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Field Evaluation of A Simplified Unit-Dose Syringe for Administration of Measles Vaccine

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Ezeject is a plungerless syringe prefilled with lyophilized measles vaccine. Ezeject syringes were compared with standard 3-cc syringes and 10-dose measles vaccine vials in the vaccination of 884 Guatemalan infants 8–23 months of age. Vaccination was performed by experienced vaccinators and by individuals without prior vaccination experience who received 2.5–3 hours of training. The overall seroconversion rate following administration was 96%, regardless of the type of syringe used or of the experience of the vaccinator. No significant adverse events were observed in children vaccinated with the new syringes. Although incomplete emptying was noted in 87% of the Ezeject syringes used, this had no effect on the serologic response to measles vaccine. Aspiration for detection of blood before injection of the vaccine was performed significantly ($P < .001$) less frequently with Ezeject than with 3-cc syringes by both experienced and inexperienced personnel. Inexperienced vaccinators administered measles vaccine significantly faster ($P < .001$) with Ezeject than with 3-cc syringes, but the times were similar for experienced vaccinators. Ezeject is an acceptable alternative to standard syringes for the administration of measles vaccine. Several design modifications that would improve the handling of the device and eliminate the possibility of its reuse have been suggested.

There is a need for a low-cost, unit-dose syringe for the administration of vaccines. Because of their lower costs, 10-dose vials of measles vaccine are the primary source of vaccine in developing countries. However, some nurses and health care providers are reluctant to open a 10-dose vial of measles vaccine to vaccinate a single child. Although the World Health Organization (WHO) has endorsed a policy of opening a 10-dose vaccine vial for one child, the availability of a prefilled unit-dose syringe would eliminate some unnecessary withholding of vaccines from infants and children [1]. Nonreusable syringes and needles would also eliminate the possibility of transmitting hepatitis B virus, Ebola virus, malarial parasites, and human immunodeficiency virus [2–4].

Ezeject (Merck Sharp & Dohme, West Point, Pa.) is a small, plungerless syringe and needle prepared from flexible plastic tubing and prefilled with lyophilized measles vaccine (figure 1). Satisfactory seroconversion rates with measles vaccine were obtained when Ezeject syringes were utilized by physicians and experienced nurses in the United States and Costa Rica [5, 6]. The syringe was licensed by the U.S. Food and Drug Administration but was never commer-

Informed consent was obtained from all parents of the study participants, and the guidelines for human experimentation of the U.S. Department of Health and Human Services were followed. This study was approved by the Committee on Human Volunteers of Johns Hopkins University School of Hygiene and Public Health and by the Ministry of Health, Guatemala.

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This paper was delivered in Spanish by Dr. Juan José Arroyo Hernandez.

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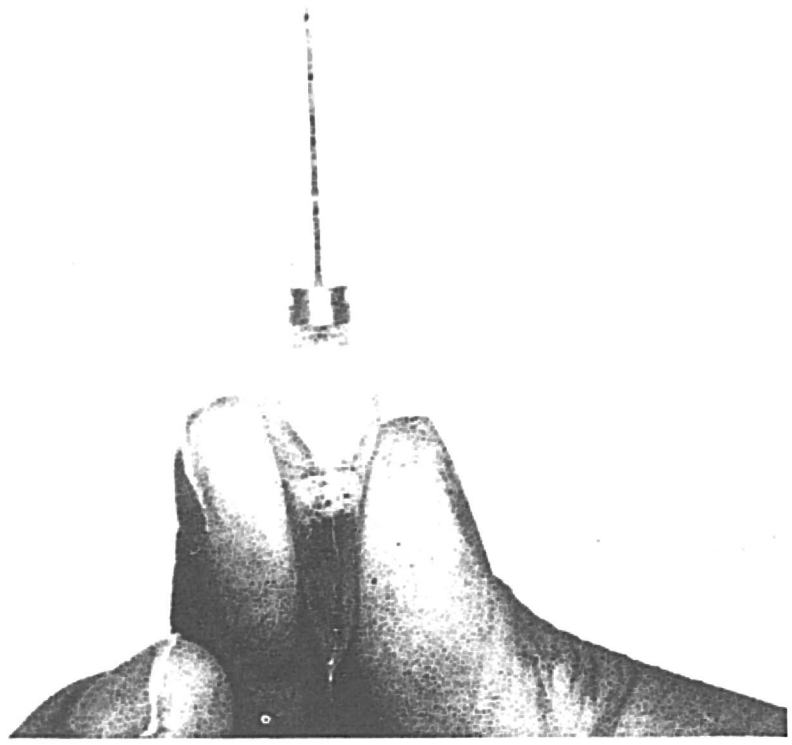

Figure 1. The Ezeject syringe.

cially produced because of the lack of an identified market in the United States.

The purpose of this investigation was to evaluate the practicality and user acceptability of Ezeject syringes as compared with that of standard syringes for the administration of measles vaccine in an ongoing immunization program in Guatemala. The study was also designed to determine if individuals who had no prior experience administering vaccines could be trained to administer measles vaccine with Ezeject syringes and to compare their performance with that of experienced vaccinators.

Methods

Participants

Vaccinees were Guatemalan infants 9–23 months of age who had not previously received measles vaccine and had not, according to their mothers, had measles. Infants were enrolled from Ministry of Health clinics serving six geographic areas: Totonicopan, Quetzaltenango, Patzicia, Comolapa, Chimaltenango, and Primero de Julio in Guatema City. All clinics except Primero de Julio served primarily rural populations.

This investigation was approved by the Committee on Human Volunteers of Johns Hopkins University School of Hygiene and Public Health, the Pan American Health Organization, and the Ministry of Health, Guatemala. Health promoters recruited parents of appropriately aged infants by visiting each household with an age-eligible infant. Prerecorded tapes explaining the study were prepared in some communities and played from loudspeakers. Informed, written consent was obtained with use of a standardized form. The study was explained verbally to illiterate women, who indicated their approval with a thumbprint. Photographs were taken of infants at the time of vaccination, and prints were made available when follow-up blood specimens were obtained as an incentive for the parents to return and to assure accurate identification of the subjects.

Vaccinators

Experienced vaccinators were chosen from lists prepared by clinic directors. These included rural health technicians, nurse auxiliaries, licensed practical nurses, and registered nurses. Inexperienced individuals were chosen from lists of health promoters, sanitarians, traditional birth attendants, and mothers. Study coordinators assigned numbers to the lists prepared by clinic directors and randomly selected, with a table of random numbers, enough experienced and inexperienced individuals so that each could administer vaccine to 24 infants.

Vaccines

Ezeject syringes were prefilled with the Moraten strain of further-attenuated measles vaccine. The vaccine vials had been stored at −70°C at Merck Sharp & Dohme in sealed aluminum packages. Titration of vaccine virus before initiation of the study indicated that the vaccine had not lost any potency since its preparation in 1976. After the study was completed, titrations of vaccine virus were repeated on the vaccine in syringes that remained at the Merck Sharp & Dohme laboratories and on samples of vaccine that had been shipped to field sites. Schwarz strain measles vaccine produced in 10-dose vials by Merieux Institute was obtained from the Ministry of Health stock. Vaccine virus titrations on the 10-dose vials that had been shipped to the field were performed simultaneously with those on the Ezeject syringes.

All vaccine was kept frozen at −20°C in a central location and subsequently maintained at 2–8°C in the clinics before use.

Training

Experienced and inexperienced vaccinators participated in 2.5–3.0-hour training sessions on the use of Ezeject syringes one or two days before the vaccine clinics. Training consisted of three demonstrations of proper technique by the primary instructor and a review of a training manual. Under supervision, each vaccinator then administered vaccine into oranges three to five times.

Vaccinators also received similar training and practice with 3-cc disposable syringes and needles used for administering vaccine from the 10-dose vials. Training was evaluated by administering standardized multiple-choice tests before and after each training session.

Vaccine Administration

All vaccination tables were set up in a standard manner, with thermal containers containing vaccines, vaccine diluent, individually wrapped disposable needles and syringes, cotton balls, and alcohol. Ten-dose vials of measles vaccine were reconstituted within 60 minutes before use. Ezeject syringes were sealed in foil packets with 10 syringes per packet. Vaccine in Ezeject syringes was reconstituted immediately before administration with sterile diluent in individual vials provided by the manufacturer.

As infants were brought into the vaccination room and after blood specimens were obtained, they were alternately assigned to receive vaccine from the Ezeject or the 3-cc syringe. Measles vaccine was administered in the deltoid region of the upper arm. Infants in need of DTP (diphtheria-tetanus-pertussis) or oral poliovirus vaccines received them at separate vaccination stations immediately after they had received the measles vaccine. DTP was injected in the anterolateral thigh or buttocks, depending on the practice used at the clinic.

Observation and Monitoring of Vaccinators

Administration of all vaccinations was observed by study collaborators who were trained to record the time required, the volume remaining in the syringe after vaccination, and the techniques for reconstitution, application, and aspiration. Standardization of observers was evaluated by having two observers simultaneously evaluate 69 vaccinations. If vaccinators made an error in technique that could result in failure to vaccinate a child successfully, the error was pointed out before the next vaccination.

After four of the six vaccination clinic sessions, vaccinators were asked to complete a standardized questionnaire regarding their opinions about ease of use and preferences for the two syringe types.

A questionnaire was administered to mothers at the time of the follow-up visit to obtain information regarding any complications or illness observed, and infants were examined if indicated.

Serologic Methods

Blood specimens were collected on filter paper at the time of vaccination and four to six weeks later, according to the method described by Nakano et al. [7, 8]. Filter papers were dried at room temperature for 24 hours and then double-sealed in plastic bags containing a desiccant and stored at −60°C until serologic testing was performed three to four months later. Assays for measles antibody were performed with a commercially available test kit (Measlestat, Whittaker M.A. Bioproducts, Walkersville, Md.) after its standardization with the hemagglutination-inhibition (HAI) antibody test [9–11].

Data Analysis

Data were entered onto microcomputer diskettes; a double-entry program was used, and entries were verified by comparing them with those on the individual data forms. Comparison of continuous variables, including antibody titers and time of administration, was by Student's t test. Seroconversion rates were compared by χ^2 analysis, and analysis of variance (with use of the standard software program Statistical Programs for the Social Sciences), was utilized when indicated for adjusting for age or vaccination sequence.

Results

Training

Training was completed by 45 experienced vaccinators (40 nurse auxiliaries, three rural health technicians, and two nurses) and 27 persons without previous vaccination experience (19 health promoters, four traditional birth attendants, two sanitarians, and two mothers).

The results of tests given before and after the training sessions revealed higher scores on questions concerning techniques for the 3-cc syringes for all vaccinators and higher scores in general for experienced than for nonexperienced individuals.

A total of 884 infants were vaccinated, 446 with Ezeject and 438 with 3-cc syringes. Only 48 of the 72 trained vaccinators participated in the actual vaccination programs because fewer children than anticipated appeared at each clinic. Of the 884 infants vaccinated, 542 (61.3%) were vaccinated by experienced individuals.

Thirty-seven (77.1%) of the vaccinators completed a standardized questionnaire evaluating the Ezeject and 3-cc syringes for administration of measles vaccine (table 1).

Simultaneous observation of 69 vaccinations revealed 83%–88% concordance by the observers for all variables evaluated.

Vaccine Administration

Reconstitution of vaccine with the Ezeject and 3-cc syringes was performed correctly 98% of the time. Inexperienced individuals administered vaccines correctly 94.8% of the time with the Ezeject syringes and 98.2% with the 3-cc syringes, percentages not significantly different from those for experienced individuals (92.2% and 97.4%, respectively).

Proper aspiration of blood before injection of vaccine was identified as a problem with Ezeject syringes in the first clinic where the auxiliary vaccinators were

Table 1. Responses to selected questions by vaccinators after completion of immunization clinics.

Question, answer	No. (%) in indicated group with response: Inexperienced	Experienced
Which syringe is easier to use?		
Ezeject	7 (43.7)	7 (33.3)
3-cc	3 (18.8)	9 (42.8)
No preference	5 (31.2)	5 (23.8)
No answer	1 (6.2)	0 (0.0)
Total	16 (100)	21 (100)
Which syringe do you prefer to use?		
Ezeject	8 (50)	9 (42.8)
3-cc	2 (12.5)	6 (28.5)
No preference	6 (37.5)	6 (28.5)
Total	16 (100)	21 (100)

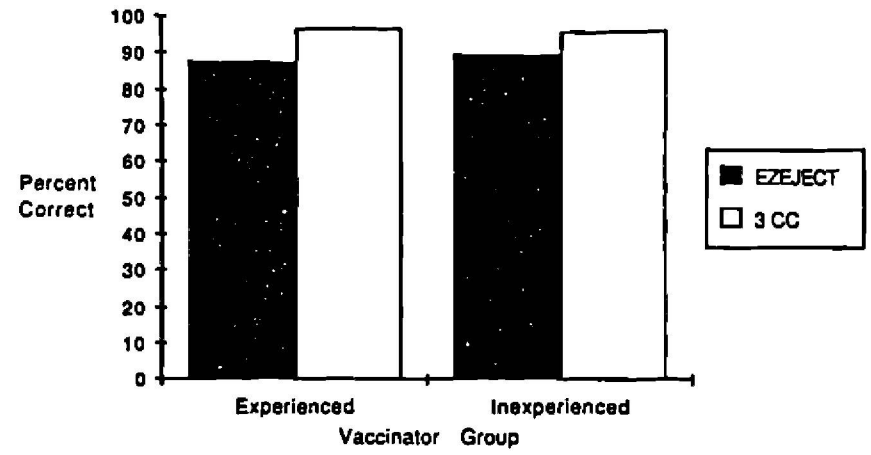

Figure 2. Percentage of vaccinators using correct aspiration techniques, by syringe type and experience of the vaccinator.

trained. Subsequent training was modified to emphasize the correct technique, and overall performance improved. Proper aspiration technique was used significantly ($P < .001$) less often with the Ezeject than with the 3-cc syringes by both experienced (87.8% vs. 97.4%) and inexperienced (90.7% vs. 97.0%) individuals (figure 2). The percentage of the Ezeject vaccinations administered with the proper aspiration technique improved as the vaccinators gained experience (figure 3).

Fewer than 10% of all vaccine administrations with 3-cc syringes resulted in the retention of a detectable residual volume of vaccine in the syringes, and the volume remaining did not exceed 0.2 mL. However, with 87% of all vaccinations with Ezeject, some residual vaccine was detectable in the syringe (figure 4). With ~10% of the Ezeject injections, ≥0.31 mL remained in the syringe.

Experienced individuals administered measles vaccine in significantly ($P < .0001$) less time than did inexperienced individuals with both the Ezeject and the 3-cc syringes, and the differences between the

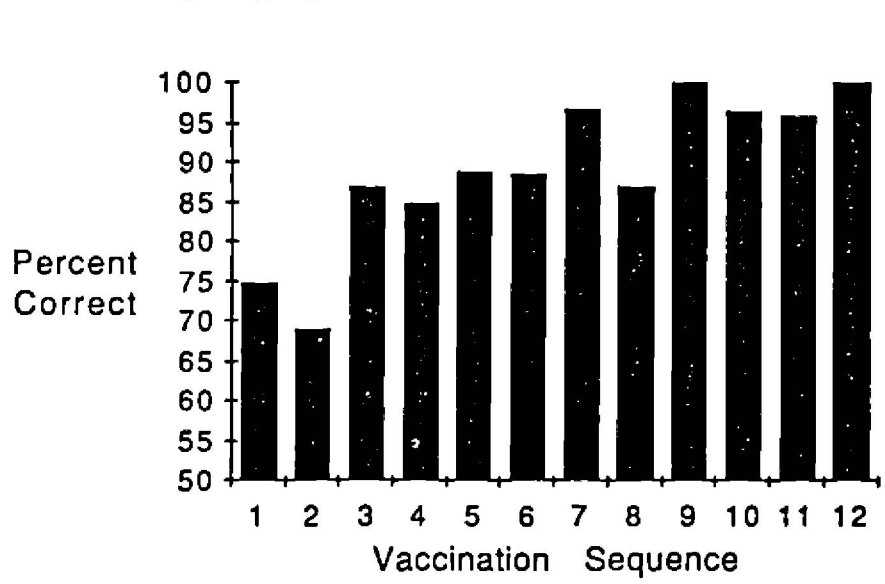

Figure 3. Percentage of vaccinators using correct aspiration technique with Ezeject syringes, by vaccination sequence.

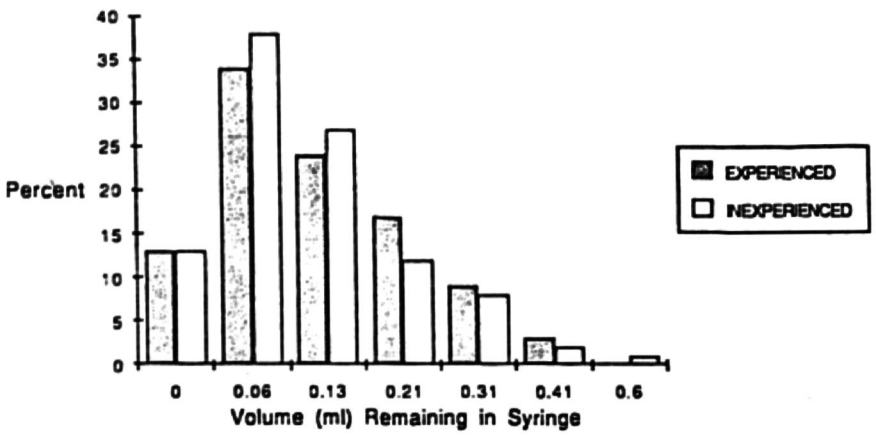

Figure 4. Percentage distribution of volume left in Ezeject syringes, by vaccinator experience.

times for the two syringe types were not significant (figure 5). Inexperienced individuals required significantly ($P < .0001$) less time to administer vaccine with Ezeject than with 3-cc syringes and required less time with each successive vaccine administration with either syringe.

Prevaccination blood specimens were inadequate for 10 of the 884 infants and children, and data for these children have been omitted from subsequent analyses. Seven hundred seventy-eight (89%) of the mothers and infants returned for the follow-up evaluation. Return rates were identical for infants vaccinated with Ezeject and 3-cc syringes, respectively (390 of 440 vs. 388 of 434).

The rates of rhinorrhea and cough, as reported by parents, in infants who received vaccine with Ezeject and with 3-cc syringes, respectively, were not significantly different. Approximately 25% of the mothers reported that their infants had fever during the 30-day interval between vaccination and the follow-up visit. However, the majority of the infants had onset of fever within the four days after vaccination (possibly in response to the DTP administered at the clinics). Fewer than 4% of the mothers reported that their infants had a rash in the four to six weeks after vaccination. There were no differences in the frequency of local signs at the site of injection for infants who received vaccine with Ezeject and 3-cc syringes, respectively.

The mothers of two infants reported that their infants had not moved their arms for 24–48 hours after vaccination. These infants were visited in their homes by two of the investigators. The results of neurologic examinations of the extremities were entirely within normal limits at the time of the follow-up evaluations. The mothers reported that the lack of arm movement had been noted on the evening of vaccination and had improved rapidly within 24–48 hours. One infant had received vaccine with the Ezeject syringe and the other with a 3-cc syringe.

One 13-month-old infant died 15 days after vaccination. This infant had fever for two to four days after vaccination. Watery diarrhea developed eight days after vaccination, and profuse vomiting developed three days later. His mother returned to the clinic only after the infant had died. Postmortem examination in the clinic revealed signs of dehydration. His mother reported no rash, cough, rhinorrhea, or symptoms other than those related to the gastrointestinal tract.

Titrations of measles vaccine virus from Ezeject syringes that had been taken to field clinics was $10^{3.8}$ $TCID_{50}$ (50% tissue culture infective doses)/0.5 mL vs. $10^{3.2}$ and $10^{3.6}$ $TCID_{50}$/0.5 mL for the two lots of Merieux vaccine utilized.

Antibody Testing

Although infants less than nine months of age were to have been excluded from the study, errors in cal-

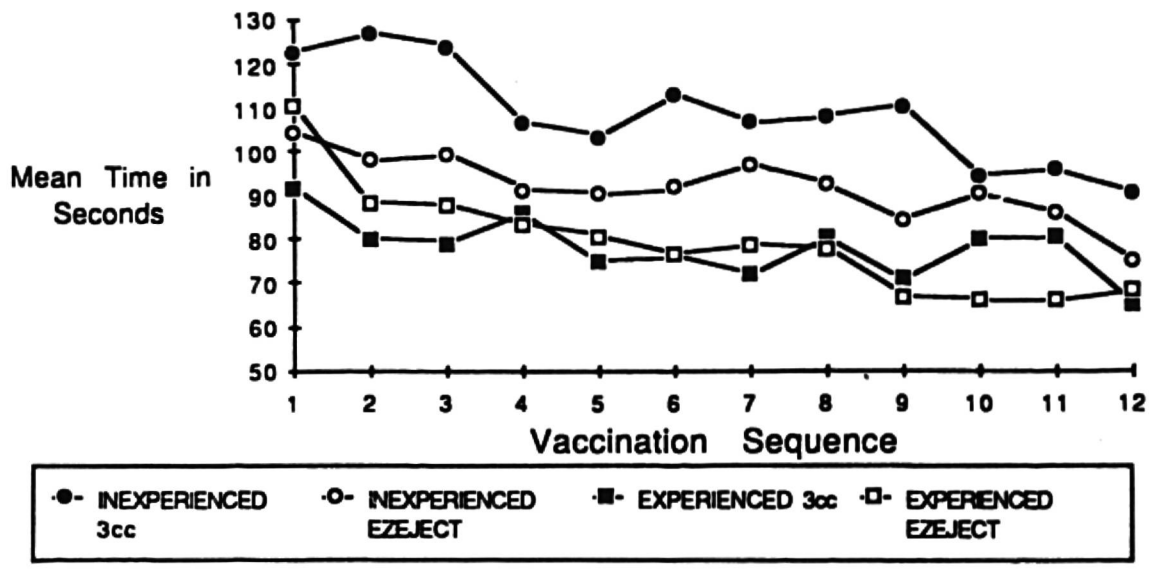

Figure 5. Average time for administration of measles vaccine with Ezeject and 3-cc syringes, by vaccinator experience and vaccination sequence.

Table 2. Percentage of Guatemalan infants seropositive for measles at the time of vaccination.

Age (mo)	No. positive/no. tested (%)
8	2/24 (8.3)
9	6/134 (4.5)
10	10/105 (9.5)
11	5/121 (4.1)
12	7/99 (7.1)
13	5/77 (6.5)
14	8/51 (15.7)
15+	65/262 (24.8)
Total	108/873 (12.4)

culation of age resulted in the inclusion of one seven-month-old infant and 24 eight-month-old infants. The seven-month-old infant was excluded from the analyses. The measles seropositivity rates by age at vaccination are shown in table 2.

An increase in rates of seropositivity with an increase in age was noted, a finding consistent with an expected increase in the rate of antibody positivity acquired through natural measles infections. Overall, 12.4% of infants tested had serologic evidence of previous measles infection, even though mothers in the study had reported that their infants had not had measles.

No outbreaks of measles were noted in the study communities during the four- to six-week interval between collection of blood specimens. Measles seroconversion rates by age of the infant and the syringe type used for vaccination are shown in table 3 for the 683 infants who were initially seronegative and were brought in for follow-up. No significant differences in seroconversion rates were noted between infants vaccinated with Ezeject and those vaccinated with the 3-cc syringes. The mean level of convalescent-phase antibody for infants who seroconverted increased somewhat until infants reached 10 months of age, a finding suggesting a modifying effect of maternal antibody in young infants (table 4). The mean level of antibody for all infants vaccinated with the Ezeject syringe was slightly but significantly ($P = .014$) higher than the mean level for infants vaccinated with Merieux vaccine in 3-cc syringes. The volume left in Ezeject syringes had no effect on seroconversion rates.

Table 3. Measles seroconversion rates by age of child and syringe type.

	No. seroconverting/no. vaccinated (%) with indicated type of syringe		
Age (mo)	Ezeject	Standard 3-cc	Total
8	10/10 (100)	9/11 (81.2)	19/21 (90.5)
9	49/55 (89.1)	59/66 (89.4)	108/121 (89.3)
10	38/38 (100)	44/46 (95.6)	82/84 (97.6)
11	58/60 (96.7)	44/45 (97.8)	102/105 (97.1)
12	44/44 (100)	36/39 (92.3)	80/83 (96.4)
13	25/26 (96.2)	32/32 (100)	57/58 (98.3)
14	19/19 (100)	19/19 (100)	38/38 (100)
15+	90/92 (97.8)	80/81 (98.8)	170/173 (98.3)
Total	333/344 (96.8)	323/339 (95.3)	656/683 (96.0)

Special Problems

Twelve (~1%) of the syringes used for training and vaccinating were defective, primarily because of leaks at the corners.

Some problems were noted in the seating of the needle in the Ezeject vaccine chamber. The needle is loosely placed in a plastic sleeve in the syringe collar. The base of the needle is seated into the chamber by forcefully pressing on the dust cover. Some vaccinators had difficulty pushing hard enough to seat the needle properly. In two instances, inversion of the syringe collar occurred. If the needle is not seated properly, it may be inadvertently pulled out before administration of vaccine. On eight occasions, vaccinators inserted the needle into the thick edge of the rubber stopper of the diluent vials. When

Table 4. Mean convalescent-phase levels of measles antibody for infants who seroconverted, by age at vaccination and syringe type used for vaccination.

	Values for infants vaccinated with indicated syringe type			
	Ezeject		3-cc syringe	
Age (mo)	No. converting	Mean level*	No. converting	Mean level*
8	10	2.24	9	2.29
9	49	2.69	59	2.31
10	38	2.84	44	2.64
11	58	2.88	44	2.73
12	44	2.92	36	2.77
13	25	3.12	32	2.64
14	19	2.82	19	2.70
15+	90	2.65	80	2.69
Total	333	2.78†	323	2.61†

* Predictive index.
† $P = .01$, t test.

vaccinators withdrew the needle from this thickened portion of the rubber stopper, they separated the needle from the Ezeject syringe. Training was subsequently modified to instruct vaccinators on the insertion of the needle into the center of the diluent rubber stopper. In one instance, the needle was partially unseated after the vaccine was reconstituted, but the needle did not completely pull out of the plastic diaphragm. The vaccinator was unable to inject any of the syringe contents because the diaphragm had resealed after the needle had been partially pulled out.

Vaccinators occasionally had difficulty applying sufficient force over the entire surface of the Ezeject syringe to inject the vaccine. The fingers of some of the vaccinators became slippery and slid over the surface of the syringe. Ribbing of the sides of the syringe should improve the grip.

Many vaccinators had difficulty understanding that Ezeject syringes must be pointed downward in order to be emptied. Attempts to demonstrate the proper angle for injection within 45° of an imaginary vertical plane were particularly difficult. Modification of Ezeject syringes so that they do not require inversion would simplify the injection process.

Discussion

Vaccination of infants with Ezeject and standard 3-cc syringes resulted in equal seroconversion rates. The slightly higher mean levels of antibody following vaccination with Moraten vaccine in Ezeject syringes was presumably due to the higher titers of measles vaccine virus in the Ezeject syringes or to differences in effectiveness of the Moraten and Schwarz strains used in the Ezeject and 3-cc syringes. Also, the longer needles used in the Ezeject syringes probably resulted in intramuscular injections rather than in subcutaneous injections, such as those given with the 25-gauge needles on the 3-cc syringes. No differences have been reported with measles vaccines for intramuscular vs. subcutaneous administration, but marked differences have occurred with hepatitis B vaccine [12]. Although 87% of injections given with Ezeject resulted in the incomplete emptying of the syringe, the difference in the volume injected had no apparent effect on seroconversion rates, even in two infants whose vaccinators left an estimated 0.6 mL of vaccine in the syringe. Thus, as has been demonstrated in other trials [13], only a small volume of measles vaccine is required for successful immunization of infants. Some vaccine (0.07–0.10 mL) was left in the needle hub of the 3-cc syringes with every injection, but this volume is not visible unless the syringe plunger is pulled back after injection.

Experienced and inexperienced vaccinators were successfully trained in the use of Ezeject syringes in a 2.5–3-hour training period. The value of the training manuals and other materials developed for this trial was not evaluated, as the same materials were utilized for all training sessions. On the basis of our experience during the training sessions, we are convinced that to properly utilize Ezeject syringes vaccinators require some special training. Hands-on experience under supervision may be more important than the specific information included in posters and manuals.

Some vaccinators had difficulty remembering the proper steps for aspirating blood before injecting vaccine. With Ezeject syringes, the vaccinator must think about the process of aspirating before the needle is inserted into the skin. The vaccinator must remember to press lightly on the syringe before inverting the needle and penetrating the skin. The release of pressure allows blood to enter the vaccine chamber if the needle is in a blood vessel. Vaccinators often had difficulty remembering to press on the sides of the syringe before inverting the needle and introducing it into the skin. Some experienced vaccinators pressed too firmly on the syringes in an effort to eliminate air from the chamber before penetrating the skin. This left them unable to apply sufficient additional pressure to collapse the syringe fully and empty its contents after penetrating the skin. However, after eight or nine injections under supervision, almost all individuals were performing this task appropriately. Aspiration before administration of measles vaccine may not be necessary. However, if the Ezeject syringe is to be utilized for administration of DTP and other vaccines, there may be risks associated with intravenous injection. Further modifications in the training materials for Ezeject should emphasize the proper steps for aspiration.

Inexperienced individuals took significantly ($P < .0001$) less time for vaccination with Ezeject than with the standard 3-cc syringes, although experienced personnel administered vaccines equally rapidly with the two types of syringes. An average of two minutes was taken for reconstitution of 10-dose vials of measles vaccine for use with the 3-cc syringes. Since the time required for reconstitution of vaccine was not

included in the calculation of the administration time, ~12 seconds should be added to the injection time for 3-cc syringes to provide an overall time comparable with that used for the Ezeject. When this adjustment was made, the time required for administration with Ezeject was significantly ($P<.01$) shorter for both experienced and inexperienced vaccinators. The times recorded in this trial were based on the first 10–12 injections given. They were obtained for purposes of comparison only and should not be considered representative for all vaccinators. With further experience, all vaccinators might have shortened the time necessary for vaccination. Two physician members of the study team administered vaccine with Ezeject in <30 seconds, less than one-half the average time used by experienced vaccinators.

The preferences of the vaccinator should be interpreted cautiously because the novelty of the new product may have influenced participants.

Several design modifications have been recommended to the manufacturer to improve the performance of Ezeject syringes, including improved surface texture, improved seating of the needle, modification of the design to allow emptying when positioned at multiple angles, and mechanisms that prevent inappropriate reuse of the syringes.

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