Aerosolized measles and measles–rubella vaccines induce better measles antibody booster responses than injected vaccines: randomized trials in Mexican schoolchildren

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Objective To compare antibody responses and side-effects of aerosolized and injected measles vaccines after revaccination of children enrolling in elementary schools.

Methods 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. Concentrations of neutralizing antibodies were determined in blood specimens taken at baseline and four months after vaccination from randomized subgroups (n = 28–31) of children in each group.

Findings 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.

Conclusion Immunogenicity of measles vaccine when administered by aerosol is superior to that when the vaccine is given by injection. This advantage persists with aerosolized doses less than or equal to one-fifth of usual injected doses. The efficacy and cost-effectiveness of measles vaccination by aerosol should be further evaluated in mass campaigns.

Keywords Measles vaccine/administration and dosage; Rubella vaccine/administration and dosage; Immunization, Secondary; Administration, Inhalation; Administration, Cutaneous; Aerosols; Nebulizers and vaporizers; Injections; Enzyme-linked immunosorbent assay; Comparative study; Randomized controlled trials; Mexico (source: MeSH, NLM).

Mots clés Vaccin antimorbilleux/administration et posologie; Vaccin antirubéoleux/administration et posologie; Rappel vaccination; Administration respiratoire; Voie cutanée; Aérosol; Nébulisateurs; Injection; ELISA; Etude comparative; Essai clinique randomisé; Mexique (source: MeSH, INSERM).

Palabras clave Vacuna antisarampio/administración y dosificación; Vacuna contra la rubéola/administración y dosificación; Inmunización secundaria; Administración por inhalación; Administración cutánea; Aerosoles; Nebulizadores y vaporizadores; Inyecciones; Test de ELISA; Estudio comparativo; Ensayos controlados aleatorios; México (fuente: DeCS, BIREME).

Introduction

Studies of measles vaccination by alternative routes were recently reviewed comprehensively (1). Routes studied have included the aerosol, intranasal, intradermal, intraocular and oral routes. Twenty-four studies of measles vaccination by aerosol were reviewed. The aerosol route seemed to be the most promising of the nonpercutaneous routes, as judged by seroresponses elicited in seronegative and seropositive children aged 9 months or older. Most of the studies of vaccination by aerosol involved small numbers of participants, and, in many, no comparison groups received injected vaccine. In the largest controlled trial, more than 1000 seronegative children without a history of measles were given primary immunization with aerosolized vaccines (2). All three of the vaccines given by ultrasonic nebulization, including the Schwarz (SW) vaccine strain, produced results superior to those with injected vaccines.

A randomized, controlled trial of response to revaccination in a large group of South African schoolchildren was...
published after the review paper (3). The results of this trial showed that previously vaccinated children given aerosolized Edmonston–Zagreb (EZ) vaccine had significantly better booster responses than those given comparable doses of EZ or SW vaccines by injection. Aerosol vaccination for measles was used in mass campaigns in Mexico nearly a decade ago (using methods similar to those in the South African trial), when about 4 million children aged 9 months–15 years were given aerosolized vaccine (4).

Revaccination for measles on school entry is required in Mexico, and this provided us with an opportunity to evaluate the reactogenicity and antibody booster responses in schoolchildren, including responses to reduced dosages of vaccine given by aerosol. We carried out studies in the autumn of 1998 in children enrolling in schools of Pachuca and Tulancingo in Hidalgo state. No cases of measles had been reported from these study areas since 1994. We evaluated antibody responses for measles and rubella after children received injected or aerosolized monovalent measles and rubella vaccines or vaccines containing measles combined with rubella. In this paper we report only the antibody responses to measles in children in the 6 study arms given measles or measles–rubella vaccines.

Materials and methods

Aerosolization method

The equipment used to generate the aerosols was devised by Jorge Fernandez de Castro and has been used in other studies, as well as in mass campaigns in Mexico (3–5) (Fig. 1; not to scale). The materials and procedures have been described elsewhere (3). Briefly, an electrically powered compressor delivered compressed air at 50 lb/in.² to a nebulizer (IPI Medical Products, Chicago, Illinois) containing reconstituted measles vaccine in a container filled with crushed ice. A motor vehicle battery could be used to power the compressor as well as outlet current. The nebulizer generated small particles (mainly ≤5 μm in diameter) as a true aerosol (not a spray). Such aerosols do not “wet” surfaces to which they are applied and efficiently reach the lower respiratory tract. In contrast, sprays generally have particles >50 μm in diameter, wet surfaces to which they are applied and are generally capable of only reaching the upper respiratory tract.

The vaccine was administered for 30 seconds, during which time about 0.1 ml of vaccine was nebulized and delivered into a disposable conical paper cup with its tip removed. The cone was held loosely over the nose and mouth of the child. Each nebulizer freshly charged with 5 ml of vaccine could be used to vaccinate about 45 children. Preliminary simulation experiments showed no detectable loss in potency of EZ measles vaccine in the nebulizer after 20 minutes of nebulization.

Vaccines

Aerosolized vaccine

Aerosolized EZ measles vaccine was given to three groups at different administered doses: 10³ pfu (low-dose measles vaccine group), 10¹⁵ pfu (measles vaccine group) or 10¹² pfu in a vaccine also containing RA27/3 rubella vaccine (measles–rubella vaccine group). The latter two doses were equivalent to the doses normally given by injection. The vaccine for the low-dose measles group was prepared at the point of use by adding 0.2 ml of a quickly thawed concentrated vaccine (10³₆ per ml) to vials containing 7.8 ml of cold stabilizer solution. The other two vaccines were supplied in 5-ml vials containing reconstituted vaccines with concentrations 10 times higher per ml than the administered doses.

Injected vaccine

Injected measles vaccine was also given to three groups in customary doses. Each of the injected vaccines was provided in single-dose vials containing lyophilized powder that was reconstituted with cold diluent just before use. Children in two groups each received a 10³⁻⁷ pfu dose of EZ vaccine given subcutaneously in 0.5 ml diluent — one group received measles vaccine only and the other measles vaccine combined with rubella vaccine. Each child in the third group received a 10⁻⁵⁷ pfu dose of Schwarz measles vaccine (SmithKline Beecham) in 0.5 ml diluent.

Study design and selection of participants

We held briefing sessions for parents, school staff and municipal authorities from the study area. A list of all public elementary schools in the area was prepared, and individual schools were randomized to different treatment groups with a table of random numbers. Seventy-nine schools were randomly assigned to one of the six treatment groups. Strategies for randomization and sampling appear in a companion paper (6).

At the time of vaccination, the parent or guardian was asked about the health of the child and about any illnesses in the previous two weeks. Each child was physically examined, and his or her height and weight were recorded. Teachers entered information in an illness diary for two weeks after vaccination and reported any absences — the reasons for which were then evaluated through home visits by project staff.

The protocol for the trial was approved by the Ethical Committee for the Instituto Nacional de Salud Pública (INSPP); the Health Services for Hidalgo state; and the Human Investigations Committee, Emory University School of Medicine. Free and informed consent for children to participate in the trial was obtained from the child’s parent or guardian.

Antibody assays

All sera were tested by enzyme-linked immunosorbent assay (ELISA) assay using a measles nucleoprotein antigen (7).
Results

Participants and baseline characteristics

Data analysis was restricted to participants who met the following requirements:

- had documentation that they had received only a single previous dose of a measles-containing vaccine (nearly always before one year of age)
- had not been given oral polio vaccine or blood transfusions within the two weeks before vaccination
- were not immunosuppressed and had no allergy to eggs
- had oral temperatures \( \leq 38.5 ^\circ C \) at vaccination
- had blood samples taken at both baseline and four months after vaccination tested for measles antibodies by ELISA test
- were followed up clinically for two weeks after vaccination.

Selected characteristics of the 1624 children in the six groups that received measles vaccines and met these criteria are shown in Table 1. No significant differences were seen between individual groups in the proportion of children aged 6–8 years. Baseline seronegativity determined by ELISA was comparable for all groups except the group that received measles–rubella vaccine subcutaneously, which had a significantly higher frequency of seronegativity. No significant differences in overall age or seronegativity evaluated by ELISA at baseline were seen between the two different routes of administration.

Characteristics of the children in subsamples with neutralizing antibody titres are presented separately in Table 1 because this data played the principal role in subsequent analyses. No significant differences were seen between groups or between routes of administration in age, seronegativity or baseline geometric mean antibody titres (GMTs). In contrast with the results from ELISA, the group that received measles–rubella vaccine subcutaneously had the lowest point estimate of seronegativity. The proportion of children identified as seronegative by ELISA in each group exceeded the proportion identified as seronegative by the neutralization test; this

<table>
<thead>
<tr>
<th>Table 1. Characteristics of children who received measles or measles–rubella vaccines</th>
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<tbody>
<tr>
<td><strong>Aerosolized vaccine</strong></td>
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<tr>
<td>Low-dose EZ measles</td>
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<td>---------------------</td>
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<tr>
<td><strong>General characteristics</strong></td>
</tr>
<tr>
<td>No. of children</td>
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<tr>
<td>Dose of measles vaccine (pfu)</td>
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<tr>
<td>No. of schools</td>
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<tr>
<td>Pupils per school (range)</td>
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<tr>
<td>Pupils aged 6–8 years (%)</td>
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<tr>
<td><strong>ELISA status</strong></td>
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<tr>
<td>Children seronegative for measles (%)</td>
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<tr>
<td><strong>Children with neutralizing antibody data</strong></td>
</tr>
<tr>
<td>No. with paired titres</td>
</tr>
<tr>
<td>Mean age (years)</td>
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<tr>
<td>Seronegative at baseline (%)(^{b})</td>
</tr>
<tr>
<td>Geometric mean antibody titres at baseline (mIU/ml)</td>
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</table>

\(^{a}\) \( \text{P/N} < 3.0 \) and \( \text{P – N} < 0.09 \).

\(^{b}\) <120 mIU neutralizing antibodies/ml of serum.

Spectrophotometric readings of test sera containing this antigen and other reagents (designated “P”) were compared with readings from test sera that differed only by the exclusion of the antigen (designated “N”); sera were considered to be seropositive if \( \frac{P}{N} \geq 3.0 \) and \( P – N \geq 0.09 \), seronegative if both readings were below these values and indeterminate if one of the two readings was below either threshold. Seroconversion was defined as a change from seronegative to seropositive.

Sera from about 11% of children in each group were randomly selected to undergo neutralization tests. Specimens taken at baseline and six months after vaccination were tested with an enhanced neutralization test to detect measles immunoglobulin G (8). Results were reported in mIU/ml serum, and titres <120 mIU/ml were classified as seronegative (9).

Data management and analysis

Information from the data collection forms and laboratory data were initially provided as Stata files; these were then converted into EpiInfo version 6.02 files for analysis and logistic regression with the companion program of Dallal (10). Seroconversion by ELISA required a change from seronegative to seropositive. Neutralizing antibody titres in the different groups were compared after vaccination by using the proportions of children with at least fourfold increases from baseline titres (seroconversion), geometric mean titres, average fold increases in titres from baseline and the proportion of children who remained seronegative after revaccination.

We used the \( \chi^2 \) or Fisher’s tests to compare the proportions of groups that underwent seroconversion or were seropositive. We used ANOVA (or the Mann–Whitney \( U \)-test if non-parametric) to compare differences in antibody titres between groups. We used multiple logistic regression to analyse seroconversions in the different groups by using the low-dose aerosol group as the reference and controlling for baseline antibody status. Weight for height, height for age and weight for age Z-scores were calculated with established norms for Mexico (11).
indicated that the neutralization test had a greater sensitivity for detecting antibodies.

**Antibody test results**

The frequency of seroconversions in baseline specimens identified as seronegative by ELISA was comparable for all groups (n = 231; frequency range 95%–100%) except the group that received measles–rubella vaccine subcutaneously. For unexplained reasons, seroconversion was significantly less frequent (82%) among the 86 seronegative children in this group.

On logistic regression analysis, the frequency of seroconversion detected by neutralization test criteria — the “gold standard” and more precise quantitative test of response — did not differ significantly between the three groups that received aerosolized vaccine (Table 2). However, the frequency of seroconversion in the group that received low-dose aerosolized measles vaccine (52%) significantly exceeded that for the three groups that received injected vaccines (range 4%–23%). Furthermore, the lower confidence bounds of the odds ratios for the other two aerosolized groups substantially exceeded the upper limits of all of the groups that received injected vaccines; this indicated that these differences were highly statistically significant. Overall, seroconversion was detected in 57% of the children in the groups that received aerosolized vaccine, but only 11% of those in the injected groups.

Importantly, seroconversion was affected by baseline neutralization antibody titres — the rate of seroconversion was 71% in the 1st quartile of baseline titres (≤303 mIU/ml) but only 2% in the 4th quartile (titres >1222 mIU/ml) (Table 2). When evaluated by route of administration and quartile of baseline titre (Fig. 2), seroconversion was significantly (P<0.0005) more frequent when vaccine was administered by aerosol in every quartile except the 4th quartile, where there was little response to either administration route. No child in any group was seronegative four months after vaccination.

The above findings were supported by both average fold increases in titres and GMTs of neutralizing antibodies. Antibodies increased on average nearly 12-fold in the combined aerosolized group versus only twofold in the combined injected group (Fig. 3), and GMTs four months after vaccination were nearly three times higher in the combined aerosol group (Fig. 4). The confidence bounds for both outcomes overlapped within each combined group. Except for slight overlaps of confidence bounds for the average fold-increase between the groups that received subcutaneous Schwartz vaccine and low-dose aerosolized measles vaccine, the lower confidence bound of each subgroup of the combined aerosol group exceeded the upper bounds of each subgroup of the combined injected group (Fig. 3 and Fig. 4).

None of age, sex, illnesses in the two weeks before vaccination (fever, rash, cough, rhinitis, conjunctivitis and diarrhea) and anthropometric scores contributed significantly when added to the logistic model shown in Table 1.

**Post-vaccination reactions**

We recorded cases of cough, rhinitis, fever, diarrhea, rash and conjunctivitis among participants that lasted one or more days in the two weeks after vaccination. The rates were 7.5% for cough, 3.0% for rhinitis, 2.9% for fever, 1.2% for diarrhea, 1.0% for rash and 0.7% for conjunctivitis. Every symptom occurred less frequently among the 760 children who received aerosolized vaccine than in the 864 who received vaccine by injection; this difference was significant (P<0.0002) for all symptoms except rhinitis and diarrhea. No Koplik’s spots were noted. The children that received low-dose aerosolized measles vaccine had one or more of the above symptoms significantly more often (12.5%; P<0.0001) than the children in the other aerosol groups (0.8% and 2.7%). The group that received low-dose aerosolized measles vaccine was significantly less frequently (P = 0.0007) affected with such symptoms, however, than those who received measles–rubella vaccine subcutaneously (23.7%). The frequency of such symptoms in the group that received low-dose aerosolized vaccine did not differ significantly from that for the groups that received EZ vaccine (16.0%) or SW vaccine (8.5%) subcutaneously. The groups that received standard dose aerosolized measles and measles–rubella vaccines had symptoms significantly less frequently than any group that received injected vaccines (P<0.004).

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**Table 2. Percentage of children with fourfold or greater increases in neutralizing antibody levels four months after receiving a booster dose of measles vaccine**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. (%) of children</th>
<th>Adjusted odds ratio (95% CI)</th>
<th>Adjusted P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccine group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aerosol administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-dose EZ measles</td>
<td>16/31 (52)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>EZ measles</td>
<td>20/31 (65)</td>
<td>2.1 (0.5–9.8)</td>
<td>0.34</td>
</tr>
<tr>
<td>EZ measles–rubella</td>
<td>15/28 (54)</td>
<td>2.6 (0.5–13.6)</td>
<td>0.24</td>
</tr>
<tr>
<td>Subcutaneous administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EZ measles</td>
<td>1/28 (4)</td>
<td>0.003 (&lt;0.001–0.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Schwartz measles</td>
<td>7/30 (23)</td>
<td>0.034 (0.003–0.39)</td>
<td>0.0003</td>
</tr>
<tr>
<td>EZ measles–rubella</td>
<td>2/30 (7)</td>
<td>0.004 (&lt;0.001–0.07)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Baseline quartile of neutralization titre (mIU/ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First (≤303)</td>
<td>32/45 (71)</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>Second (304–637)</td>
<td>17/44 (39)</td>
<td>0.041 (0.005–0.38)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Third (638–1222)</td>
<td>11/45 (24)</td>
<td>0.006 (&lt;0.001–0.07)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fourth (&gt;1223)</td>
<td>1/44 (2)</td>
<td>&lt;0.001 (&lt;0.001–0.007)</td>
<td>&lt;0.07001</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by multivariate analysis using low-dose aerosol as the reference group and controlling for baseline antibody titres.

<sup>b</sup> Likelihood ratio statistic.

<sup>c</sup> Figures in parentheses are percentages of children responding over total.
This randomized, controlled trial strongly confirms previous results that showed a superior boosting response for aerosol vaccination compared with vaccination by injection. Substantially better boosting responses were obtained with aerosol doses of only 1000 pfu than with vaccines given in their usual doses by injection.

The standard titre vaccines — that is, doses <10^4.7 pfu — provided for injection in this study each had 5000 or more pfu per dose. Such vaccines, when reconstituted and nebulized in a 0.1ml volume, deliver doses of vaccine containing ≥1000 pfu. The minimum acceptable dose of measles vaccines for injection is 1000 times the tissue culture infectious dose 50 (TCID50), but most vaccines used in the Expanded Programme on Immunization contain ≥5000 TCID50 per 0.5ml dose in order to meet stability test requirements. The lyophilized vaccine powder must lose <1 log in titre after 7 days at 37 °C and still contain a minimally acceptable dose (Julie Milstien, personal communication, 24 July 2000). A 5000 TCID50 dose is equivalent to 3500 pfu (12). Aerosol doses of 1000 pfu or more can thus be achieved with vaccines of this potency simply by extending the time of administration from 30 seconds to about 45 seconds. This means that no specially prepared vaccine is needed for aerosol vaccination campaigns, which could vaccinate several times as many children as injection campaigns with the same amount of vaccine as needed for injection and with the expectation of significantly better antibody responses. The public health implications of better antibody responses from aerosolized vaccines include an increased duration of protection from measles and less viral replication upon exposure to wild measles virus in those receiving aerosolized vaccines and longer protection in the infants of mothers so vaccinated (13).

Thirty seconds of exposure to aerosolized vaccine is a time short enough to provide efficient vaccination but long enough to accommodate variations in breathing patterns. Some children breathe slowly and deeply (as instructed), others seem to take only tidal breaths and a few even stop inhaling briefly on initial exposure to aerosol. Such differences doubtlessly produce widely varying retained doses, which may be only approximately one quarter of the inhaled dose (14). The superior antibody responses observed after aerosol vaccination show that these and other variables that adversely affect aerosol performance are not enough to offset its advantages over subcutaneous injection.

The superior boosting effect of low-dose aerosolized vaccines compared with injected vaccines was convincingly documented with highly significant differences, despite relatively small numbers of neutralizing antibody tests. The equivalence of responses within the aerosol and injected groups, however, was less confidently established. In this regard, the increased point estimate of response to injected SW vaccine compared with other injected vaccines in our trial contrasts with the significantly better responses with injected EZ compared with injected SW vaccine seen in the South African trials (3).

Studies in progress will further evaluate the reasons for the observed lack of stability of SW vaccine under field conditions of nebulization (3). It is clear from Terskikh's experience that aerosolized SW can perform well when delivered by a different type of nebulizer (2). Until these issues are clarified, it seems prudent to use only vaccines shown to be stable under simulated aerosol field conditions.

The use of a single nebulizer for aerosol immunization of multiple children was extensively employed in Mexico nearly a
decade ago with the same equipment and procedures used in our trial, and it was noted to be well tolerated and without serious side-effects (4). Furthermore, in both this and the South African trial (3), the frequencies of respiratory illnesses after vaccination were higher in those given injected vaccines than in those receiving aerosolized vaccines. Although aerosol vaccination may be less reactogenic than vaccination by injection, differing rates of background illnesses at the times when vaccines were given to different groups could have played a role in both studies. Such a mechanism may underlie the different frequencies of symptoms within the three groups that received aerosolized vaccines in our trial. In addition, the actual dose the child receives from an aerosol is substantially less than the nebulized dose administered over 30 seconds because the vaccine is only taken into the lungs during inspirations that occur during those 30 seconds and only about one quarter of the inspired vaccine is retained (4/4).

The US Pharmacopeia permits low levels of microbial contaminants in substances delivered by aerosols (15). Such standards are consistent with the lack of sterility of inhaled air and the natural defences of the respiratory tract. All vaccines were chilled when placed in the nebulizer and then kept cold on crushed ice, thus providing inhospitable conditions for outgrowth of any contaminants over the time needed to deliver 40 doses. The prospect for retrograde contamination of vaccine in the nebulizer is greatly reduced by the loose fit of the disposable paper mask over the nose and mouth of the child and the high pressure inside the nebulizer.

Concerns about the safety of aerosol vaccination for those receiving the vaccine, as well as for vaccinators, have been expressed elsewhere (1). One of the most frequently expressed concerns has been the safety of repeated exposures of vaccinators to aerosolized vaccine. In this regard, it should be re-emphasized that health care workers have been repeatedly exposed to wild measles virus itself while caring for sick children, but that such exposures have never been recognized as a source of harm for immune people.

The aerosol route for measles vaccination is painless, simple, quick, well tolerated, more immunogenic in lower doses than injected vaccine and avoids the risk of unsafe injections. Currently available vaccines and equipment are suitable for mass campaigns, and subsequent studies may show aerosolized vaccines to be an inexpensive alternative to mass injections, as envisioned by the late Albert Sabin many years ago (16). Aerosols could be a critically useful complement to injected vaccines in the ultimate global elimination and eradication of measles.

Acknowledgements
The generous donation of vaccines by the Swiss Serum and Vaccine Institute is gratefully acknowledged, as is the constructive advice and assistance extended to us by Drs Reinhard Gluck and Mateo Schaffhauser. We are also grateful for the assistance of Mr Heriberto Lara Boy (SmithKline Beecham, Mexico) for donating the Schwarz vaccine used in this study. The assistance of health services staff in Hildalgo state was essential to the success of these studies, and the collaboration of Dr Irma Eugenia Gutierrez is especially acknowledged. We are also grateful to Dr Paul Rota of the Centers for Disease Control and Prevention, who assayed viral titres in pretrial aerosol simulations with measles vaccine, and to Dr William Bellini and Irene Williams of CDC, who assisted in antibody assays.

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Conflicts of interest: none declared.

Résumé
Les vaccins antirougeoleux et antirougeoleux-antirubéoleux en aérosol induisent une meilleure réponse de rappel en anticorps antirougeoleux que les vaccins administrés par injection : essais randomisés chez des écoliers mexicains

Objectif Comparer les réponses en anticorps et les effets secondaires de vaccins antirougeoleux administrés par aérosol et par injection après revaccination d’enfants entrant à l’école primaire.


Résultats Après correction des titres d’anticorps de référence, la fréquence des quadruplements, ou davantage, des titres d’anti-corps neutralisants ne variait pas de façon significative entre les trois groupes ayant reçu le vaccin par aérosol (intervalle : 52 %-64 %), mais était significativement supérieure à celle des trois groupes ayant reçu le vaccin par injection (intervalle : 4 %-23 %). L’élévation moyenne des titres et le titre moyen géométrique après vaccination suivait le même schéma. Les effets secondaires étaient moins nombreux après administration du vaccin par aérosol qu’après injection.

Conclusion Administré par aérosol, le vaccin antirougeoleux est plus immunogène que lorsqu’il est administré par injection. Cet avantage persiste avec des doses d’aérosol inférieures ou égales à 1/5 des doses habituellement administrées par injection. L’efficacité et le rapport coût-éfficacité de la vaccination antirougeoleuse par aérosol devront être évalués plus avant lors de campagnes de masse.
**Resumen**

Las vacunas aerosolizadas contra el sarampión y el sarampión–rubéola inducen mejores respuestas de refuerzo de los anticuerpos antisarampionosos que las vacunas inyectadas: ensayos aleatorizados en escolares mexicanos

**Objetivo**
Comparar las respuestas de producción de anticuerpos y los efectos secundarios de las vacunas antisarampionosas aero-solizadas e inyectadas después de la revacunación de niños matriculados en escuelas primarias.

**Métodos**
Cuatro grupos de niños recibieron vacunas contra el sarampión (Edmonston–Zagreb) o contra el sarampión–rubéola (Edmonston–Zagreb con RA27/3) mediante aerosol o por inyección. Un quinto grupo recibió la vacuna antisarampionosa Schwarz mediante inyección. Estos cinco grupos recibieron las vacunas a las dosis habituales. Un sexto grupo recibió sólo 1000 unidades formadoras de placas de la vacuna Edmonston–Zagreb mediante aerosol. Los grupos fueron aleatorizados por escuelas. Las concentraciones de los anticuerpos neutralizantes se determinaron en muestras sanguíneas obtenidas en condiciones basales y cuatro meses después de la vacunación a partir de subgrupos aleatorizados (n = 28–31) de niños de cada grupo.

**Resultados**
Después de ajustar según los títulos de anticuerpos basales, la frecuencia de incrementos de cuatro o más veces de los anticuerpos neutralizantes no difirió significativamente entre los tres grupos que habían recibido la vacuna mediante aerosol (intervalo: 52%–64%), pero fue significativamente más alta que la de los tres grupos a los que se había inyectado la vacuna (intervalo: 4%–23%). Los aumentos medios de los títulos y sus medias geométricas posvacunación corroboraron esos resultados. Se observaron menos efectos secundarios con el aerosol que con las inyecciones.

**Conclusión**
La inmunogenicidad de la vacuna antisarampionosa aerosolizada es superior a la de la vacuna inyectada. Esta ventaja se mantiene en las dosis aerosolizadas equivalentes a un quinto o menos de las dosis inyectadas habituales. La eficacia y la relación costo-eficacia de la vacunación antisarampionosa mediante aerosol se deben seguir evaluando en campañas masivas.

**References**