Alternative routes of measles immunization: a review
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Authors' objectives
To evaluate the potential for non-percutaneous routes of vaccine administration for measles to improve control.

Searching
The authors state that a literature search was conducted but do not report the names of databases, dates searched or keywords used in the search. Early studies, not presently cited in electronic retrieval sources, were initially identified in references of later papers, and subsequently within references of older papers themselves. Abstracts of unpublished work which had been presented at international meetings were obtained from researchers.

Study selection
Study designs of evaluations included in the review
Study designs are not stated.

Specific interventions included in the review
Intradermal (needle and syringe, jet injector, or bifurcated needle), conjunctival (drops in the eye), oral (drops on sugar, spray on back of oropharynx, or cotton swab), aerosol (nebuliser with reconstituted vaccine placed in a container of crushed ice and attached to a compressor, with dose assumed of 0.145 ml per 30 seconds) and intranasal (swab in anterior nares, drops or bolus instillation in the anterior nares, or large particle spray) administrations of measles vaccine.

Participants included in the review
Participants were children who were grouped into categories of:
1. Nine months of age or younger.
2. Those who were at least 9 months of age or older.

Participants were screened pre-study for seronegativity before vaccination, the presence (or absence) of upper respiratory infections (URIs), previous measles vaccinations, and no history of measles.

Outcomes assessed in the review
Serological response measured by serological assay including plaque neutralisation.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not report the method used to assess quality, or how the quality assessment was performed.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative discussion of study characteristics and results of individual trials. Data from the sets of trials for each type of intervention are presented in tables, as is a summary of the advantages and disadvantages of each route of administration of vaccine.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

**Results of the review**

For the intradermal route there were 7 studies with 1,063 participants (five studies had a control group who were given vaccine via percutaneous routes).

For the conjunctival route there were 4 small studies with 63 participants.

For the oral administration route there were 3 studies with 85 participants.

For the intranasal administration route, in children predominantly over 9 months of age, there were 7 studies with 922 participants.

For the intranasal administration route, in infants younger than 9 months of age, there were 4 studies with 270 participants.

For the aerosol administration route, in children predominantly over 9 months of age, there were 15 studies with 2,167 participants.

For the aerosol administration route, in infants younger than 9 months of age, there were 9 studies with 850 participants.

In the intradermal group, the percentage of seroresponse ranged from 10-100%. Needles and syringes and jet injectors had higher seroresponses (53-100%) while bifurcated needles, multiple puncture cylinders and needle implanted cylinders had the lowest seroresponses (10-74%).

In the conjunctival group, one study (2 participants) had a 100% seroresponse rate; the other 3 studies had 79% (29 participants), 10% (22 participants), and 0% (10 participants) seroresponse percentages. In the oral route group, studies showed ineffective results of 0%, 10%, 47% and 76% seroresponse.

Studies of the intranasal administration route, in children predominantly over 9 months of age, showed over 80% seroresponse, but others within the group found less than 20% seroresponse, variation sometimes being manifest within the same study.

Studies of the intranasal administration route, in infants younger than 9 months of age, reported seroresponses of 74-100% in two studies, but seroresponses of 0-10% in two other studies.

Studies of the aerosol administration route, in children predominantly over 9 months of age, showed a seroresponse between 0- 100% compared with a seroresponse of 36-100% in control groups. High seroresponse rates were observed (93-100%) in four of the fifteen studies which directly sprayed into the mouth. A seroresponse rate of 86-100% was found in a further six trials which administered vaccine through a mask.

Studies of the aerosol administration route, in infants younger than 9 months of age, reported seroresponses of greater than 80% in seven of the nine studies at 3-6 months post-vaccination.

**Authors’ conclusions**

Of the non-percutaneous routes of vaccination, the aerosol route appeared to be the most promising (with the possible exception of very young infants), and offers several theoretical and practical advantages as well. Oral and conjunctival
routes generally gave poor results, and intradermal administration of vaccine using a needle and syringe is more difficult than subcutaneous vaccination.

CRD commentary
The authors have stated their research question and inclusion and exclusion criteria for the review. The literature search is poor because the authors do not name the databases or the dates and keywords used and have not stated whether there were any language restrictions. For these reasons, it is possible that relevant studies may have been missed.

The authors have not reported on how the articles were selected, or how the quality of the included studies was assessed and there is no report as to who, or how many of the reviewers, selected the articles or extracted the data. The studies are combined in a narrative discussion and the advantages and disadvantages of each intervention are summarised in a table. The differences between studies and complications of results in several of the groups make a statistical combination inappropriate and there is no test for homogeneity. The included studies are very different in design and for this reason, along with the lack of detail about the selection, inclusion and quality assessment in the review, although the results follow from this review, the authors’ conclusions should be viewed with caution.

Implications of the review for practice and research
Practice: The authors state that the development of improved technology for aerosol delivery of measles vaccine would greatly advance the potential for wide-scale use of this route, especially in mass campaigns in low income countries.

Research: The authors state that further RCTs should be conducted to evaluate comparative responses to aerosolised, intranasal, and subcutaneous vaccine, especially in those age ranges targeted for mass campaigns (most commonly 9 months to 15 years).

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.