

Research Paper

A Meta-Analysis of Studies Comparing the Respiratory Route with the Subcutaneous Route of Measles Vaccine Administration

Girish S. Hiremath¹

Saad B. Omer^{1,2,*}

¹Department of International Health; Johns Hopkins Bloomberg School of Public Health; Baltimore, Maryland USA

²Institute for Vaccine Safety; Johns Hopkins Bloomberg School of Public Health; Baltimore, Maryland USA

*Correspondence to: Saad B. Omer, M.B.B.S., M.P.H.; Associate Director for Data Management, Institute for Vaccine Safety; Research Associate, Department of International Health; Johns Hopkins Bloomberg School of Public Health; 615 North Wolfe Street; Room W5507; Baltimore, Maryland 21205 USA; Tel.: 410.502.2709; Fax: 410.502.6733; Email: somer@jhsph.edu

Received 09/01/04; Accepted 11/12/04

Previously published online as a *Human Vaccines* E-publication:
<http://www.landesbioscience.com/journals/vaccines/abstract.php?id=1423>

KEY WORDS

meta-analysis, aerosol vaccine, measles vaccine, aerosol measles vaccine, vaccine administration

ABSTRACT

The respiratory tract has been suggested as an optimal alternative site to target measles vaccine delivery. We performed a meta-analysis to evaluate the efficacy of measles vaccine administered through the respiratory route compared to the subcutaneous route. We analyzed 20 reported results from 16 eligible studies. Seroreponse was 4% higher amongst vaccinees in the respiratory group compared to the subcutaneous group (M-H pooled RR = 1.04; 95% CI = 0.98–1.10). For vaccinees over 9 months of age, seroreponse was 15% higher in the respiratory group (M-H pooled RR = 1.15; 95% CI = 1.08 to 1.17). When Edmonston Zagreb (EZ) strain was used, the vaccine was found to be neither more nor less efficacious when administered through respiratory route (M-H pooled RR=1.00; 95% CI = 0.94 to 1.08). Seroreponse in the vaccinees receiving aerosol measles vaccine was 10% higher (M-H pooled RR = 1.10, 95% CI = 1.04–1.17) compared to those who received measles vaccine through the subcutaneous route. Seroreponse due to aerosolized EZ vaccine was 9% higher than subcutaneous EZ vaccine (M-H pooled RR = 1.09; 95% CI = 1.02–1.16). The seroreponse among seropositive vaccinees was 60% higher (M-H RR = 1.60; 95% CI = 1.40 to 1.80). The results suggest that the respiratory route of delivery of measles vaccine is at least as efficacious as measles vaccine administered through the subcutaneous route. However, more research is required on standardization of dosage, administration equipments, efficacy, and safety of respiratory (aerosol) route of administration of measles vaccine.

INTRODUCTION

Measles is responsible for the highest number of deaths due to a vaccine-preventable childhood disease.¹ It is estimated that over 30 million cases and 875,000 deaths occur every year from measles. Of the deaths attributable to measles, 98% occur in developing countries and case-fatality rates are estimated to be in the range of 1–5% but may reach 10–30% in some emergency situations.¹

Failure to deliver at least one dose of measles vaccine to all eligible children remains the primary reason for high measles morbidity and mortality. There is an increased momentum towards measles control and elimination worldwide. This has encouraged researchers and policy makers to explore, among many options, the potential for an easier and cheaper delivery method for existing measles vaccine that could induce safe levels of immune response and be useful in immunizing large number of susceptible children in a safe, cost effective, and efficient way.^{1,2}

The respiratory tract has been suggested as an optimal alternative site to target vaccine delivery.³ This mode of vaccination could be even more appropriate for measles vaccine, as it happens to be similar to the route of natural infection.¹ Since the respiratory route of delivery of measles vaccine has the potential to be an effective, harmless, simple, inexpensive, and practical method to decrease the measles burden worldwide,⁴ it is attracting more attention than ever before. The World Health Organization (WHO) has set up a WHO Product Development Group for Measles Aerosol Vaccine,² to look into the various aspects of feasibility of the aerosol route of administration of measles vaccine.

A couple of reviews^{5,6} of different routes of administration of measles vaccine have been published earlier; however, to our knowledge, no meta-analysis has been conducted to compare the alternative routes of administration for measles vaccine. We performed a meta-analysis to evaluate if the respiratory route of administration of measles vaccine has comparable or better efficacy in eliciting a seroreponse in vaccinees and to critically analyze the available research evidence of administration of measles vaccine through the respiratory route.

Table 1 **Descriptive characteristics of included studies (result wise)**

Author	Year	Country	Quality Score	Random Allocation of vaccines	Age	Exposed before intervention	Respiratory technique	Vaccine	Dosage		Seroreponse		Follow up period
									Respiratory route	Subcutaneous	Respiratory (%)	Subcutaneous (%)	
			(Max = 25)										
Black et al. (26)	1960	USA	14	No	2 wks–12 yrs	No	Nasal swab of anterior nares	EE* A&B	5000–10,000 TCID ₅₀	50 TCID ₅₀	4/11 (36)	9/9 (100)	6 wks
Okuno et al. (19)	1965	Japan	12	No	Children	Yes	Inhalation by Nisso-type nebuliser	Biken	20 TICD ₅₀	Not mentioned	16/16 (100)	8/15 (53)	4 wks
Ueda et al. (a) (20)	1966	Japan	12	No	1–7 yrs	Yes	Nasal spray	Biken (Plain)	20 TICD ₅₀	Not mentioned	12/13 (92)	4/6 (67)	4 wks
Ueda et al. (b) (20)	1966	Japan	12	No	1–7 yrs	Yes	Nasal spray	Biken (Aluminium phosphate as an adjuvant)	20 TICD ₅₀	20 TICD ₅₀	5/11 (45)	1/8 (13)	4 wks
Saidi et al. (24)	1969	Iran	15	No	5–7yrs	No	Nasal drops	Measles (SW #) + Rubella antigen 27/3	0.2 ml of 10 ^{2.8} TCID ₅₀	0.5 ml of 10 ^{2.8} TCID ₅₀	9/11 (82)	7/7 (100)	Not mentioned
Kok et al. (31)	1983	Kenya	22	Yes	9–23 mo	No	Nasal drops	EZ** - Attenuvax	1260 TCID ₅₀	1260 TCID ₅₀	4/25 (16)	17/23 (74)	4 wks
Cernescu et al. (33)	1984	Romania	7	No	Children	Not Mentioned	Nasal spray	L-16***	5000–10,000 TCID ₅₀	50 TCID ₅₀	7/8 (88)	11/11 (100)	30 days
Sabin et al. (27)	1984	Mexico	13	No	4–6 mo	Not Mentioned	Aerosol	HDC\$ (EZ)	3,750 PFU	5000 PFU	51/78 (65)	16/37 (43)	7 wks
Whittle et al. (29)	1984	Gambia	13	No	4–6 mo	Not Mentioned	Aerosol	EZ	3500–7000 PFU	39,800 PFU	48/51 (94)	21/21 (100)	Not mentioned
F de Castro et al. (34)	1986	Mexico	10	Blinded	6–9 mo	Not Mentioned	Aerosol	HDC (EZ)	10 ^{5.2} TCID ₅₀ /ml	10 ^{3.3} TCID ₅₀ /ml	39/46 (85)	16/16 (100)	6 wks
Torigoe et al. (13)	1986	Ghana	14	Yes	5 mo–5 yrs	Not Mentioned	Aerosol	Connaught	5.5 x 10 ⁵ TCID ₅₀ /ml	5.5 x 10 ⁵ TCID ₅₀ /ml	13/22 (59)	24/25 (96)	4 wks
Khannum et al. (a) (17)	1987	Bangladesh	13	No	4–6 mo	Not Mentioned	Aerosol	EZ	5000 PFU(e)	5000 PFU	25/72 (35)	25/42 (60)	4 wks
Khannum et al. (b) (17)	1987	Bangladesh	13	No	5–6 mo	Not Mentioned	Aerosol	SW	6310 PFU(e)	6310 PFU	20/59 (34)	24/65 (37)	4 wks
Simasethin et al. (a) (35)	1997	Thailand	22	Yes	6 mo	No	Nasal instillation	EZ	2000 - 25,000 PFU/ dose	6500 PFU	0/12 (-)	14/23 (62)	12 ± 4 wks
Simasethin et al. (b) (35)	1997	Thailand	22	Yes	7 mo	No	Nasal spray	EZ	11,600 PFU/dose	6500 PFU	2/20 (10)	14/23 (62)	12 ± 4 wks
Dilraj et al. (23)	2000	South Africa	22	Yes	5–14 yrs	No	Aerosol	EZ	5000 PFU/dose	10 000 PFU/dose	326/385 (85)	257/326 (79)	4 wks
Amor et al. (21)	2002	Mexico	22	Yes	6.5 yrs (Mean)	Yes	Aerosol	EZ + RA 27/3	EZ component = 3.9 log 10/ml PFU	EZ component = 3.9 log 10/ml PFU	85/86 (99)	103/125 (82)	4 mo
Bennett et al. (a) (22)	2002	Mexico	22	Yes	6–8 yr	Yes	Aerosol	EZ	10 ^{3.9} PFU	10 ^{3.9} PFU	20/31 (65)	1/28 (4)	4 mo
Bennett et al. (b) (22)	2002	Mexico	22	Yes	6–8 yrs	Yes	Aerosol	EZ+RA 27/3	EZ component = 10 ^{4.2} PFU	10 ^{3.9} PFU	15/28 (54)	2/30 (7)	4 mo
Wong Chew et al. (30)	2004	Mexico	22	Yes	15 mo	No	Aerosol	EZ	10 ^{3.6} PFU/0.1 ml	10 ^{4.27} PFU/0.5 ml	10/20 (50)	8/23 (35)	12 wks

* EE = Edmonston Ender; **EZ = Edmonston Zagreb; *** L-16= Leningrad – 16; \$HDC= Human Diploid Cell; #SW= Schwartz.

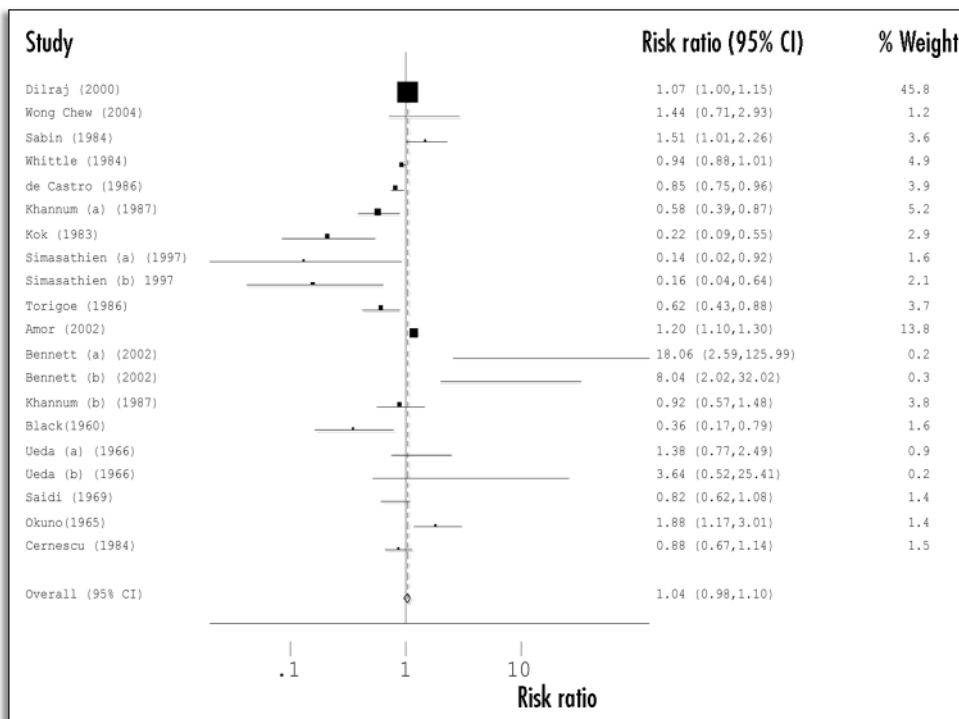


Figure 1. Forest plot of all included results.

MATERIALS AND METHODS

Search. We performed an online search on Pub Med/Medline for published studies from 1952 to May 2004, Cochrane database for both published and unpublished studies, and UMI ProQuest I database for online digital dissertations. The search keywords were measles vaccine, measles aerosol vaccine, nasal route, inhalation of measles vaccine, and vaccine preventable diseases. We sought references of published studies and review articles. We separately searched for relevant documents on the names of individual authors known to be working in this field. We contacted some authors working in this field for clarification about their study design, and to obtain information about unpublished data.

Selection of studies. We included a study if it compared the proportion of seroresponse amongst vaccinees when measles vaccine was administered by the respiratory route and the subcutaneous route. We excluded a study if (A) it was not published in English, (B) seroresponse was not measured, (C) if different strains of vaccine (i.e., either Edmonston Zagreb (EZ) or Schwarz strain (SZ) or Edgers Edmonston (EE) strain) were used in each group (i.e., respiratory group and subcutaneous group), D) only one route (either respiratory or subcutaneous route) was used to deliver vaccine.

Primary outcome and unit of analysis. We chose the proportion of seroresponse in different vaccinee groups in each study as the primary outcome. Due to advances in the scientific knowledge and availability of sophisticated tests, the definition of seroresponse has undergone modifications over the period during which the studies were carried out. Therefore, to minimize the bias we chose to use the authors' definition of seroresponse. In the studies where the seroresponse was measured by different techniques, we considered seroresponse measured by plaque neutralization (PN) studies. In the studies which reported serial seroresponse over a period of time, we considered the earliest reported seroresponse for the analysis. We stratified the studies into those with vaccinee ages less than nine months and those with vaccinee ages more than nine months. For the studies that reported comparison of more than one respiratory technique to the subcutaneous route, we included all the reported results as individual units of analysis.

Quality assessment and data abstraction. We developed a quality assessment framework (available on request) to facilitate the assessment of the

design and the methodology of each study.⁷⁻⁹ Each of the studies was independently assessed as per (1) population description, (2) study design, (3) selection of subjects, (4) mechanism of enrollment, (5) description of vaccine, (6) description of vaccine administration technique.

Without the knowledge of the outcome, we designed a data abstraction form to extract relevant data from each of the included studies. We abstracted information on the baseline characteristics of the study population, the design, and the seroresponse in each study. The information included name of the first author, year of publication, the country in which the study was carried out, if the vaccinees were randomly allocated to different groups, age of vaccinees, prior exposure status of vaccinees, and first reported follow up duration of vaccinees, the vaccine employed, different respiratory techniques of delivery of vaccine, and the seroresponse among the vaccinees in each group.

Quantitative data analysis. We performed the meta-analysis using the *metan* command of Stata 8™ statistical software. We chose risk ratio of seroresponse between the respiratory route and the subcutaneous route as the principal measure of effect. We calculated combined risk ratio among studies

by the Mantel Haenszel method. The risk ratio was calculated at alpha value of 0.05, the confidence interval values including 1 were considered statistically nonsignificant. Owing to significant heterogeneity among all included studies as measured by these tests, we performed meta-analysis using the random effects model. We used the χ^2 test for heterogeneity to calculate the heterogeneity between the trials.¹⁰ We used the *metabias* command proposed by Begg and Mazumdar¹¹ and by Egger et al.¹² to assess the potential publication bias.

RESULTS

Our primary search yielded a total of 38 relevant published articles. We further evaluated the studies as per inclusion and exclusion criteria. Thirteen articles were excluded, as they were either not clinical trials evaluating the route of measles vaccine administration or were not in English. Of the remaining 25 studies, we excluded two studies because the intramuscular route was employed; we excluded three studies as these evaluated only the respiratory route of delivery; one study did not report the proportion of seroresponse amongst the vaccinees of the two groups; two studies evaluated only the respiratory route of delivery with both Human Diploid Cell Measles Vaccine (Mexico) strain and Chick Embryo Fibroblast Measles Vaccine (Slavo) strain and we excluded one study because it employed only the inhalation route and evaluated the specific clinical reaction(s). On complete data abstraction, we identified 20 reported results as units of the analysis from sixteen eligible studies.

Study characteristics

The selected studies showed substantial diversity in terms of geographical distribution, strains of vaccine employed, dosage administered in each arm of the study, technique of administering vaccine through the respiratory route, and assessing the outcome intervention. The largest number of trials was reported from Mexico. Seven studies clearly mentioned that the vaccinees were allocated to the respiratory and the subcutaneous routes of delivery through the process of randomization. The age group of the vaccinees in different studies ranged from 2 weeks to 14 years. Two studies broadly

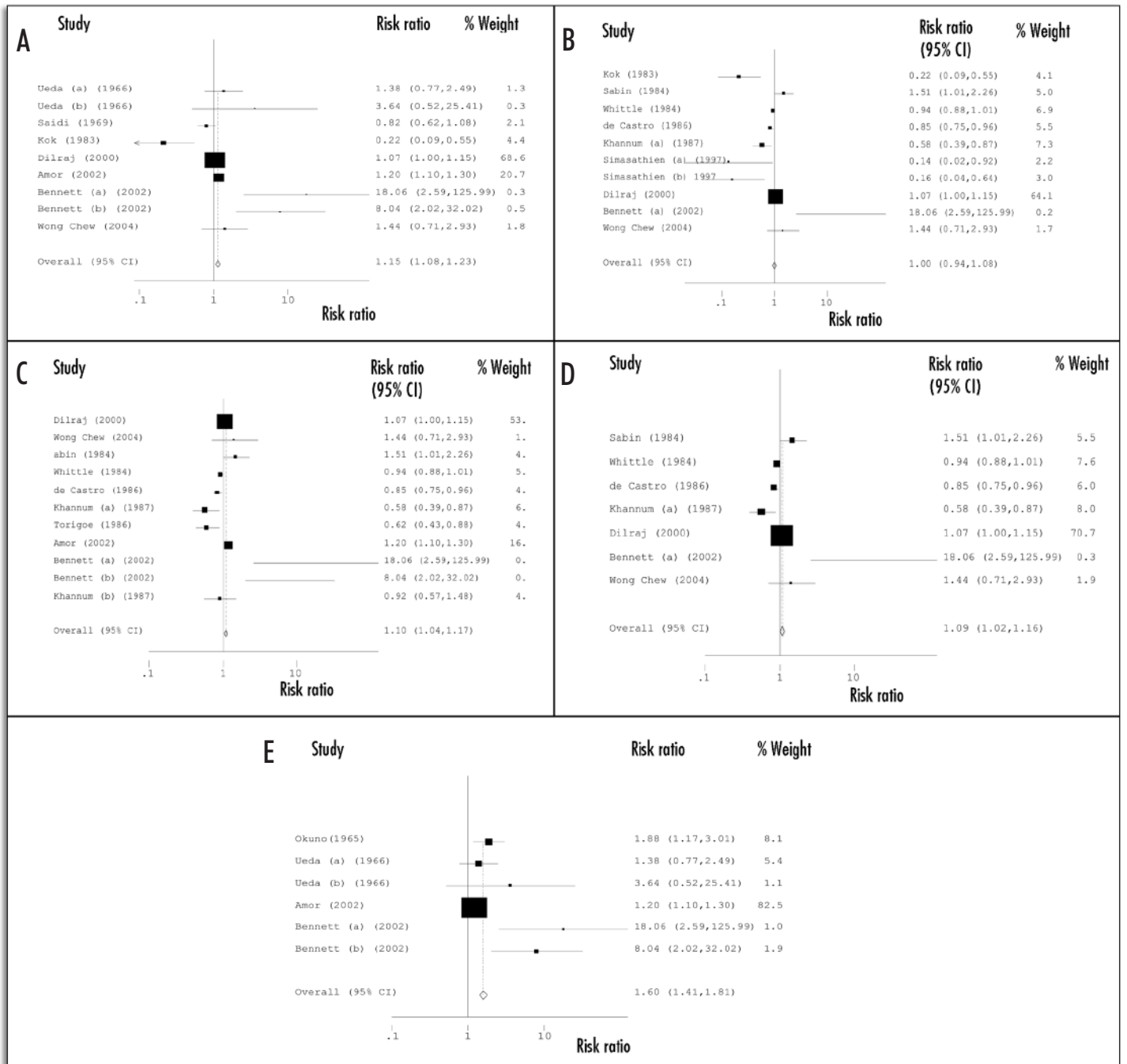


Figure 2. (A) Forest Plot of results with children over 9 months of age. (B) Forest Plot of all included results employing only EZ measles vaccine. (C) Forest plot of included results employing only aerosol technique of delivery. (D) Forest plot of included results employing only EZ measles vaccine and only aerosol technique of administration. (E) Forest Plot of results including vaccinees with prior exposure to measles antigen.

mentioned the age as “children”,^{19,33} and age among vaccinees in two studies spanned across 9 months.^{13,26} Four studies mentioned that the vaccinees were exposed to measles virus (either through infection or vaccination) prior to the study, six studies did not clearly mention the prevaccination serostatus of vaccinees, and the rest of the studies mentioned that the vaccinees were seronegative at the beginning of the study. Nine studies employed the EZ strain, two studies employed Biken Lot, two employed Measles (EZ) + RA 27/3 strain, one study employed Measles (SW) + RA 22/7. Other strains employed were Connought strain, L 16, Human Diploid Cell and Enders Edmonston in different comparison groups within individual studies. Eight studies mentioned that vaccinees were not exposed to measles virus (either

in the form of an infection or vaccination), and in seven studies the vaccinees were exposed to measles virus (either as infection or vaccination). In the parenteral group, the vaccine was administered through subcutaneous injection. In the respiratory route group; nine studies employed the aerosol technique, other techniques employed were nasal inhalation, nasal instillation, nasal spray, nasal drops, and nasal swabbing of anterior nares. There were several differences in vaccine dose between studies and between study arms (see Table 1). The median and mode of the quality scores achieved by the various results were 14 and 22 respectively; out of a maximum score of 25. We have presented the quality assessment scores and a summary of study characteristics in Table 1.

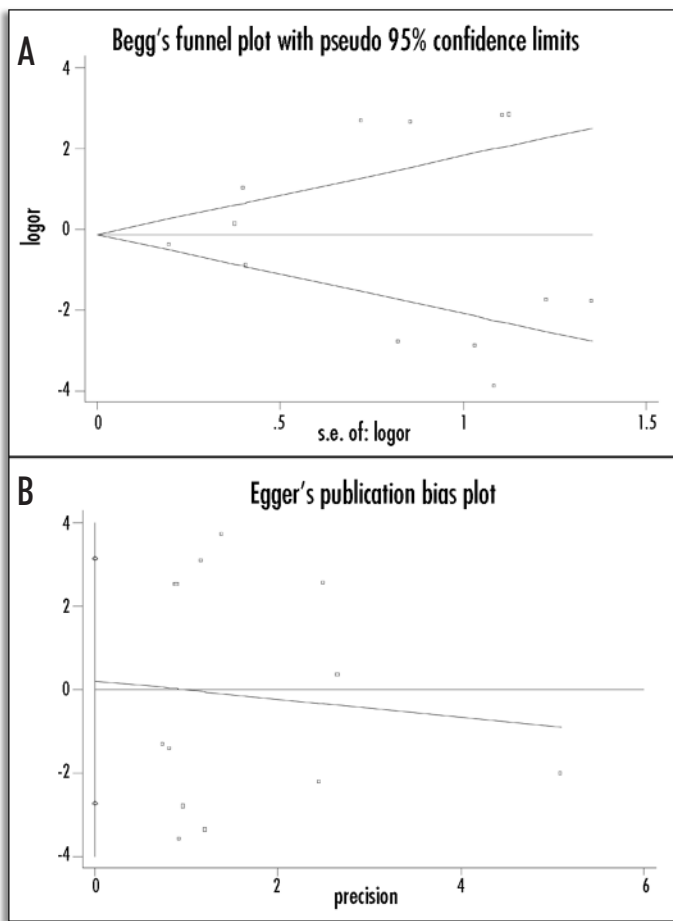


Figure 3. (A) Begg's Funnel plot (Publication bias) for all included results. (B) Egger's Plot (Publication bias) for all included results.

Results of statistical analysis

Overall analysis. Of the twenty results analyzed, nine showed the point estimate of risk ratio of more than one (Fig. 1). The summary estimate of effect suggested that the seroresponse was 4% higher amongst vaccinees in the respiratory group than those in the subcutaneous group (M-H pooled RR = 1.04; 95% CI = 0.98–1.10) (Fig. 1). Out of nine results, five results attained statistical significance (confidence interval did not cross 1.0). The test for heterogeneity of effect across the studies was consistent with random variation ($p < 0.001$).

Effect of route of administration of measles vaccine by age groups. We stratified seven results into less than nine months stratum, nine results enrolling children nine months and older were stratified into more than nine months stratum. We did not include four studies in this subgroup analysis, two of these four studies merely mentioned "children",^{19,33} and two studies included vaccinees spanning across nine months of age.^{13,26}

Of the seven results involving children less than nine months of age, the point estimate of risk ratio for one of these results showed a higher seroresponse in the respiratory group compared to the subcutaneous group. The summary effect of the respiratory route of administration of measles vaccine compared to the subcutaneous route of administration in children less than nine months was lower by 19% (M-H pooled RR = 0.81; 95% CI = 0.70 to 0.95). The test for heterogeneity of effect across the studies was consistent with random variation ($p < 0.001$).

Of the nine results involving children over nine months of age, the point estimate of risk ratio for seven of these studies showed a higher seroresponse amongst vaccinees receiving vaccine by the respiratory route (Fig. 2A). The summary measure showed that 15% (M-H pooled RR = 1.15; 95% CI = 1.08 to 1.22) more vaccinees over nine months of age vaccinated through the

respiratory route had a seroresponse compared to the vaccinees immunized through the subcutaneous route. Three results attained statistical significance. The result of the test for heterogeneity ($p < 0.001$) was consistent with random variation of the studies.

Effect of respiratory route of administration by different strains of vaccine. There were 10 results reporting administration of EZ vaccine. The point estimate of risk ratio of three of them was greater than one, and two of these attained statistical significance. The summary estimate for seroresponse suggested that EZ vaccine when administered through respiratory route was neither more nor less efficacious than EZ vaccine administered through subcutaneous route (M-H pooled RR=1.00; 95% CI = 0.94 to 1.08) (Fig. 2B).

Effect of aerosol technique and other respiratory administration techniques. Subgroup analysis was performed for studies comparing aerosol technique with subcutaneous administration of measles vaccine. Of the twenty results, eleven results were based on the delivery of vaccine by aerosol technique. The point estimate of risk ratio of six of these results showed a higher seroresponse among vaccinees immunized by aerosol technique and five of them attained statistical significance (Fig. 2C). The summary estimate for seroresponse in the vaccinees receiving measles vaccine through aerosol technique was 10% higher (M-H pooled RR = 1.10, 95% CI = 1.04–1.17) compared to those who received measles vaccine through the subcutaneous route. An analysis was carried out by selecting the results that had EZ vaccine delivered by aerosol technique, and comparing it to EZ vaccine delivered through the subcutaneous route. The EZ vaccine was delivered through aerosol technique in seven of the included results (Fig. 2D). The seroconversion due to EZ vaccine administered by aerosol technique was 9% higher for the respiratory route compared to EZ vaccine administered through the subcutaneous route (M-H pooled RR = 1.09; 95% CI = 1.02–1.16). The point estimate of 4 results was greater than one and two of them attained statistical significance.

Effect of route of administration by randomized studies. Of the twenty results included, vaccinees were randomly allocated to different groups in nine results. On analyzing the effect of respiratory route of administration of measles vaccine compared to subcutaneous administration of measles vaccine in these randomized studies, the point estimate in five results showed increased seroresponse in the respiratory group. The summary estimate of the combined effect of seroresponse, among the vaccinees in the respiratory group was 7% higher than the seroresponse in the subcutaneous group (M-H pooled RR = 1.07; 95% CI = 1.00–1.14), and four results attained statistical significance.

Effect of route of administration by preintervention exposure status. For 15 results information on pre-intervention exposure was available. Among 9 results involving children not exposed to measles virus in any form (either by immunization or infection), the point estimate for two result showed a higher seroresponse. The summary estimate of the combined effect of seroresponse, among unexposed vaccinees was 8% lower (M-H RR = 0.92; 95% CI = 0.86 to 0.99). Among 6 results involving children with exposure to measles virus in any form (either by immunization or infection), the point estimate for all of the 6 results showed a higher seroresponse, and five of them attained statistical significance. The summary estimate for the combined effect of seroresponse, among exposed vaccinees was 60% higher (M-H RR = 1.60; 95% CI = 1.40 to 1.80) (Fig 2E).

Influence analysis. In all of the analysis models, we recognized that the results of Dilraj et al.³³ greatly influenced the overall results due to its sample size. Therefore, we also carried out the above mentioned analyses excluding the results of the Dilraj et al. study. The pooled M-H RR of overall results was reduced to 1.01 (95% CI = 0.93–1.10) and the pooled M-H RR for subgroup analysis for EZ strain of vaccine was 0.76 (95% CI = 0.65–0.88), but the pooled M-H RR increased for the aerosol route [RR = 1.14 (95% CI = 1.03–1.25)], EZ vaccine administered through the aerosol route [RR = 0.96 (95% CI = 0.83–1.11)], results of randomized studies [RR = 1.06 (95% CI = 0.94–1.21)], and for children over 9 months of age [RR = 1.32 (95% CI = 1.17–1.50)].

Publication bias. There was evidence of publication bias as ascertained by Begg adjusted rank correlation test (Fig. 3A) or the Egger test (Fig. 3B), for the overall analyses (p value = 0.760), and each of the subgroup analysis (results not presented).

DISCUSSION

Within the limitations stated below, the results of our meta-analysis suggest that the respiratory route of delivery of measles vaccine is at least as efficacious as administering the vaccine through the subcutaneous route. The results remained qualitatively consistent for EZ strain and aerosol route, age more than nine months, serostatus and aerosol technique. The results from the influence analysis further consolidate our findings in terms of both overall analysis and the subgroup analysis. The results of our meta-analysis assume more significance, as these have been derived from very diverse studies carried out in various parts of the world, and could suggest the generalizability of this route of administration of measles vaccine.

Coverage of measles vaccine is low in many countries due to multiple reasons. The inherent disadvantages of the needle and syringe technology, such as requirement of relatively skilled personnel to administer the vaccine, risk of transmission of blood-borne infections, and injection pain are some of the major reasons for low coverage.^{3,5} Moreover, only a limited amount of antigen can be given through injections¹³ and maternal IgG antibodies can inhibit the vaccine viral replication if the vaccine is administered to vaccinees under 9 months of age through the subcutaneous route.^{6,14}

Biologically, administration of vaccine (even in doses lower than the subcutaneous dose) through lungs could mimic the natural route of measles transmission and may potentially lead to development of natural immunity first at the portal of entry, produce superior local respiratory tract immunity,^{6,15} induce measles specific T cell immunity in infants,¹⁶ and induce a more generalized systemic immunity.¹³ The antibodies lining the respiratory epithelium, predominantly IgA, are less likely to have been acquired from the mother and to inhibit viral replication.¹⁷ Mucosal immunity does not undergo age associated changes; therefore, the vaccine can be administered to both the elderly and infants. Studies have shown that the respiratory route of administration of vaccine has a favorable effect on overcoming the blocking antibodies derived from the mother.¹⁸ This route holds more relevance in infants as it is not adversely affected by maternal antibodies,¹⁹ serostatus and nutritional status of children.¹³ By stimulating local respiratory tract immunity, it also has the potential to prevent reinfection.³ The aerosol route has better immunogenicity in seronegative, seropositive and malnourished children.^{16,20}

Mucosal immunization can be used to enhance induction of both mucosal and systemic immune responses.²¹ Therefore, it can be employed for priming for parenteral immunization and aiding booster administrations.^{17,22,23} If required, the mucosal route can administer a greater volume of vaccine.¹⁶ This route can also be employed to administer combined antigens such as Measles and Rubella: studies have shown that there is no interference between antigens, instead, it is likely to elicit superior mucosal immunity for both.^{13,24} The EZ vaccine administered by aerosol gives better short term immunity and better antibody persistence, which could lead to longer duration of protection. This has prompted some researchers to suggest administration of vaccine by the aerosol route to young adults to boost immunity of women in their early child bearing years –so that the passive immunity in newborn could protect the infant for more than 6 months.²³ It has been hypothesized that induction of immunity in the nasal (olfactory) mucosa may have a special importance for protection of the central nervous system against certain infectious diseases.³ However, this theory requires further investigation.

As the aerosol route is non invasive and requires very little cooperation by the subjects, it may be a better option for childhood inoculations and may have better acceptance in the population. Ease of administration and better acceptability could make aerosol technique ideal for planned mass immunization, outbreak control, and in disaster settings without the need for extensive training programs. As the personnel administering vaccine through this route have a lower risk of injection related injuries, they will be better protected against iatrogenic infections.^{6,25}

Clinically, the aerosol route of delivery of vaccine is less reactogenic than the subcutaneous route. A number of studies have documented that the administration of vaccine through the parenteral 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 conjunctival discharge. The aerosol group in each of the studies showed significantly lower frequency of fever, rhinitis, cough, generalized morbilliform rash, arthralgias, and conjunctival hyperemia in infants.^{5,13,20,26-28}

Lower respiratory tract is the optimum target and optimal deposition in the alveolar region occurs with particle size 1–5 microns, while the greatest deposition in the tracheobronchial region occurs with the particle sizes ranging from 3–10 microns.^{3,15,20,29} Hence, the seroconversion due to the aerosol inhalation method would depend on certain factors such as the type of mask, duration of aerosol inhalation, composition of aerosol especially with regards to particle size characteristics of inhalational device.

Factors such as duration of exposure,^{13,17} presence of respiratory illness, variation in the breathing pattern in different age groups, and inhaled biological dose^{17,30} can influence seroconversion in a vaccinee.^{31,32} One potential shortcoming of this technique could be spread of respiratory infection or cross infection due to sharing of inhalational device between vaccinees. Employing single use disposable masks for each vaccinee can minimize this. The safety of the vaccinees and vaccinators exposed to large amounts of aerosolized vaccine also merits investigation. Only one study¹⁶ reported a fourfold increase in the antibody titer of investigators who had inhaled large amounts of aerosolized vaccines escaping from the masks.

Limitations of this study. The results of this study are limited by the fact that we had a relatively small number of eligible studies. The studies had substantial differences in terms of design and quality of the reported results. Based on the quality analyses, a substantial proportion of the studies were found to have methodological problems; however, there were no serious flaws that could have invalidated the results.

We considered the authors' definition of seroresponse to compare the two arms. It is plausible that the definitions used by the various authors and the time at which post intervention serostatus was assessed may have had an impact on the determination of the primary outcome. However, since we only had access to published data and the fact that the studies were spread over a relatively long period of time, the approach least prone to bias was to consider the authors' definition of seroconversion. Over a period of time, there has been variability in terms of equipment, which could have also influenced the measurement of seroresponse.

A majority of the chosen studies employed the aerosol route, whereby we did not have enough data to evaluate the effectiveness of other techniques of administration of vaccine through the respiratory route. Moreover, the dose of vaccine administered was different in each study, and in some cases, even varied between two arms of the

same study. The difference in dosage could have influenced the results. We did not include unpublished data and studies published in other languages and we found evidence of publication bias in our results.

CONCLUSION

The results of our analysis concur with the views expressed in the previously published reviews,^{5,6} and provide a quantitative evidence to support the ongoing efforts of the Measles Aerosol Project, an initiative for Vaccine Research (IVR/BAC) of the World Health Organization. The possible use of the respiratory route for the administration of the available measles vaccine, particularly through the aerosol technique, has a lot of global public health implications. With significant advantages of administration of vaccine through the aerosol route, there is tremendous potential for this technique to boost the ongoing measles control and elimination efforts worldwide; especially in resource poor countries. It is critical at this stage to encourage research to standardize this technique in terms of vaccine dosages, vaccine delivery, safety, and efficacy.

References

- WHO, Unicef. Unconf. Measles- mortality reduction and regional elimination. Strategic Plan 2001-2005. (WHO/V&B/01.13 Rev. 1). 2003.
- WHO. Geneva: Measles technical working group: Strategies for measles control and elimination-report of a meeting. 2000 (WHO/V&B/01.37). 2001.
- LiCalsi C, Christensen T, Bennett JV, Phillips E, Witham C. Dry powder inhalation as a potential delivery method for vaccines. *Vaccine* 1999; 17:1796-803.
- Fernandez De CJ, Kumate J. Vaccination against measles. The situation in Mexico and America. *Advances in the method of aerosol immunization. Bol Med Hosp Infant Mex* 1990; 47:449-61.
- Cutts FT, Clements CJ, Bennett JV. Alternative routes of measles immunization: A review. *Biologicals* 1997; 25:323-38.
- Sabin AB. Immunization against measles by aerosol. *Rev Infect Dis* 1983; 5:514-23.
- Ioannidis JPA, Lau J. State of the evidence: Current status and prospects of meta-analysis in infectious diseases. *Clinical Infectious Diseases* 1999; 29:1178-85.
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials* 1996; 17:1-12.
- Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, Pham B, Klassen TP. Assessing the quality of reports of randomised trials: Implications for the conduct of meta-analyses. *Health Technol Assess* 1999; 3:i-98.
- Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001; 323:101-5.
- Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50:1088-101.
- Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315:629-34.
- Torigoe S, Biritwum RB, Isomura S, Kobune F, Mingle JA, Toba M, Antwi P, Ofosu-Amaah S. Measles in Ghana: A trial of an alternative means of administration of measles vaccine. *J Trop Pediatr* 1986; 32:304-59.
- Putz MM, Bouche FB, de Swart RL, Muller CP. Experimental vaccines against measles in a world of changing epidemiology. *Int J Parasitol* 2003; 33:525-45.
- LiCalsi C, Maniaci MJ, Christensen T, Phillips E, Ward GH, Witham C. A powder formulation of measles vaccine for aerosol delivery. *Vaccine* 2001; 19:2629-36.
- Sabin AB, Flores AA, Fernandez De CJ, Sever JL, Madden DL, Shekarchi I, Albrecht P. Successful immunization of children with and without maternal antibody by aerosolized measles vaccine. I. Different results with undiluted human diploid cell and chick embryo fibroblast vaccines. *JAMA* 1983; 249:2651-62.
- Khanum S, Uddin N, Garelick H, Mann G, Tomkins A. Comparison of edmonston-zagreb and Schwarz strains of measles vaccine given by aerosol or subcutaneous injection. *Lancet* 1987; 1:150-3.
- Roth Y, Chapnik JS, Cole P. Feasibility of aerosol vaccination in humans. *Ann Otol Rhinol Laryngol* 2003; 112:264-70.
- Okuno Y, Ueda S, Hosai H, Kitawaki T, Nakamura K, Chiang TP, Okabe S, Onaka M, Toyoshima K. Studies on the combined use of killed and live measles vaccines. II. Advantages of the inhalation method. *Biken J* 1965; 8:81-5.
- Ueda S, Hosai H, Minekawa Y, Okuno Y. Studies on the combined use of killed and live measles vaccines. III. Conditions for the "take" of live vaccine. *Biken J* 1966; 9:97-101.
- Sepulveda-Amor J, Valdespino-Gomez JL, Garcia-Garcia ML, Bennett J, Islas-Romero R, Echaniz-Aviles G, de Castro JF. A randomized trial demonstrating successful boosting responses following simultaneous aerosols of measles and rubella (MR) vaccines in school age children. *Vaccine* 2002; 20:2790-5.
- Bennett JV, Fernandez De CJ, Valdespino-Gomez JL, Garcia-Garcia ML, Islas-Romero R, Echaniz-Aviles G, Jimenez-Corona A, Sepulveda-Amor J. Aerosolized measles and measles-rubella vaccines induce better measles antibody booster responses than injected vaccines: Randomized trials in mexican schoolchildren. *Bull World Health Organ* 2002; 80:806-12.
- Dilraj A, Cutts FT, de Castro JF, Wheeler JG, Brown D, Roth C, Coovadia HM, Bennett JV. Response to different measles vaccine strains given by aerosol and subcutaneous routes to schoolchildren: A randomised trial. *Lancet* 2000; 355:798-803.
- Saidi S, Naficy K. Subcutaneous and intranasal administration of RA 27-3 rubella vaccine. Alone and in conjunction with live attenuated measles vaccine. *Am J Dis Child* 1969; 118:209-12.
- Sabin AB. Measles, killer of millions in developing countries: Strategy for rapid elimination and continuing control. *Eur J Epidemiol* 1991; 7:1-22.
- Black FL, Sheridan SR. Studies on an attenuated measlesvirus vaccine. IV. Administration of vaccine by several routes. *N Engl J Med* 1960; 263:165-9.
- Sabin AB, Flores AA, Fernandez De CJ, Albrecht P, Sever JL, Shekarchi I. Successful immunization of infants with and without maternal antibody by aerosolized measles vaccine. II. Vaccine comparisons and evidence for multiple antibody response. *JAMA* 1984; 251:2363-71.
- Whittle HC, Rowland MG. Failure of measles vaccine sprayed into the oropharynx of infants. *Lancet* 1983; 1:1045.
- Whittle HC, Rowland MG, Mann GF, Lamb WH, Lewis RA. Immunisation of 4-6 month old Gambian infants with Edmonston-Zagreb measles vaccine. *Lancet* 1984; 2:834-7.
- Wong-Chew RM, Islas-Romero R, Garcia-Garcia ML, Beeler JA, Audet S, Santos-Preciado JI, Gans H, Lew-Yasukawa L, Maldonado YA, Arvin AM, Valdespino-Gomez JL. Induction of cellular and humoral immunity after aerosol or subcutaneous administration of Edmonston-Zagreb measles vaccine as a primary dose to 12-month-old children. *J Infect Dis* 2004; 189:254-7.
- Kok PW, Kenya PR, Ensering H. Measles immunization with further attenuated heat-stable measles vaccine using five different methods of administration. *Trans R Soc Trop Med Hyg* 1983; 77:171-6.
- Kress S, Schluederberg AE, Hornick RB, Morse LJ, Cole JL, Slater EA, McCrumb Jr FR. Studies with live attenuated measles-virus vaccine. II. Clinical and immunologic response of children in an open community. *Am J Dis Child* 1961; 101:701-7.
- Cernescu C, Cajal N. Antimeasles vaccination by natural routes—experimental background and practical consequences. *Virologie* 1984; 35:259-71.
- Fernandez De CJ, Valdespino Gomez JL, az Ortega JL, Zarate Aquino ML. Diploid cell measles vaccine. *JAMA* 1986; 256:714.
- Simasathien S, Migasena S, Bellini W, Samakoses R, Pitisuttitham P, Bupodom W, Heath J, Anderson L, Bennett J. Measles vaccination of Thai infants by intranasal and subcutaneous routes: Possible interference from respiratory infections. *Vaccine* 1997; 15:329-34.