

# Intradermal Administration of Measles Vaccines<sup>1</sup>

J. C. DE MORAES,<sup>2</sup> M. E. LEÓN,<sup>3</sup> V. A. U. F. SOUZA,<sup>4</sup> C. PANNUTI,<sup>4</sup>  
C. TRAVISANELLO,<sup>5</sup> N. A. HALSEY,<sup>3</sup> & C. A. DE QUADROS<sup>6</sup>



*The aim of the study reported here was to determine if bifurcated needles or multiple puncture cylinders would prove suitable for administration of measles vaccines.*

Children 9 to 11 months old in São Paulo, Brazil, were assigned to receive either Biken-Cam 70 (5 000 TCID<sub>50</sub>/0.5 ml) or Edmonston-Zagreb (7 000 TCID<sub>50</sub>/0.5 ml) measles vaccine intradermally with a bifurcated needle or a multiple puncture cylinder. These devices are usually used to administer smallpox or BCG vaccine. The volume of vaccine inoculated was approximately 0.003 ml. Measles IgG antibodies were measured by enzyme-linked immunosorbent assay (ELISA) at the time of vaccination and 8 weeks later. The study participants were examined 14 days after inoculation for possible adverse reactions.

Overall, the children's average age was  $9.5 \pm 0.66$  months at vaccination. None of the 45 recipients of Biken-Cam vaccine responded serologically. The 49 Edmonston-Zagreb vaccine recipients immunized with the multiple puncture cylinder had a somewhat higher serologic response rate (35%) and mean concentration of measles antibodies (323 mIU/ml) than those 51 who received the same vaccine administered with the bifurcated needle (26% and 291 mIU/ml, respectively). The rates of reported symptoms after vaccination did not differ significantly among the groups.

Overall, the low serologic response rates following intradermal immunization with the devices tested in this study indicate that this route of administration is not suitable for routine administration of standard-titer vaccines.

**M**easles vaccine is routinely administered subcutaneously in a 0.5 ml dose of standard titer with a needle and syringe. Unconventional administration routes, including aerosol inhalation and intradermal application, have been used to immunize children (1–3). During the smallpox eradication program in Brazil and several African countries, measles and smallpox vaccines were administered in-

tradermally using a jet injector with a nozzle especially modified for intradermal vaccine administration (3, 4).

Possible alternative tools for delivering measles vaccine intradermally are the bifurcated needle that contributed to success of the smallpox eradication program (3) and the multiple puncture cylinder (MPC) used to administer BCG vaccine (5). These simple devices would be easy

<sup>1</sup>This article will also be published in Spanish in the *Boletín de la Oficina Sanitaria Panamericana*, Vol. 118, 1995. Reprint requests and other correspondence should be sent to Dr. José Cássio de Moraes, MD; Centro de Estudos Augusto Leopoldo Ayrosa Galvão; Departamento de Medicina Social; Faculdade de Ciências Médicas da Santa Casa de São Paulo; Rua Cesário Motta 112, Pavilhão Conde Lara; 6º andar CEP-01221 - 020 São Paulo, SP, Brasil.

<sup>2</sup>Faculty of Medical Sciences, University of São Paulo, São Paulo, Brazil.

<sup>3</sup>Department of International Health, The Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland, U.S.A.

<sup>4</sup>Virology Laboratory, Institute of Tropical Medicine of São Paulo; Faculty of Medicine, University of São Paulo.

<sup>5</sup>São Paulo State Hospital of the Civil Servant (Hospital do Servidor Público Estadual de São Paulo), São Paulo, Brazil.

<sup>6</sup>Pan American Health Organization, Washington, D.C., U.S.A.

to use in national vaccination campaigns, since minimal training is required and volunteers can readily be taught to employ them. Such national vaccination campaigns have been introduced as part of a measles eradication effort in the English-speaking Caribbean community (6).

The aim of the study reported here, which was conducted in São Paulo, Brazil, was to see whether intradermal administration of measles vaccine with either a bifurcated needle (BN) or a multiple puncture cylinder (MPC) might prove an acceptable alternative to the traditional subcutaneous administration with a needle and syringe.

## MATERIALS AND METHODS

### Study Design

Children 9 to 11 months of age were randomly assigned to receive either Biken-Cam 70 or Edmonston-Zagreb measles vaccine administered intradermally with a bifurcated needle during the period of June–August 1991. In August of 1991 a third group of 9- to 11-month-old children received Edmonston-Zagreb measles vaccine that was administered with a multiple puncture cylinder (Japan BCG Laboratory, Japan—5). Overall, the children's average age was  $9.5 \pm 0.66$  months at vaccination.

### Study Population

After informed consent was obtained, healthy infants attending well-child clinics in São Paulo were recruited for the trial. Children with prior measles immunization, lack of an immunization card, a history of measles infection, severe malnutrition as indicated by a weight-for-age below 60% of the reference median (Gomez' criteria—7), or a history of fever (axillary temperature  $37.5^\circ\text{C}$ ) in the 24

hours preceding the visit were not eligible to participate.

### Vaccines

Edmonston-Zagreb strain measles vaccine (7 000 TCID<sub>50</sub>/0.5 ml) was produced at the Zagreb Institute in Zagreb, Croatia. Biken-Cam 70 vaccine (5 000 TCID<sub>50</sub>/0.5 ml) was produced at the Oswaldo Cruz Institute (Fiocruz) in Rio de Janeiro, Brazil.

The vaccines were reconstituted with diluent provided by the manufacturer immediately before administration. No vaccine vials were used more than 3 hours after reconstitution. The vaccines were administered in the deltoid region in the left arm. After cleaning the skin with acetone, those subjects inoculated with the bifurcated needle received fifteen rapid strokes with a needle dipped in reconstituted measles vaccine; those inoculated with the multiple puncture cylinder received only a single stroke. After inoculation, the drop of vaccine on the skin was allowed to dry for 30 seconds.

### Blood Collection

Seven ml of blood were collected from the antecubital vein by a phlebotomist at the time of enrollment and 8 weeks after immunization for the purpose of determining measles antibody concentrations. Complete hematologic profiles and blood typing of the subjects were offered to parents as an incentive for allowing their children to participate in the study.

### Serology

Measles IgG antibodies were measured by enzyme-linked immunosorbent assay (ELISA), using Vero cells infected with the Toyoshima strain of measles virus as a source of antigen (8). Serologic results were standardized, converted to international units, and expressed in milli-

international units per milliliter (mIU/ml) with international reference sera provided by the National Institute for Biological Standards and Control, Hertfordshire, England (9). Standard curves were derived from serial dilutions of reference sera containing 20, 10, 5, 2, and 1 mIU/ml and were included in each test run. At the end of the study all the children, regardless of their seroconversion status, received a second dose of Biken-Cam measles vaccine (5 000 TCID<sub>50</sub>/0.5 ml), the same as that normally utilized by the State Health Department in its routine schedule of subcutaneous vaccination.

### Adverse Reactions

Participating children were scheduled to visit the clinic on the 14th day after immunization to ascertain the presence of fever, coryza, cough, rash, or diarrhea during the preceding 2 weeks. Children who did not attend the clinic at the stipulated time were visited by a physician.

### Analysis

The study population's demographic characteristics, frequency of postvaccination symptoms, frequency of serologic responses  $\geq 100$  mIU/ml, and frequency of serologic responses  $\geq 200$  mIU/ml were

compared using a Chi-square test correcting for continuity. The mean age, weight, and length of the children in each immunization group at the time of immunization, together with their mean measles antibody concentrations in mIU/ml before and after vaccination, were compared using either one-way analysis of variance (ANOVA) or Kruskal-Wallis *H* statistics.

## RESULTS

As indicated in Table 1, a total of 181 children received the intradermal measles vaccines. Complete study information and 8-week postimmunization blood specimens were obtained from 145 of the children. The distribution of these children by sex, age at immunization, mean weight, and mean length were similar in each of the three vaccination groups.

None of the recipients of the Biken-Cam measles vaccine showed a positive immunologic response (see Table 2). There were positive responses among the children who received Edmonston-Zagreb measles vaccine; and while the difference was not significant, those inoculated with the multiple puncture cylinder had a somewhat higher serologic response rate than those inoculated with the bifurcated needle. Those inoculated with the mul-

**Table 1.** Characteristics of the study participants, by vaccine strain received and inoculation device.

	Intradermal administration of:		
	Edmonston-Zagreb vaccine with:		Biken-Cam vaccine with bifurcated needle
	Bifurcated needle	Multiple puncture cylinder	
No. vaccinated	61	61	59
No. included	51	49	45
% male	52.9	44.9	53.3
Mean age in months (SD)	9.5 (0.7)	9.4 (0.7)	9.6 (0.8)
Mean weight in kg (SD)	9.3 (1.7)*	8.6 (2.9)	8.7 (2.5)
Mean length in cm (SD)	68.2 (14.6)	66.0 (17.3)	65.1 (29.2)

\*Only 50 subjects included.

**Table 2.** Serologic responses of the study participants, by vaccine strain received and inoculation device.

	Intradermal administration of:		
	Edmonston-Zagreb vaccine with:		Biken-Cam vaccine with bifurcated needle
	Bifurcated needle	Multiple puncture cylinder	
No. included	51	49	45
Postvaccination antibody levels:			
% $\geq 100$ mIU/ml*	33.3	55.1	0.0
% $\geq 200$ mIU/ml†	25.5	34.7	0.0
Mean concentration before vaccination (CI)‡	1.8 (0.2; 3.4)	1.6 (0.2; 3.0)	4.0 (2.5; 5.5)
Mean concentration after vaccination (CI)§	291.2 (93.4; 489.0)	323.1 (155.8; 488.4)	0.44 (0.0; 1.3)

\*% with ELISA antibody concentration  $\geq 100$  mIU/ml.

†% with ELISA antibody concentration  $\geq 200$  mIU/ml.

‡Mean antibody concentration and confidence interval before vaccination.

§Mean antibody concentration and confidence interval after vaccination.

tiple puncture cylinder also had a higher mean titer (323 mIU/ml) than those who received the same vaccine via the bifurcated needle (291 mIU/ml) ( $P = 0.02$ ). Overall, however, only 35% and 26% of those respectively receiving this vaccine via the multiple puncture cylinder and the bifurcated needle developed a protective antibody concentration (200 mIU/ml). The responses in males and females were similar.

No statistically significant differences were found between the three vaccination groups with respect to the rates of symptoms reported during the 14-day postinoculation clinic visit (Table 3).

## DISCUSSION

Intradermal administration of measles vaccines using the bifurcated needle and multiple puncture cylinder induced lower

**Table 3.** Possible side-effects reported among the study participants during the first two weeks following inoculation, by vaccine strain received and inoculation device.

	Intradermal administration of:		
	Edmonston-Zagreb vaccine with:		Biken-Cam vaccine with bifurcated needle
	Bifurcated needle	Multiple puncture cylinder	
No. vaccinated	61	61	59
No. included	51	49	45
% with fever	7.8	19.1	22.2
% with coryza	23.5	25.5	31.1
% with cough	13.7	23.4	24.4
% with rash	15.7	14.9	15.9
% with diarrhea	5.9	8.5	4.4

serologic response rates than have been observed in children immunized subcutaneously using standard vaccine doses. None of the children receiving the Biken-Cam measles vaccine responded, and only 26–35% of the children who received the Edmonston-Zagreb measles vaccine intradermally developed protective antibody concentrations. In a study conducted in Kenya (10), low seroconversion rates (25%) were also reported following administration of Attenuvax strain measles vaccine using bifurcated needles.

The most likely explanation for the low response rates following intradermal immunization is the small dose (approximately 0.003 ml) of vaccine administered. Although children without any traces of maternal antibody have been immunized with as little as 20 TCID<sub>50</sub> of measles vaccine, the usual recommended dose is 3 000 TCID<sub>50</sub> (11). We estimate that we administered 30 to 42 TCID<sub>50</sub> of vaccine with the bifurcated needle.

The children in our study were 9 to 11 months of age and most likely had some low concentration of maternal antibody that interfered with the minimal vaccine dose. Maternal antibodies have been shown to blunt or block the antibody response to measles vaccines through 11 months of age in developing countries (12). If the concentration of the vaccine virus were increased by 10 to 1 000 times, then the bifurcated needle or the multiple puncture cylinder might be effective. (Approximately 2 000 TCID<sub>50</sub> could be inoculated using the bifurcated needle if a vaccine with a titer of  $10^5$  TCID<sub>50</sub>/0.5 ml were used. However, care would need to be taken to ensure that children did not inadvertently receive the standard 0.5 ml dose of this vaccine, since the higher-titer vaccines may cause harm and have been discontinued—13, 14.)

Regarding symptoms sometimes associated with adverse reactions, the similar rates of these symptoms found in each

of the three study groups probably reflect the high baseline rate of other illnesses in the study population. The slightly higher serologic response rates and geometric mean antibody concentrations observed in children immunized with the cylinder versus the bifurcated needle may have been due to a larger volume of vaccine being inoculated with the cylinder.

The lower rate of response following inoculation with the Biken-Cam vaccine (as compared to the Edmonston-Zagreb vaccine) cannot be ascribed to a preservation problem (since both had been maintained in the same refrigerator) or to the application technique (since all the children were inoculated by one of the authors). The reason could relate to characteristics of the Edmonston-Zagreb strain, which several studies have found to present a superior response to the Biken-Cam (15) and Schwarz (15–18) strains under similar application conditions (dose, age, and manner of administration).

## CONCLUSION

The low serologic response rates following intradermal immunization with the devices tested in this study indicate that this route of administration is not suitable for routine administration of standard-titer vaccines.

## REFERENCES

1. Sabin AB, Flores Arechiga A, Fernández de Castro J, et al. 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;249:2651–2662.
2. Sabin AB, Flores Arechiga A, Fernández de Castro J, et al. Successful immunization of children with and without maternal antibody by aerosolized measles vac-

- cine: II, vaccine comparisons and evidence for multiple antibody response. *JAMA* 1984;251:2363–2371.
3. Fenner F, Henderson DA, Arita I, Jesek P, Ladnyi ID, eds. *Smallpox and its eradication*. Geneva: World Health Organization; 1988.
  4. Millar JD, Roberto RR, Wulff H, et al. Smallpox vaccination by intradermal jet injection: I, introduction, background, and results of pilot studies. *Bull World Health Organ* 1969;41:749–760.
  5. *Volume 17: International Symposium on BCG Vaccine, Frankfurt (Main)*. Basel: Karger; 1971:295–302. (Symposium series in immunobiology standards).
  6. Pan American Health Organization. Make measles history. *EPI newsletter* 1991;13(3):2.
  7. Gómez F, Galván RR, Frenk S, Muñoz J, Chávez R, Vázquez J. Mortality in second and third degree malnutrition. *J Trop Pediatr* 1956;2:77–83.
  8. Souza V, Pannuti CS, Sumita LM, Albrecht P. Enzyme-linked immunosorbent assay (ELISA) for measles antibody: a comparison with haemagglutination inhibition, immunofluorescence and plaque neutralization tests. *Rev Inst Med Trop São Paulo* 1991;33:32–36.
  9. Job JS, Halsey NA, Boulos R, et al. Successful immunization of infants at 6 months of age with high dose Edmonston-Zagreb measles vaccine. *Pediatr Infect Dis J* 1991;10:303–311.
  10. 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;77:171–176.
  11. Preblud SR, Katz SL. Measles vaccines. In: Plotkin SA, Mortimer EA, eds. *Vaccines*. Philadelphia: WB Saunders; 1988.
  12. Halsey NA, Boulos R, Mode F, et al. Responses to measles vaccines in Haitian infants 6 to 12 months old: influence of maternal antibodies, malnutrition, and concurrent illnesses. *N Engl J Med* 1985;313:544–549.
  13. World Health Organization. Expanded Programme on Immunization: safety of high-titer measles vaccines. *Wkly Epidemiol Rec* 1992;67:357–361.
  14. World Health Organization. Expanded Programme on Immunization: measles. *Wkly Epidemiol Rec* 1993;15:14–15.
  15. Berry S, Hernández H, Kanashiro R, et al. Comparison of high titer Edmonston-Zagreb, Biken-CAM and Schwarz measles vaccines in Peruvian infants. *Pediatr Infect Dis J* 1992;11:822–827.
  16. Markowitz LE, Bernier RH. Immunization of young infants with Edmonston-Zagreb measles vaccine. *Pediatr Infect Dis J* 1987;6:809–812.
  17. Whittle HC, Mann G, Eccles M, et al. Effects of dose and strain of vaccine on success of measles vaccination of infants aged 4–5 months. *Lancet* 1988;1:963–966.
  18. Gendrel D, Garin D, Dutailly C, et al. Immunization of young infants with high doses of Schwarz measles vaccine. *Pediatr Infect Dis J* 1988;7:523–525.