRN titers correlate with protection from measles. Persons with PRN titers < 120 mIU/ml have a high risk of measles disease if exposed and a high likelihood of seroconverting in response to vaccination. Persons with titers 120–1052 mIU/ml are typically protected from measles disease but may get subclinical or mild measles infections if exposed and may have an increase in antibody titer following vaccination. Persons with PRN titers > 1052 mIU/ml are unlikely to be infected with measles virus following exposure and unlikely to develop immune response following vaccination [28]. Thus, in assessing immune responses to vaccination, it is critical to consider baseline PRN titers. In this study, almost all subjects had protective PRN titers before vaccination. The two subjects without protective titers, one in each of the MVDP groups, seroconverted in response to vaccination. A few subjects in each vaccination group had PRN titers in the 120–1052 mIU/ml range and a comparable proportion in each group showed a fourfold increase in PRN titer. Most of the subjects in each vaccination group had PRN titers > 1052 mIU/ml and few of these subjects had an increase in PRN titer after vaccination. Overall, the immune responses across the vaccination groups were comparable, though the small numbers of responders prevents statistical comparison of the response rate by group and baseline titer.

A group of experts met in 2012 to recommend a list of research priorities for global measles control and eradication. One of the recommendations was the need for improved vaccine delivery methods [29]. As an alternate vaccine delivery system, inhalation of MVDP offers many potential advantages including needle free delivery, lower skill level required for vaccinators and potential cost reduction. The benefits of needle free vaccination are widely recognized and have provided motivation for this work [7,30]. An economic model of the potential cost effects of alternate vaccine delivery systems indicated that dry powder vaccination provided the most cost advantage of the systems studied. Dry powder vaccination reduced the estimated $2.52 average cost per dose delivered in the developing world by $0.17 [31].

Respiratory delivery of measles vaccine as MVDP offers several advantages that could help overcome some of the logistic challenges associated with subcutaneous injection. However, there are several theoretical concerns with the respiratory route of measles vaccine administration. First, since the vaccine is deposited in the lower airways, the risk of pulmonary inflammation should be considered. Many pharmaceuticals are delivered to the lungs via dry powder administration in frequently repeated doses without pulmonary adverse effects. Also, liquid measles aerosol vaccine has been studied in multiple clinical trials without report of pulmonary adverse effects. This clinical trial also showed no pulmonary adverse effect following inhalation of MVDP. The few instances of abnormal respiratory rate measurement seen during this study were not clinically significant and occurred in similar rates in all groups.

A second theoretical risk is that live attenuated measles vaccine may be more virulent when delivered by the inhalation route, especially in high risk, HIV-infected, and other immunosuppressed individuals. Clinical trials with liquid aerosol measles have not shown increased virulence of live measles vaccine delivered by inhalation even in subjects not immune to measles, though studies in immunocompromised patients and HIV infected individuals have not been performed. In this study, there was no evidence of increased virulence with live vaccine virus, though all subjects were immune competent, HIV seronegative, and almost all had protective titers of neutralizing antibody on the day of vaccination.

A third theoretical risk is the potential for adverse events in the central nervous system due to exposure of the olfactory nerve via the cribiform plate in the upper nasal airway. An increased incidence of Bell's palsy was reported in a nasally delivered influenza vaccine which included an endotoxin as an adjuvant. This vaccine is no longer in clinical use [32]. However, millions of doses of currently available live attenuated influenza vaccine have been administered intranasally without reports of neurologic effects. Also, no neurologic events have been reported from the clinical trials with liquid measles vaccine, which administered the vaccine via a mask, permitting nasal inhalation and potential exposure of the cribiform plate. In this study, vaccine was administered via a mouthpiece which prevented nasal inhalation of the vaccine and exposure of the cribiform plate (except potentially on exhalation). Therefore the risk of neurologic adverse events due to vaccine virus deposition on the cribiform plate was not specifically assessed by this study.

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Finally, aerosolization of live measles vaccine, as a liquid or a powder, raises the potential risk of escape of the aerosol vaccine into the environment, with potential inadvertent vaccination of bystanders in the room. Clinical trials of liquid aerosol vaccine indicated no evidence of immune responses among vaccinators administering aerosol measles vaccine, suggesting the risk of inadvertent bystander vaccination is low [10,33,34]. We did not assess this risk in this phase I trial.

Previous efforts to develop dry powder measles vaccine for inhalation used jet milling of lyophilized measles vaccine to generate particle sizes appropriate for pulmonary delivery (1–5 μm), and demonstrated adequate potency retention of the live measles vaccine. However, delivery of the powder measles vaccine was not successful in producing immune responses in preclinical trials in non-human primates [35]. In contrast, MVDP was immunogenic in rhesus macaques and protected these animals from challenge with measles virus [24].

This Phase I clinical trial demonstrated a comparable safety and immunogenicity profile of MVDP via Puffhaler® and Solovent™ devices to that of a commercial measles vaccine given by injection in a healthy measles immune adult population. Further development of MVDP to achieve the potential advantages of this needle-free, cost effective delivery system will require additional larger clinical trials especially in younger subjects without pre-existing immunity who are the primary target for measles vaccination.

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Conflict of interest statement

Prasad S Kulkarni, Rajeev M Dhere, Bhagwat Gunale, Vivek Vaidya, Ravindra Mulay, Amol Chaudhari are employed by Serum Institute of India Ltd. Scott Winston is a consultant to and Robert Sievers and Stephen Cape are employees of AktivDry LLC, Boulder. Ken Powell and Charles Shermer are employed by Becton, Dickinson & Company, USA.

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