MEASLES AEROSOL VACCINE PROJECT - REPORT TO SAGE

GOAL OF THE MEASLES AEROSOL VACCINE PROJECT

The goal of the Measles Aerosol Project is to license at least one method (vaccine and delivery device) for respiratory delivery of currently licensed measles vaccines. A measles vaccine that is effective, safe, easier to administer and with a comparable cost to subcutaneous administration.

WHY A MEASLES AEROSOL VACCINE?

The potential to reduce the challenges link to injection safety and waste management

Measles immunization campaigns are effective elements of a comprehensive strategy for preventing measles cases and deaths[i]. However, if immunizations are not properly administered or if immunization waste products are not safely managed, there is the potential to transmit bloodborne pathogens (e.g., human immunodeficiency virus and hepatitis B and hepatitis C). A safe injection can be defined as one that results in no harm to the recipient, the vaccinator, and the surrounding community. Proper

equipment, such as the exclusive use of auto-disable syringes and safety boxes, is necessary, but these alone are not sufficient to ensure injection safety in immunization campaigns. Equally important are careful planning and managerial activities that include policy and strategy development, financing, budgeting, logistics, training, supervision, and monitoring. The key elements that must be in place to ensure injection safety in measles immunization campaigns are outlined.
According to the Safe Injection Global Network (SIGN) 2010 meeting report[ii], the global burden of disease from unsafe medical injections has been estimated for the year 2008 by the World Health Organization from a probabilistic model. In total unsafe medical injections led to 340,000 HIV infections, 15 million HBV infections, 1 million HCV infections, 3 million bacterial infections and 850,000 injection site abscesses in 2008. These infections accounted for 14% of HIV infections, 25% of HBV infections, 8% of HCV infections and 7% of infections with bacteraemia worldwide and accounted for 28 million disability adjusted life years, a metric of the years of life lost to death and disability from AIDS, acute hepatitis, liver cancer, end-stage liver disease and fatal sepsis. After adjustment for a change in methodology in calculating the number of HIV infections resulting from unsafe medical injections, these figures represent a reduction in the burden of disease from unsafe medical injections since the year 2000.

Positive lessons learned from polio campaigns suggest that a vaccine that can be given by volunteers and be provided house to house can reach high coverage in low resource environments

The use of the bifurcated needle was one of the key elements in the achievement of smallpox eradication goal, together with strong political support and the adequate implementation of appropriate strategies. Similarly, experiences with polio eradication suggest that vaccination by volunteers using a house to house strategy had resulted in effective outbreak control and interruption of wild poliovirus transmission. Selected experiences over time are described below.

In 1993, due to persistence of poliomyelitis cases in the Pacific Coast of Mexico and particularly in the state of Sinaloa, a house to house vaccination strategy named "Sinaloa Operation" was carried out in 100% of the territory of this state[iii]. Simultaneously, teams of nurses carried out a population census of children less than five years old and pregnant women and vaccinated the children with Sabin trivalent vaccine in undiscriminating form. In total, 301, 441 Sabin vaccine doses were administered. As a result of this programme Sinaloa has not had any other polio case ever since. In a 1993, during a mass immunization campaign in Egypt, the vaccine coverage rate and per child vaccination costs were compared for house-to-house versus fixed-site oral poliovirus vaccine (OPV) delivery [iv]. House-to-house delivery achieved 100% OPV coverage, compared to about 86% for fixed-site delivery (p 0.01). The cost for house-to-house vaccination was 25% higher than for fixed-site vaccination in urban areas, while they were similar in rural areas. In urban areas, the cost per child vaccinated was similar for both fixed-site and house-to-house vaccinations ($0.11). In rural areas, it was higher for fixed-site delivery than for house-to-house delivery ($0.14 vs. $0.11). OPV wastage for both delivery approaches was the same (around 25%) in urban areas, while it was much higher for fixed-site vaccination than for house-to-house vaccination (41.5% vs. 23.5%). These findings suggested that, in Egypt, house-to-house delivery was the most cost-effective strategy to achieve universal coverage and thus to eradicate polio. A cross-sectional study in Ethiopia aimed at collecting qualitative and quantitative data for the systematic and epidemiological assessment of the extent of a polio outbreak in three regions between December 2004 and February 2006 (24 confirmed wild poliovirus cases), its determinants, and the lessons learned as well as the implications for future control strategies to interrupt wild poliovirus transmission[v]. In

response to the outbreak, Ethiopia implemented detailed outbreak investigations and large-scale, house-to-house vaccination campaigns. As a result, the three regions interrupted the wild poliovirus transmission within the regions within one year of confirmation of the index case. Outbreak response vaccination were successful in interrupting the imported wild poliovirus transmission within a one-year period of time.

IS THE MEASLES AEROSOL VACCINE SAFE?

A systematic review examined the safety of aerosolized measles vaccine one month or more after vaccination[vi]. Fever was the most frequently reported adverse event in six of the eight studies, followed by cough and rhinitis. Adverse events following aerosolized vaccine delivery were generally mild and infrequent. The studies reviewed did not identify severe side effects. The definitions and reporting of adverse events, was however, inconsistent and the authors were not able to synthesize data meaningfully.

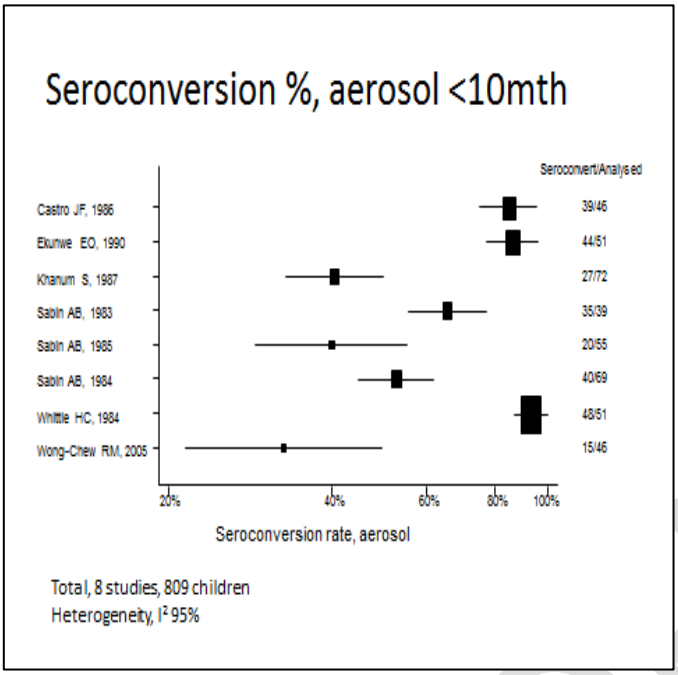
Another systematic review[vii] suggested that clinically, the aerosol route of delivery of vaccines is less reactogenic than the subcutaneous route. According to the authors, a numbers of studies have documented that the administration of vaccine through the injectable route is associated with a comparatively higher rate of adverse events. Measles vaccine administered through the aerosol or the respiratory route is well tolerated; common clinical adverse reactions are fever and mild conjuctival discharge. The aerosol group in each of the studies reviewed showed significantly lower frequency of fever, rhinitis, cough, generalized morbilliform rash, arthalgias and conjuctival hyperemia in infants.

During a Phase I trial in India[viii], the measles aerosol vaccine was administered to healthy measles immune volunteers 1-35 years of age using three different devices with comparable performance characteristics to the Classic Mexican Device (CMD) in three different sites in India. In total 145 volunteers were followed, among them 53 children 5-17 years of age and 32 children 1-4 years of age. The study found that the measles aerosol vaccine was safe, well tolerated and immunogenic in three different sites in India (WHO unpublished data).

A Phase II/III trial in India[ix] assessed the frequency of adverse events following measles aerosol and subcutaneous vaccination. Two thousand children 9 to 11.99 months of age received measles vaccine and were followed-up to 91 days after vaccination. A sub-set of 100 children enrolled were followed-up to 365 days after vaccination to ascertain the frequency of adverse events. The study reported adverse events that were generally mild and not related or unlikely to be related to vaccination. The most commonly reported adverse event was coryza followed by cough, diarrhoea, fever and vomit. One serious adverse event (urticaria with angioedema) that was deemed possibly vaccine related. It was resolved without sequelae. An independent Data Safety Monitoring Board (DSMB) had access to unblinded data for the assessment of serious adverse events. Based on the information presented in the Final Safety Report dated June 2012, the DSMB members concluded that they have no concerns regarding the safety profile of the aerosolized measles vaccine. Furthermore, the DSMB stated that the adverse event profile of the aerosol vaccine was similar to that of the subcutaneous vaccine. However, the DSMB noted the differences in symptoms and behaviour between the two groups during vaccine administration with a lower percentage of children crying, struggling or exhibiting shallow breathing in the aerosol group, suggesting better immediate tolerability. Aerosol administration was, however, associated with coughing in a minority.

IS THE MEASLES AEROSOL VACCINE EFFICACIOUS AND EFFECTIVE?

Evidence on immunogenicity of Measles Aerosol Vaccine in infants below 10 months of age



A systematic review examined the immunogenicity of aerosolized measles vaccine . In children below 10 months, eight studies provided data from a total of 809 infants. Serological responses were heterogeneous. Serological responses in infants < 10 month-old receiving measles aerosol vaccine ranged from 33% amongst 8-10 month-old infants in Mexico to 94% of 4-6 months old in the Gambia and; with subcutaneous measles vaccine from 51% in 4-6 month-old in Bangladesh to 100% in 6-9 months old in Mexico. In four trials that compared subcutaneous and aerosol routes the seroconversion was lower with aerosol than subcutaneous.

Seroconversion rates in children receiving the aerosol vaccine and with measles antibodies at baseline were lower than those for subcutaneous vaccination.

Conversely, a meta-analysis of studies comparing the aerosol route with the subcutaneous route reviewed seven studies involving children less than nine months of age . The summary estimate suggested that the seroresponse was 4% higher amongst vaccinees in the aerosol group than those in the subcutaneous group (M_H pooled RR=1.04, 95% CI = 0.98-1.1). %/). Inclusion criteria may account for some of the differences between these two systematic reviews.

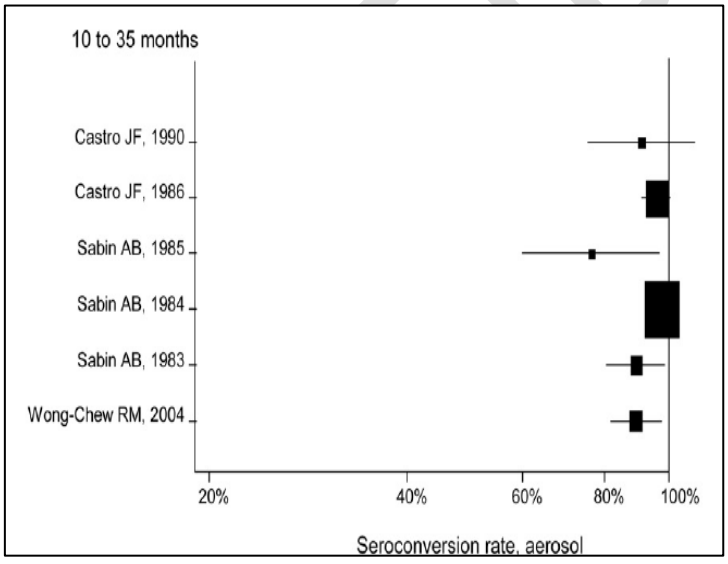
A phase II/III randomized, open-label, active-control, parallel group, non-inferiority trial of measles vaccine in healthy infants from 9-11.9 months of age was initiated in India in 2009[1]. The same dose (NLT 1000 CCID50) was administered by aerosol or by subcutaneous injection to a total of 2000 infants randomized 1:1 to the two arms. A subset of 100 subjects per arm was followed-up for 364 days for any serious or unexpected adverse events. Blood samples were taken at baseline and 91 days post-vaccination. Subjects in the sub-set also had blood samples taken at 28 days and 364 days post vaccination. Preliminary results are summarized below[x]. As per the PP analysis, the sero-positivity at Day 91 in aerosol group was 85.42% (CI: 82.53% to 87.90%) and of subcutaneous group was 94.65% (CI: 92.79% to 96.05%). The difference between aerosol and subcutaneous seropositive rate is -9.23% (CI: -12.22% to -6.30%) ($p<0.05$). As per the ITT analysis, the sero-positivity at Day 91 in aerosol group was 85.39% (CI: 82.44% to 87.91%) and of subcutaneous group was 94.72% (CI: 92.81% to 96.14%). The difference between aerosol and subcutaneous seropositive rate is -9.33% (CI: -12.30% to -6.42%) ($p<0.05$). The Product Development Group for this project reviewed the results of this trial and stated[xi]

[1] (http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=862).

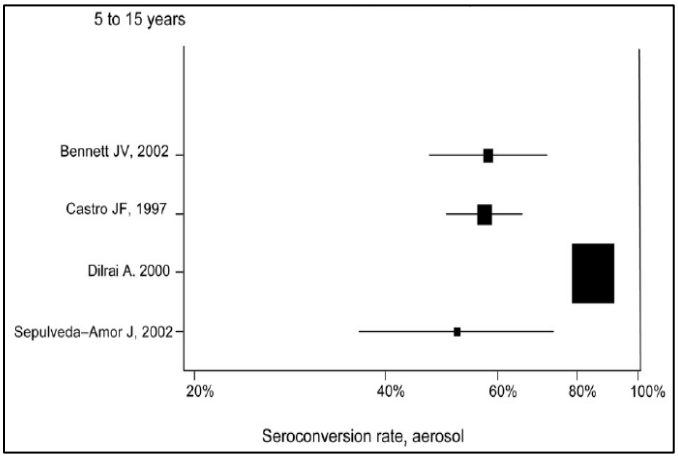
that the primary conclusion of this trial is that although the aerosol arm achieved seropositivity of 85.42% (CI: 82.53% to 87.90%) as per protocol analysis and of 85.39% (CI: 82.44% to 87.91%) as per intention to treat analysis, the non-inferiority criteria was not met. The difference in seropositivity between both study arms in this trial was -9.23% (CI: -12.22% to -6.30%) as per protocol analysis and -9.33% (CI: -12.30% to -6.42%) as per intention to treat analysis. This is greater than the non-inferiority margin of 5% defined in the study protocol. Therefore, the results of this trial suggest that measles aerosol vaccination is inferior to subcutaneous vaccination as a primary means of immunization in 9-11 months old children. The analysis of risk factors did not show any evidence that any of the factors investigated had a significant association to remaining seronegative. Data available suggest that there may be differences in the kinetics of the immune responses between the aerosol and subcutaneous routes. However, the PDG members acknowledged that they lack the data that would allow a clear interpretation that this differences exists and of the potential relevance. The results are applicable to the trial settings and aerosol delivery device used in this trial.

In a recent study in Mexico[xii], 113 healthy 9-month-old infants were enrolled; 58 received aerosol EZ measles vaccine for 2.5 minutes and 55 received the vaccine subcutaneously. Adaptive immunity was induced in 97% after aerosol and 98% after subcutaneous administration. Seroconversion rates and GMCs were 95% and 373 mIU/mL (95% confidence interval [CI], 441-843) following aerosol vaccination and 91% and 306 mIU/mL (95% CI, 367-597) after subcutaneous administration at 3 months. CD8 memory cell frequencies were higher in the aerosol group at 3 months compared with the subcutaneous group. The authors concluded that increasing exposure time to aerosol measles vaccine (i.e. from 30 seconds to 2.5 minutes) elicits immune responses that are comparable to those seen when an equivalent dose is administered by the subcutaneous route in 9-month-old infants.

Evidence on immunogenicity of Measles Aerosol Vaccine in older infants and children



A systematic review examined the immunogenicity of aerosolized measles vaccine .
In children 10-35 months of age, six studies included data on 449 children (five in Mexico and one in Brazil). Two studies included comparisons of seroconversion rates with aerosol and subcutaneous delivery. Four studies assessed only the aerosol route. The summary weighted seroconversion rates in aerosol (93.5%, 95% CI 89.4-97.7%) and subcutaneous (97.1%, 95% CI 92.4-100%) groups were similar and there was no statistical evidence of between study heterogeneity.

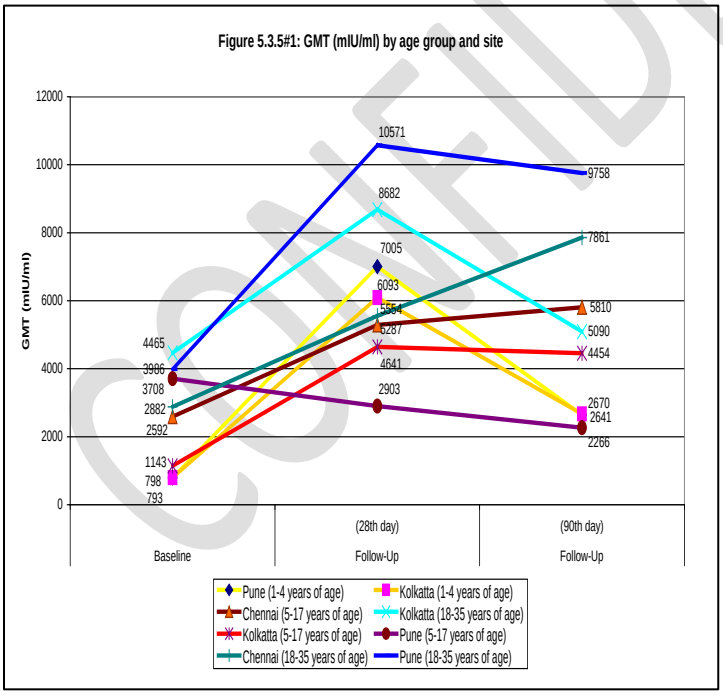


There were five reports (from 4 studies) including data about serological response in children 5-15 years old.

The studies were heterogeneous; therefore no pooled estimate was calculated. In all studies and all settings serological response rates were higher with aerosol than subcutaneous vaccination

A meta-analysis to evaluate the efficacy of measles vaccine administered through the respiratory route compared to the subcutaneous route reported that for vaccinees over 9 months of age, seroresponse was 15% higher in the respiratory group (M-H pooled RR = 1.15; 95% CI = 1.98 to 1.17).

During a Phase I trial in India (2007) , the measles aerosol vaccine was administered to healthy measles immune volunteers 1-35 years of age in three different sites in India. In total the study followed up 145 volunteers (WHO unpublished data). Blood samples were taken at baseline, 28 days and 90 after aerosol immunization.



Because all subjects in the study were measles immune (PRN titer ⩾ 120 mIU/mL), signs of immunogenicity are documented by boosting of baseline antibody titers.

This boosting effect was best documented in subjects with low (⩽ 2000 mIU/mL) and medium (2000 – 6000 mIU/mL) anti-measles antibodies, throughout the study (all groups, all sites).

Subjects with lower baseline anti measles titers showed very good boosting at 28 days and at 90 days, thus indicating that measles aerosol vaccine has good potential immunogenicity.

In summary, the measles aerosol vaccine was immunogenic in healthy volunteers 1-35 years of age in three different sites in India, using three different nebulizers.

Evidence on immunogenicity of measles aerosol vaccine when administered as a second dose.

In a randomized controlled trial of aerosol and subcutaneous measles vaccines in South African schoolchildren[xiii], 4327 schoolchildren (aged 5-14 years), assigned by block randomization of classrooms, received standard titre doses of either Schwarz or Edmonston-Zagreb measles vaccines subcutaneously or by aerosol. Blood samples for antibody assay were collected before vaccination at 1 month, and 1 year after vaccination. Eighty five per cent of all enrolled children had either had measles or been vaccinated. Serological responses were measured in all children who were seronegative and a 9% random sample of seronegatives. Overall, amongst those followed up 85% seroconverted. 14 (3.6%) of 385 children who received Edmonston-Zagreb vaccine by aerosol were seronegative 1 year after vaccination, compared with 28 (8.6%) of 326 children who received Edmonston-Zagreb subcutaneous vaccine and 39 (13.9%) of 281 children who received Schwarz subcutaneous vaccine. At 1 month, 326 (84.7%) children who received aerosol Edmonston-Zagreb vaccine had seroconverted compared with 257 (78.8% who received subcutaneous Edmonston-Zagreb vaccine and 176 (62.6%) who received subcutaneous Schwarz vaccine.

Evidence of long-term persistence of measles antibody titer after measles aerosol vaccine administration

To assess the long-term persistence of measles antibody after vaccination by the aerosol route the children in the South African trial described above were followed up 6 years after their re-vaccination with Edmonston–Zagreb (EZ) and Schwarz (SW) measles vaccine given by aerosol and subcutaneous routes[xiv]. Measles antibody levels and the proportion of children who were seropositive at year 6 remained significantly higher in the Edmonston–Zagreb aerosol group compared to the groups that received Schwarz or Edmonston–Zagreb vaccine subcutaneously. Authors concluded that measles re-vaccination by aerosol evokes a stronger and much longer lasting antibody response than injected vaccine and should thus provide more durable protection against measles.

Proportion seropositive 6 years after re-vaccination among younger and older children receiving aerosol or injected vaccine.

	Aerosol (%; 95%CI)	Injected (%; 95%CI)	*p*-value
Younger (5-9 years at re-vaccination)			
Baseline seropositive	56/65 (86%; 75-94)	68/98 (69%; 59-78)	0.01
Baseline seronegative	38/47 (81%; 67-91)	36/71 (51%; 39-63)	0.001

Seropositivity at 6 by vaccine group and other covariates

	Number seropositive/total (%)	Adjusted odds ratio	95%CI	*p*-value
Vaccine group				
EZae	105/124(84.7)	1.00	-	-
EZsc	72/99(72.7)	0.33	0-16-0-69	0.003
SWsc	59/101(58.4)	0.20	0.10-0.40	0.000
Age when vaccinated				
5-9 years	188/270(69.6)	1.00	-	-
10-14 years	48/54(88.9)	3.90	1.6-10	0.001
Gender				
Female	142/181(78.5)	1.00	-	-
Male	94/143(65.7)	0.60	0.35-1.0	0.06

Adapted from Dilraj et al, 2007.

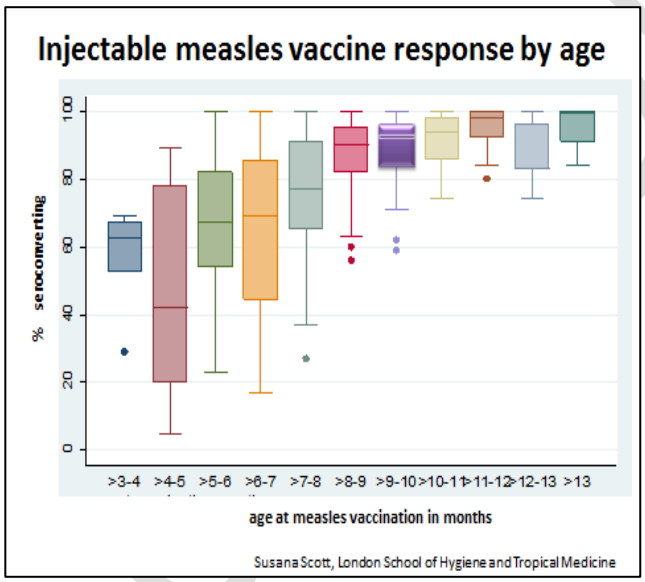
Evidence of impact of measles aerosol vaccine when used during outbreaks

In 1988-90, at the time of a large measles outbreak in Mexico a mass campaign using measles aerosol vaccine was conducted[xv]. A total of 3,760,684 children were vaccinated with measles aerosol vaccine. Of those 10.5% were aged 1-5 years old and 89.5% were 6-12 years old.

The authors acknowledged difficulties with impact evaluation due to different coverage in the various States involved and the fact that the vaccine administration was not simultaneous everywhere and spread over a long time period. However, data from cases 1-4 years of age in the State of Aguas Calientes where the vaccination status could be ascertained yielded a vaccine efficacy of 95.5%. Similarly, in a town in Jalisco State (San Juan Cosala) where 95% of the population from 8 months to 14 years of age were vaccinated with measles aerosol vaccine. The attack rates among the unvaccinated was 0.0035 (58/16167) and among the vaccinated it was 0.00015 (9/58370). The estimated vaccine effectiveness was 95.7%.

Evidence on the efficacy and effectiveness of measles injectable vaccine in infants and older children

Frequently cited figures are that approximately 85% of children develop protective antibody levels when given one dose of measles vaccine at nine months of age, and 90% to 95% respond when vaccinated at 12 months of age[xvi].



Among the 44 studies included in a systematic review[xvii], for children vaccinated between 8 and 9 months of age, the median proportion of children responding was 89.6% (mean 86.7; minimum 56; maximum 100; interquartile range (IQR) 82, 95).
Among the 24 studies included in which children were vaccinated between 9 and 10 months of age, the median proportion of children responding was 92.2% (mean 88.2; minimum 59; maximum 100; IQR 84, 96).
Among the 21 studies included in which children were vaccinated between 11 and 12 months of age, the median proportion of children responding was 99% (mean 95.7; minimum 80; maximum 100; IQR 93, 100).

A review of vaccine effectiveness studies published during 1960–2010 included seventy papers with 135 vaccine effectiveness (VE) point estimates[xviii]. For a single dose of vaccine administered at 9–11 months of age and at 12 months of age, the median VE was 77.0% (interquartile range [IQR], 62%–91%) and 92.0% (IQR, 86%–96%), respectively. When analysis was restricted to include only point estimates for which vaccination history was verified and cases were laboratory confirmed, the median VE was 84.0% (IQR, 72.0%–95.0%) and 92.5% (IQR, 84.8%–97.0%) when vaccine was received at 9–11 and at 12 months, respectively. Published VE vary by World Health Organization region, with generally lower estimates in countries belonging to the African and Southeast Asian Regions. For 2 doses of measles-containing vaccine, compared with no vaccination, the median VE was 94.1% (IQR, 88.3%–98.3%). The VE of the

first dose of measles-containing vaccine administered at 9–11 months was lower than what would be expected from serologic evaluations but was higher than expected when administered at $12 months. The median VE increased in a subset of articles in which classification bias was reduced through verified vaccination history and laboratory confirmation. In general, 2 doses of measles-containing vaccine provided excellent protection against measles.

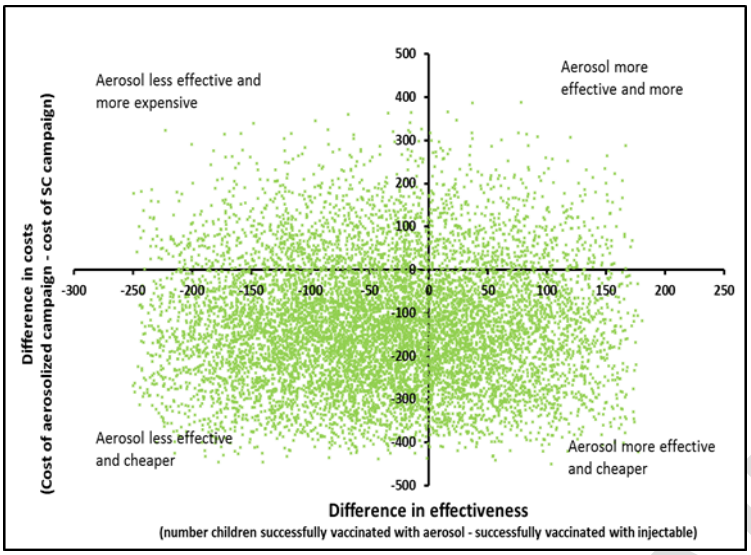
Evidence on the cost and cost-effectiveness of a measles aerosol vaccine

A study evaluated 4 new measles vaccine technologies[xix]: aerosol delivery, needle-free injection, inhalable dry powder, and early administration DNA vaccine included 4 major components: (1) identifying potential innovations, (2) developing transmission models to assess mortality and morbidity impacts, (3) estimating the unit cost impacts, and (4) assessing aggregate cost-effectiveness in United Nations Children's Fund countries through 2049. Results suggested that these technologies are projected to have a small absolute impact in terms of reducing the number of measles cases in most scenarios because of already improving vaccine coverage. Three (all but the DNA vaccine) are projected to reduce unit cost per dose by $0.024 (jet injector), $0.044 (aerosol nebulizer) to $0.170 (inhalable dry powder) and would improve overall cost-effectiveness. Each will require additional investments to reach the market. Over the next 40 years, the aggregate cost savings could be substantial, ranging from $98.4 million (jet injector), $154.1 million (aerosol nebulizer) to $689.4 million (inhalable dry powder). Authors concluded that these three new measles vaccination technologies under development hold promise to be cost-saving from a global perspective over the long-term, even after considering additional investment costs.

Another study used a modified Child Health and Nutrition Research Initiative (CHNRI) methodology for setting priorities in health research investments assessed the strengths and weaknesses of measles aerosol vaccine to decrease the burden of childhood pneumonia[xx]. A panel of experts expressed mixed feelings about an aerosol measles vaccine. The group expressed low levels of optimism regarding the criteria of likelihood of efficacy and low cost of development (scores around 50%); moderate levels of optimism regarding answerability, low cost of production, low cost of implementation and affordability (score around 60%); and high levels of optimism regarding deliverability, impact on equity and acceptability to health workers and end-users (scores over 80%). Finally, the experts felt that this intervention will have a modest but nevertheless important impact on reduction of burden of disease due to childhood pneumonia (median: 5%, interquartile range 1-15%, minimum 0%, maximum 45%). Aerosol measles vaccine is at an advanced stage of development, with evidence of good immunogenicity. This new intervention will be presented as a feasible candidate strategy in the campaign for global elimination of measles. It also presents a unique opportunity to decrease the overall burden of disease due to severe pneumonia in young children.

A study evaluated the incremental cost-effectiveness ratio of delivery of measles vaccine with an aerosol device as compared to delivery with traditional subcutaneous injection. The model used data from a Phase II/III RCT in India.[xxi] A model of the possible impact of reduced personnel costs for the delivery of the aerosolized on the 'Incremental Cost Effectiveness Ratio' of Aerosol vs. Injectable measles vaccine used the same base values as for the RCT of 2000 children. The researchers ran a simulation to estimate the incremental cost-effectiveness ratio (ICER) comparing the aerosolized to the injectable vaccine in the context of a very small vaccination campaign (n=2000, the size of the trial). The difference in the costs of the two approaches included the treatment of adverse events, estimated from the trial data, and salaries of the vaccinators, which depended on the time required to deliver the vaccine and the person who were to give the vaccine (i.e. nurse vs. non-health professionals). The difference in effectiveness

was varied by assuming that the coverage would vary between 70% and 90% for the injectable vaccine and between 70% and 99% for the aerosolized vaccine. The efficacy estimates are from the trial results.



Preliminary results are available
Running this scenario resulted in a median ICER of $0.65 (95% CI: -$12.23; $12.61) in favour of the aerosolized vaccine. In summary, 53% of the iterations resulted in the aerosolized vaccine being less effective but cheaper, and in 29% of iterations resulted in a cheaper and more effective aerosol vaccine.
Work is ongoing to refine the assumptions and parameter estimates and to run the model using a larger population size and using even more realistic costs for the treatment of adverse events.

Assessment of the usability and acceptability of a measles aerosol vaccine

Four qualitative assessments of acceptability of the measles aerosol vaccine were conducted (Guyana, Oman, Burkina Faso and Vietnam). Methods included: focus groups (informal, semi-structured and flexible group dynamic), semi-structured interviews (Ministry of Health staff at national, regional and health facility level; community members: parents of children with target age groups, children, community leaders) and immunizations session observations. In general the results from these four studies supported the introduction of measles aerosol vaccine on the grounds that it is pain free, easy to use, less anxiety for parents, no injection safety concerns, easier waste management, potential for less AE and, “modernity". Different groups also raised concerns related to aerosol vaccination including: health workers were concerned about not providing the correct dose, parents/community members raised concerns about potential risk of cross-contamination and potential for measles aerosol vaccine to result in greater number of AE. Managers where reportedly anxious about potential costs of introduction and use of an additional route of administration. Although there are common findings, these are likely to be setting and background-specific and therefore caution should be exercised on the generalizability of these results.

During a Phase II/III trial in India a qualitative evaluation of the acceptability and usability of the measles aerosol vaccine device from the perspective of the vaccinators and the parents/guardians was conducted. In general the majority of vaccinators found that the device was: easy to assemble and operate, easy to place the vial in the dropper, easy to squeeze the dropper to obtain a defined number of drops, easy to store after use and, appeared easy to use and to function. Nearly 65% of the parents interviewed expressed their preference for the aerosol route of administration if both methods (aerosol or subcutaneous) were equally good to protect their child against measles. 38% of the parents whose child received the subcutaneous vaccine and 91% of the parents whose child received the aerosol vaccine expressed their preference for the aerosol.

Evidence on immunogenicity of Aerosol Measles Rubella and measles Rubella Mumps containing vaccines

There are an increasing number of studies where subjects were randomized to receive either MR or MMR vaccines. Below we summarized two studies to illustrate the progress and potential but this information is not comprehensive.

A study compared antibody responses and side-effects of aerosolized and injected measles vaccines after revaccination of children enrolling in elementary schools[xxii]. Vaccines for measles (Edmonston-Zagreb) or measles-rubella (Edmonston-Zagreb with RA27/3) were given by aerosol or injection to four groups of children. An additional group received Schwarz measles vaccine by injection. These five groups received vaccines in usual standard titre doses. A sixth group received only 1000 plaque-forming units of Edmonston-Zagreb vaccine by aerosol. The groups were randomized by school. Blood specimens were taken at baseline and four months after vaccination from randomized subgroups (*n*=28-31) of children in each group. After baseline antibody titres were controlled for the frequencies of fourfold or greater increases in neutralizing antibodies did not differ significantly between the three groups that received vaccine by aerosol (range 52%-64%); but they were significantly higher than those for the three groups that received injected vaccine (range 4%-23%). Mean increases in titres and post-vaccination geometric mean titres paralleled these findings. Fewer side-effects were noted after aerosol than injection administration of vaccine.

A trial to assess the reactogenicity and immunogenicity of combined measles and rubella (MR) booster vaccination, via aerosol and subcutaneous routes in 562 healthy children was conducted[xxiii]. Rates of rubella seroconversion and geometric means titers (GMT) were similar for both routes. Rates of measles PN seroconversion, GMT and measles ELISA post-vaccination seropositivity and seroconversion rate were each higher for aerosol vaccine (54%, 3928 IU/l, 99.6 and 98.8%), than for subcutaneous vaccine (7%, 866 IU/l, 92.2 and 82.4%) (P<0.01). Reactogenicity was higher for subcutaneous vaccines (P<0.05). This study reported that aerosol vaccine was more immunogenic for measles antibodies, and equally immunogenic for rubella antibodies. Aerosol vaccine was less reactogenic.

Potential additional research

During the 11th Meeting of the Product Development Group, PDG members noted that additional studies should be considered to further evaluate the measles aerosol vaccine, namely: immunogenicity in older children (e.g. >12 months of age) and; evaluation of the immune response using other immunological criteria including the assessment of the kinetics and duration of antibodies, and the differences in T cell responses. They also noted that shall individual countries consider moving forward with the licensure and introduction of the measles aerosol vaccine, other key factors besides the immunogenicity results should be included in the assessment such as: the incremental cost effectiveness analysis ; the evidence on its acceptability and usability; the potential performance of the measles aerosol vaccine in older children and in mass campaigns, its likely use for the administration of the second dose of measles vaccine and, the potential device improvements to facilitate its use in low resource environments. They recommended that the results of this trial should be considered in a context of a change in global measles immunization policies and goals, which encompasses recent recommendations for a widespread introduction of a second dose of a measles vaccine, primary vaccination at 12 months of age in countries with high levels of coverage or in the elimination phase and, recommendations for introduction of rubella vaccine.

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