



Efficacy of Measles Vaccines after Controlling for Exposure

Michel Garenne,¹ Odile Leroy,² Jean-Pierre Beau,³ and Ibrahima Sene⁴

The clinical efficacy of measles vaccines was investigated in Niakhar, a rural area of Senegal under demographic surveillance in 1987–1990. Three measles vaccines were tested: a standard Schwarz, a high-titer Edmonston-Zagreb, and a high-titer Schwarz. The two high-titer vaccines were administered at 5 months of age and the standard Schwarz vaccine at 10 months. In addition to a formal randomized vaccine trial, data from national campaigns using the standard Schwarz vaccine were also analyzed. Clinical efficacy was estimated after controlling for exposure. In the randomized trial, the estimate of the efficacy of the standard Schwarz vaccine was 97.2% (95% confidence interval (CI) 91.3–98.1). In the 1986–1987 national campaign, the efficacy of the standard Schwarz vaccine was lower: 92.5% (95% CI 88.8–94.6). In the randomized trial, the efficacy of the high-titer vaccines was lower than that of the standard vaccine. High-titer vaccines were not used in national campaigns. Other factors associated with vaccine efficacy were age at exposure, intensity of exposure, and age at vaccination. Controlling for the intensity of exposure did not change the relative ranking of the efficacy of the three vaccination strategies. The theoretical efficacy of the standard measles vaccine for a single unit of exposure was estimated at 98.0%. *Am J Epidemiol* 1993;138:182–95.

child; measles; measles vaccine; multivariate analysis; population surveillance; prospective studies; rural population

Measles is a leading cause of mortality and morbidity among children in developing countries (1, 2). Vaccination is the most effective measure to control measles, and measles vaccination is recognized as one of the most cost-effective public health measures. Recent studies have shown that mea-

sles vaccination has a major impact on child survival in developing countries (3, 4). However, the efficacy of the vaccines used in developing countries, which determines the impact of vaccination strategies, remains poorly documented.

The further attenuated live measles vaccines have been marketed in Western countries since 1966 (5). After 1979, the major producers of measles vaccines introduced a new stabilization technique, the use of which may have increased the efficacy of the vaccines in the field (6). These vaccines are usually referred to as “Schwarz vaccines” in comparison with other vaccines, such as the Edmonston-Zagreb and the Leningrad-16, which have been used primarily in the countries of the former Eastern block.

Age at vaccination has been shown to be a major determinant of vaccine efficacy: children vaccinated too early do not sero-

Received for publication September 3, 1992, and in final form April 1, 1993.

Abbreviations: CI, confidence interval; pfu, plaque-forming unit; TCID₅₀, 50 percent tissue culture infectious dose.

¹ Harvard School of Public Health, Harvard University, Boston, MA.

² Pasteur-Mérieux Sérums et Vaccins, Paris, France.

³ Institut Français de Recherche Scientifique pour le Développement en Coopération (ORSTOM), Unité de Recherche Population et Santé, Dakar, Senegal.

⁴ Circonscription Médicale de Fatick, Fatick, Senegal.

Reprint requests to Dr. Michel Garenne, Center for Population and Development Studies, Harvard University, 9 Bow Street, Cambridge, MA 02138.

convert and are not protected by the vaccine (7). The recommended age at vaccination with standard vaccines ranges from 12 to 15 months in most Western countries, but in developing countries, it has been lowered to 9 months to increase the protection of infants, who can contract measles as early as 4 months of age (8).

The recommended titer of measles vaccines is at least 1,000 TCID₅₀ (50 percent tissue culture infectious dose), as defined by the World Health Organization. Standard vaccines often contain 5,000–10,000 TCID₅₀, although they have been shown to be efficient even with a titer as low as 20 TCID₅₀ (5). Studies conducted in The Gambia and in Mexico found that increasing the titer of the vaccine by 10- or 100-fold increased its immunogenicity and that the Edmonston-Zagreb strain produced better seroconversion than the Schwarz strain. These results suggested that children could be vaccinated at 4–6 months of age with the high-titer Edmonston-Zagreb vaccine. In 1990, the World Health Organization recommended the use of the high-titer Edmonston-Zagreb vaccine at 6 months of age in countries where measles was a significant cause of death in children less than 9 months of age (9).

There are several ways to estimate the clinical efficacy of vaccines: prospective or retrospective cohort studies, investigations of outbreaks, case-contact studies, and case-control studies. Estimates of vaccine efficacy depend on the following: the vaccine, its strain and titer, the age at vaccination, the intensity of exposure to measles during the study period, the interval between vaccination and exposure, and the case definition of clinical disease and whether the exposure is similar among vaccinated and unvaccinated persons. In addition, in prospective studies, estimates of vaccine efficacy may depend on the duration of the study (10–12).

Little is known about the efficacy of measles vaccines in Africa, primarily because few extensive clinical trials have been conducted there. Therefore, most estimates of

vaccine efficacy are derived from evaluations of national vaccination campaigns. Such estimates not only reveal the efficacy of the vaccine, but also reflect the conditions under which the vaccines were administered, including failures in maintaining the vaccine at low temperature (the cold chain) and inappropriate age at vaccination. Furthermore, many of these estimates are based on suboptimal methodologies of data collection. Estimates of efficacy range from less than 50 percent in the difficult conditions of Mozambique to 94.2 percent in Ivory Coast (13–17). The most reliable estimates come from The Gambia, where an efficacy of 85.6 percent was found among children vaccinated at 9–14 months of age in a national campaign (13).

This study reports the results of a 3-year clinical trial conducted in a rural area of Senegal. During this trial, the efficacy of three vaccination strategies was analyzed. Period efficacy was estimated directly by analyzing the incidence of clinical measles after vaccination. More important, case-contact efficacy was estimated by controlling for exposure to measles in the compound (household) of residence, and a theoretical definition of efficacy after controlling for the intensity of exposure in the compound is presented.

MATERIALS AND METHODS

Study population

The study area was located near Niakhar, in the *département* of Fatick in central Senegal. It comprises 30 villages whose total population includes about 25,000 people of Sereer origin. A comprehensive demographic and epidemiologic surveillance system based on weekly visits to each compound of the study area and on the annual census was ongoing before the study began (July 1987) and has been maintained since that time. The demographic surveillance system recorded births, deaths, and in- and out-migration, and defined the resident population at all points in time. The resident

population was divided into two categories: present or absent. Nonresidents who were present were called visitors. The epidemiologic surveillance system routinely recorded the reported cases of measles every week for the present population (resident or visitor). In addition, the annual census recorded the reported cases of measles among those in the resident population who were absent at the time of infection. Therefore, two studies of vaccine efficacy were conducted: a prospective period study of efficacy among the resident population (present or absent) and a case-contact study of efficacy in the compound among the present population (resident or visitor).

The efficacy study was part of a randomized vaccine trial conducted from August 1987 to July 1990 to compare two high-titer live measles vaccines, the Edmonston-Zagreb and the Schwarz, with the standard Schwarz vaccine with regard to efficacy, safety, and immunogenicity. The details of the vaccine trial and the main results concerning immunogenicity and safety have been reported (18–20). Since the measles surveillance system was based on the entire population, the study also provided the opportunity to estimate the efficacy of the standard Schwarz measles vaccine administered before the start of the study in the same villages.

The study was approved by the Senegalese health authorities (Ministère de la Santé Publique, Dakar); by authorities of the Office de la Recherche Scientifique et Technique Outre-Mer (ORSTOM) (Institut Français de Recherche pour le Développement en Coopération, Paris, France); and by the ethical committee of the British Medical Research Council in Fajarah, The Gambia. During the 3 years of the project, comprehensive vaccinations were made available to everyone, and free drugs and medical services were provided to all children and adults of the study population. As a consequence, both mortality and case fatality due to measles were significantly lower than during the preceding 3 years (1984–1986).

Vaccinations

Three series of vaccination were studied.

Randomized trial of three vaccines. The randomized trial of high-titer measles vaccines covered the cohorts of children born between February 1987 and January 1989. Children were randomized into three groups: high-titer Edmonston-Zagreb vaccine administered at 5 months, high-titer Schwarz vaccine at 5 months, and standard Schwarz vaccine at 10 months. Randomization was done by allocating children just after birth to one of the three groups, using a random number generator. Children of the same birth cohorts who were not vaccinated were used as the control group. They were mostly children living under the same conditions who were not available on the day scheduled by the research team for the vaccination. They did not differ in any socioeconomic characteristic from the others. They were followed up in exactly the same way as the participants in the vaccine trial. For the participants, the age at vaccination was strictly standardized: 5.0 months (range, 18–28 weeks) for the high-titer vaccines and 10.0 months (range, 40–47 weeks) for the standard vaccine. Only a few children received the standard vaccine after 10 months of age. All three vaccines were supplied by the manufacturers: the high-titer Edmonston-Zagreb by the Institute of Immunology, Zagreb, Yugoslavia (batch 81/3; titer, $5.4 \log_{10}$ plaque-forming units (pfu)); the high-titer Schwarz by the Institut Mérieux, Lyon, France (batch 0980; titer, $5.4 \log_{10}$ pfu); and the standard Schwarz by the Institut Mérieux, Lyon, France (titer, $3.7 \log_{10}$ pfu). The potency of the vaccines was monitored routinely and found to be constant over time. By January 1, 1990, 1,566 children had been vaccinated; vaccine coverage was 81.6 percent of the resident target population.

Monitored vaccination. A series of vaccinations was organized and monitored by the principal investigator of this study in March of 1981, 1982, and 1983 in eight of the vil-

lages within the Primary Health Care Project (Ms. Irene Van Dyck, Coordinator). Standard Schwarz vaccines from the Institut Mérieux were kindly furnished by Dr. Martin Schlumberger, the representative of the Association pour la Médecine Préventive (APMP, Paris, France) in Senegal. Strict control of the cold chain and vaccination procedure was observed. A total of 1,089 children were vaccinated according to the guidelines of the Ministry of Public Health of Senegal, which recommended vaccinating children between the ages of 9 and 23 months. Vaccine coverage was 73 percent of the resident target population of children born between 1980 and 1982. Among them, 386 were still resident at the time of the efficacy study.

National vaccination campaign and routine vaccinations. A major national vaccination campaign took place from December 1986 through April 1987. Records on health cards were taken during the demographic surveillance and checked in the dispensary registers whenever possible. The survey showed that 1,420 children born between 1978 and 1986 and still resident during the efficacy study were vaccinated against measles; the coverage was 44.1 percent among the cohorts born in 1984–1985. The demographic census also routinely and systematically recorded vaccinations done outside the study area by asking for health cards for all children under 15 years of age. Most of these routine vaccinations were given in large cities, where the child was traveling with his or her mother. Only a small number of children were in this group: 5.9 percent of the 1978–1986 cohorts. The measles vaccines used in the routine vaccination campaigns were standard Schwarz vaccines from various Western producers. No attempt was made to find the exact producer. The potency of these vaccines at the time of injection and the quality of the cold chain could not be verified. Only a small proportion of the children (6.9 percent) were vaccinated before the age of 9 months, the recommended age at vaccination.

Investigation of measles cases

The three measles outbreaks occurring in the study area between August 1987 and July 1990 were investigated: 27 cases occurred between May and September 1988, 161 cases between October 1988 and July 1989, and 413 cases between August 1989 and July 1990. When a family suspected a case of measles or when a case was seen in the clinic, a physician who was a permanent resident in the villages and specifically trained for this work was called to the compound to do a comprehensive clinical examination. The physician monitored the measles cases by visiting the family twice a week until the last case was cured. The physician was blind to the type of vaccine received during the vaccine trial, but was able to find out whether the child had been vaccinated by asking the mother or the caretaker. For serologic confirmation, an initial blood sample was taken by finger prick from all susceptible children (those who had never had measles) in the family during the first visit, and a second sample was taken from the clinical cases at least 4 weeks after the onset of the rash.

Exposure in compounds

Exposure was defined as the condition of being susceptible and present in a compound of the study area where there was a clinical case. Secondary cases were defined as those occurring in the same compound 7–18 days after the index case. The mean time lag between index and secondary cases was 12.2 days, a value equivalent to that reported in classic studies (21–23). For both cases and noninfected contacts (susceptible children who were present), the following linear score of intensity of exposure to index cases was devised: 1 = living in a different compound; 2 = living in the same compound but not eating from the same kitchen; 3 = eating from the same kitchen but not sleeping in the same hut; and 4 = sleeping in the same hut (24). Other cases among the resident population that occurred outside the study area were investigated primarily by questioning

the family members; sometimes confirmation of a case was by record of a proper clinical examination found in a dispensary; other cases were confirmed by a blood sample taken within a few weeks after the onset of the rash showing high levels of measles antibodies. However, these indirect pieces of evidence were not considered for final case validation. The surveillance system based on weekly visits to each compound and on systematic questioning during the annual census was very tight, and chances that a case was missed during the 3 years were very slim.

Case definition

A clinical score was defined by examining seven clinical signs observed during the physician's examination and summing up the values for each sign: 1) typical rash or desquamation (value = 6); 2) Koplik spot (value = 5); 3) atypical rash (value = 2); 4) conjunctivitis (value = 2); 5) stomatitis (value = 2); 6) cough (value = 1); and 7) rectal temperature greater than 38.0°C (value = 1). A reported case with a score of 8 or more was considered clinically confirmed. Of all reported cases, 80.1 percent were clinically confirmed; of reported cases examined during the 3–10 days after the onset of clinical signs, 92.4 percent were clinically confirmed.

Serologic confirmation was defined as an increase of at least fourfold in the titer of hemagglutination inhibition antibodies to measles virus during the acute phase. Of all the reported cases occurring before January 1, 1990, 63.7 percent were serologically confirmed. Of all the reported cases whose first blood sample was taken before day 2 and whose second blood sample was taken after day 28, 100 percent were serologically confirmed ($n = 112$). All had at least a 16-fold increase in hemagglutination inhibition antibodies titer. The high confirmation rate from serology ensures that the clinical definition was highly specific in these circumstances. Failure to obtain serologic confirmation occurred when the family refused to

allow the blood sample, when the case was first investigated after the onset of the rash, or when the second blood sample could not be taken.

A case was considered directly confirmed if it met both the clinical and the serologic criteria for confirmation. A case was considered indirectly confirmed when it occurred in a compound where another case was directly confirmed. Altogether, 61.1 percent of all reported cases were confirmed, either directly or indirectly. The proportion of confirmed cases was higher among secondary cases in the compound (79.2 percent), since these were more likely to have been examined since the onset of the disease. Two definitions were used in the final analysis: reported cases and confirmed cases (direct or indirect confirmation). A vaccine failure was defined as a case of measles in a child who was vaccinated at least 14 days before the onset of the rash.

Vaccine efficacy

Vaccine efficacy was estimated by comparing vaccinated children with unvaccinated children who had never had measles before. As soon as a child had clinical measles, he or she was removed from the pool of susceptible children. For the calculation of period efficacy, exact person-days at risk were computed for the resident population using dBASE IV (Ashton-Tate, Torrance, California). The starting point was 14 days after vaccination for vaccinated children or age 140 days (20 weeks) for unvaccinated children. The incidence rate was computed as the ratio of the cases to the person-years at risk lived by the susceptible population. Period efficacy was computed by the standard formula: $1 - (\text{incidence rate among vaccinated children} \div \text{incidence rate among unvaccinated children})$.

For calculation of the case-contact efficacy, exact exposure within the residence compound was determined for each outbreak. The secondary attack rate was computed as the ratio of secondary cases to the number of susceptible children exposed to

the index cases in the compound. Case-contact efficacy was computed by the standard formula: $1 - (\text{secondary attack rate among vaccinated children} \div \text{secondary attack rate among unvaccinated children})$.

The 95 percent confidence intervals were computed using Taylor series approximations when the sample was large (for period estimates of the campaigns) and asymptotic estimates when the sample was small. The later computations were performed with EPI INFO (USD Inc., Stone Mountain, Georgia) (11).

RESULTS

During the study period, a total of 601 measles cases of all ages were investigated. Among them, 396 belonged to the cohorts kept for the final analysis, and 312 were secondary cases among the same cohorts.

Rate of exposure to measles

The rate of exposure to measles in the study area during the investigation was computed by dividing the number of children

exposed by the number at risk on January 1, 1990. For the randomized vaccine trial, the average exposure rate was 9.2 percent among children born between February 1, 1987, and January 31, 1989, with no significant difference among the three vaccination groups. However, in the unvaccinated group, the exposure rate (13.2 percent) was significantly higher (table 1). The exposure rate was also slightly higher (10.0 percent) among older children, i.e. those born between 1978 and 1986. Differences in exposure rates between the two groups vaccinated in national programs and the control group were significant, but of relatively small magnitude; in the group vaccinated during 1981–1983, the children were much older and the exposure rate was significantly lower (2.6 percent).

Efficacy of standard vaccines

Among children vaccinated with standard vaccines during the randomized trial, there was only one case of vaccine failure, which was a secondary case (table 2). The period efficacy was 98.0 percent (95 percent con-

TABLE 1. Study population and exposure to measles in compounds of the study area, according to vaccination status: Niakhar, Senegal, 1987–1990

Vaccination strategy	Children		
	No. resident on January 1, 1990	Mean age (years)	% exposed
Randomized trial of 3 vaccines in 30 villages, 1987–1989 (birth cohorts: 1987–1989)			
Standard Schwarz at 10 months of age	740	1.8	7.3*
High-titer Edmonston-Zagreb at 5 months of age	552	1.8	9.6
High-titer Schwarz at 5 months of age	274	2.3	8.8
Controls (unvaccinated)	348	1.8	13.2†
Monitored vaccination in 8 villages, 1981–1983 (birth cohorts: 1978–1982)			
Standard Schwarz at 9–23 months of age	386	9.5	2.6*
Other routine vaccinations with standard Schwarz vaccines (birth cohorts: 1978–1986)			
National campaign of 1986–1987	1,224	5.0	12.8*
Other vaccinations, 1981–1989	720	8.1	7.2*
Controls (unvaccinated)	4,403	7.3	10.0†

* Significant difference from the controls, $p < 0.05$.

† Reference category.

TABLE 2. Incidence and secondary attack rates of measles among the various groups of the susceptible population: Niakhar, Senegal, 1987-1990

Group	Prospective study		Case-contact study	
	Incidence per 1,000 person-years	No. of cases reported/ no. confirmed	Secondary attack rate per 1,000 children at risk	No. of cases reported/no. confirmed
Randomized trial of 3 vaccines in 30 villages, 1987-1989 (birth cohorts: 1987-1989)				
Standard Schwarz at 10 months of age	0.80	1/0	18.5	1/0
High-titer Edmonston-Zagreb at 5 months of age	4.12	5/3	56.6	3/2
High-titer Schwarz at 5 months of age	6.67	5/2	83.3	2/1
Controls (unvaccinated)	40.63	54/21	652.2	30/13
Monitored vaccination in 8 villages, 1981-1983 (birth cohorts: 1978-1982)				
Standard Schwarz at 9-23 months of age	1.22	1/1	0.0	0/0
Other vaccinations with standard Schwarz vaccines (birth cohorts: 1978-1986)				
National campaign of 1986-1987	4.56	15/7	44.9	7/5
Other vaccinations, 1981-1989	5.14	8/3	96.2	5/2
Controls (unvaccinated)*	33.62	307/157	598.6	264/101

* Also used as the control group for the monitored vaccination.

fidence interval (CI) 88.9-99.9), and the case-contact efficacy was 97.2 percent (95 percent CI 91.3-98.1) (table 3, figure 1). There was no confirmed case among the cases of vaccine failure. Among children vaccinated in 1981-1983, there was only one case of vaccine failure, which was an index case. For this group, the period efficacy was 96.4 percent (95 percent CI 74.2-99.5) among reported cases and 92.9 percent among confirmed cases (95 percent CI 49.4-99.0). Details of the computations can be derived from table 2 according to the definitions given above. For instance, the period efficacy of 98.0 percent is obtained as follows: $1 - (0.80 \div 40.63)$.

The efficacy of standard vaccines was somewhat lower among children vaccinated during the national campaigns. Among the children vaccinated during the 1986-1987 campaign, there were 15 cases of vaccine failure, five of them secondary cases. The period efficacy was 86.4 percent (95 percent CI 77.2-91.9), and the case-contact efficacy was 92.5 percent (95 percent CI 88.8-94.6). When the analysis was restricted to con-

firmed cases, the values were 87.6 percent for period efficacy (95 percent CI 73.6-94.2) and 86.0 percent for case-contact efficacy (95 percent CI 69.7-92.9). Among the children vaccinated elsewhere, there were eight cases of vaccine failure, two of them secondary cases. For this group, the period efficacy was 84.7 percent (95 percent CI 69.2-92.4), and the case-contact efficacy was 83.9 percent (95 percent CI 74.1-88.6). When the analysis was restricted to confirmed cases, the corresponding values were 88.8 percent for period efficacy (95 percent CI 64.9-96.4) and 83.2 percent for case-contact efficacy (95 percent CI 45.2-94.2).

Efficacy of high-titer vaccines

The efficacy of high-titer vaccines was studied only during the randomized trial and was found to be lower than the efficacy of the standard vaccine administered in the same cohorts. There were five vaccine failures among children vaccinated with the high-titer Edmonston-Zagreb vaccine; three of these were secondary cases.

TABLE 3. Clinical efficiency of measles vaccines: Niakhar, Senegal, 1987-1990

Source of vaccination and vaccine	Period efficacy*		Case-contact efficacy*	
	%	95% CI†	%	95% CI†
Randomized trial of 3 vaccines, 1987-1989				
Standard Schwarz				
Reported cases	98.0	88.9-99.9	97.2	91.3-98.1
Confirmed cases	100.0	80.0-100.0	100.0	78.0-100.0
High-titer Edmonston-Zagreb				
Reported cases	89.9	75.7-96.6	91.3	82.1-93.4
Confirmed cases	84.4	47.9-96.8	86.6	49.1-95.3
High-titer Schwarz				
Reported cases	83.6	59.6-94.4	87.2	68.8-90.8
Confirmed cases	83.1	31.9-97.7	85.3	14.4-95.8
Monitored vaccination using standard Schwarz, 1981-1983				
Reported cases	96.4	74.2-99.5	100.0	70.0-100.0
Confirmed cases	92.9	49.4-99.0	100.0	0.0-100.0
National campaign using standard Schwarz, 1986-1987				
Reported cases	86.4	77.2-91.9	92.5	88.8-94.6
Confirmed cases	87.6	73.6-94.2	86.0	69.7-92.9
Other routine vaccinations using standard Schwarz, 1981-1989				
Reported cases	84.7	69.2-92.4	83.9	74.1-88.6
Confirmed cases	88.8	64.9-96.4	83.2	45.2-94.2

* Directly computed from table 2; see "Vaccine efficacy" under "Materials and Methods" for details.

† CI, confidence interval.

In addition, there were five failures among children vaccinated with the high-titer Schwarz vaccine, two of them secondary cases. The period efficacy of the high-titer Edmonston-Zagreb vaccine was 89.9 percent (95 percent CI 75.7-96.6) and the case-

contact efficacy was 91.3 percent (95 percent CI 82.1-93.4) (table 3). When the analysis was restricted to confirmed cases, the corresponding values were 84.4 percent (95 percent CI 47.9-96.8) for period efficacy and 86.6 (95 percent CI 49.1-

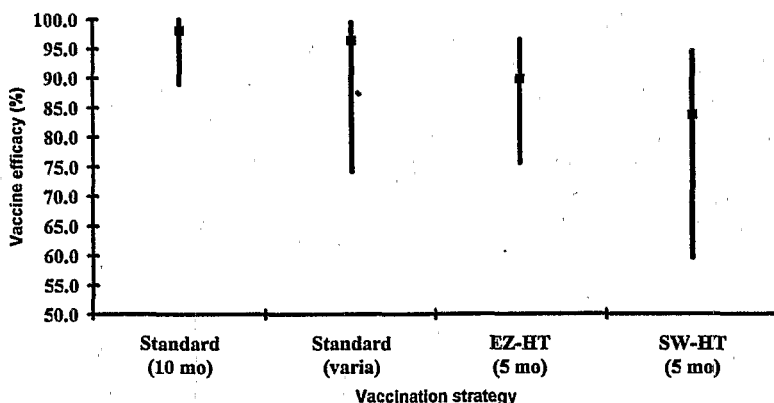


FIGURE 1. Clinical efficacy of measles vaccines, Niakhar, Senegal, 1987-1989, (vertical bars show 95% confidence interval). Children in the second group were vaccinated at various ages (varia) above 9 months, whereas children in other groups were vaccinated at the exact age of 5 or 10 months. (Standard, standard Schwarz vaccine; EZ-HT, high-titer Edmonston-Zagreb vaccine; SW-HT, high-titer Schwarz vaccine. The age in months (mo) at which the vaccine was administered is given below the name of the vaccine.)

TABLE 4. Estimates of the theoretical case-contact efficacy of three measles vaccines in a randomized trial, from linear logistic regression controlling for intensity of exposure: Niakhar, Senegal, 1987–1990

Covariate	Results of the linear logistic model*		Estimates†	
	OR‡	95% CI‡	Theoretical efficacy	Relative failure
Standard Schwarz vaccine	0.007	0.001–0.117	0.980	1.00
High-titer Edmonston-Zagreb vaccine	0.020	0.005–0.236	0.944	2.82
High-titer Schwarz vaccine	0.053	0.001–0.272	0.861	7.06
Intensity of exposure	2.291	1.125–4.667		

* The reference group are unvaccinated children exposed in the same conditions in the household.

† See text and appendix for computations of theoretical efficacy. The relative failure is equal to the ratio of the failure rate after a high-titer vaccine given at 5 months of age to the failure rate after the standard Schwarz vaccine given at 10 months of age (reference category).

‡ OR, odds ratio; CI, confidence interval.

95.3) for case-contact efficacy. The period efficacy of the high-titer Schwarz vaccine was 83.6 percent (95 percent CI 59.6–94.4) and the case-contact efficacy was 87.2 percent (95 percent CI 68.8–90.8). When the analysis was restricted to confirmed cases, the corresponding values were 83.1 percent (95 percent CI 39.9–97.7) for period efficacy and 85.3 (95 percent CI 14.4–95.8) for case-contact efficacy.

Control for intensity of exposure

A linear logistic model was developed to control for the intensity of exposure to measles. The dependent variable was the secondary attack rate and the independent variables were the vaccine and the intensity of exposure. Once exposure to measles occurred in a compound, the mean intensity of exposure among vaccinated (3.21) and unvaccinated (3.18) children was not significantly different ($p = 0.581$). The results indicate that the intensity of exposure was a major determinant of secondary infection in the family (table 4). The odds ratio was 2.3 per unit of exposure; assuming an exposure rate of 8.0 percent, this is equivalent to a relative risk of 2.1, which can be interpreted as a 4.4 times greater risk of infection from sleeping in the same hut with an index case than from living in the same compound with an index case. Similar values of relative risks associated with intensity of exposure were found for the vaccinated and unvaccinated children. There was no significant

interaction between the vaccine and the intensity of exposure ($p = 0.967$).

Controlling for intensity of exposure in the logistic regression allows one to define a theoretical efficacy for a minimal unit of exposure. Details of the derivations are given in the Appendix. The theoretical case-contact efficacy of the standard vaccine was 98.0 percent, as compared with 94.4 percent for the high-titer Edmonston-Zagreb vaccine and 86.1 percent for the high-titer Schwarz vaccine. In other words, controlling for intensity of exposure did not change the ranking of the vaccination strategies. There were 2.8 times more vaccine failures among those who received the high-titer Edmonston-Zagreb vaccine at 5 months of age and 7.1 times more failures among those who received the high-titer Schwarz vaccine at 5 months of age than there were among those who received the standard vaccine at 10 months of age.

TABLE 5. Factors of the theoretical case-contact efficacy of standard measles vaccines in national campaigns, from linear logistic regression*: Niakhar, Senegal, 1987–1990

Covariate	OR†	95% CI†
Vaccination (standard)	0.021	0.006–0.084
Age at exposure		
(1-year increase in age)	1.088	1.000–1.183
Intensity of exposure (4 units)	3.532	1.149–10.83
Vaccination 5 months earlier		
(if before age 12 months)	3.467	1.015–11.76
Vaccination 10 years earlier	2.709	0.204–36.13

* The reference group are unvaccinated children exposed in the same conditions in the household.

† OR, odds ratio; CI, confidence interval.

Factors associated with the efficacy of standard vaccines

Several factors associated with the efficacy of standard vaccines in national campaigns were analyzed in a similar linear logistic regression. The dependent variable was the secondary attack rate among children born between 1978 and 1986, and the four independent variables were age at exposure, intensity of exposure, an indicator of age at vaccination (the number of months before 12 months of age), and the time elapsed since vaccination (table 5). Two other variables were also analyzed but not found to be significant: the sex of the child and the vaccination campaign in which he or she was vaccinated. The results showed the same theoretical efficacy in the vaccination campaigns as in the randomized trial (97.9 percent, 95 percent CI 91.6–99.5). Age at exposure was found to be a significant risk factor for vaccine failure, with a relative risk of 1.088 per year of age. Intensity of exposure was significant, with a relative risk of vaccine failure of 3.53 for maximal exposure (i.e., sleeping in the same hut). Vaccination before 12 months of age had a significant effect on vaccine failure, with a relative risk of 1.28 per month. Vaccination 5 months earlier multiplied the risk of vaccine failure by 3.47 (95 percent CI 1.01–11.9), a value similar to the relative failure rate of high-titer vaccines given at 5 months compared with standard vaccines given at 10 months in the randomized trial. This finding indicates that the potential gain of using high-titer vaccines early in life was marginal. The time elapsed since vaccination, which measures waning immunity, was not significant when all other factors were controlled for in the regression.

DISCUSSION

Several studies have provided estimates of the clinical efficacy of standard vaccines in North America (6, 8, 25, 26). They show

a median estimate of 96.0 percent for clinical protection, with a range from 93.2 to 96.9 percent. Two factors having an impact on efficacy were identified: the age at vaccination (before or after 15 months) and the type of vaccine (produced before or after 1979). Most of these estimates were derived from case-contact studies or retrospective cohorts among children in school or college after exposure during an outbreak. Similar results were found in Europe. A study conducted in England and Wales produced an estimate of 93.1 percent during a 21-year follow-up of children vaccinated at 10–23 months of age with a Schwarz vaccine, a rate equivalent to 97.0 percent efficacy on a single exposure (27). In France, a study found a vaccine efficacy of 94.6 percent in a 4-year period among children vaccinated at 12–23 months with a Schwarz vaccine a rate equivalent to 95.5 percent on a single exposure (28). A study of the Edmonston-Zagreb vaccine conducted in three sites in Yugoslavia found an efficacy of 97.3 percent among children vaccinated at 10 months of age or older. When properly administered, measles vaccines seem to protect about 96 percent of children against clinical measles.

The estimates of vaccine efficacy found in Senegal were very close to these values found in developed countries. They can be taken as the standard against which the efficacy of measles vaccines in other contexts is evaluated. Note that the efficacy of measles vaccines remains very satisfactory, much higher than that of some other vaccines (pertussis, influenza) and close to that of the best vaccines available (tetanus, yellow fever). The estimates of vaccine efficacy from the randomized trial were higher than most estimates reported from developing countries. This may reflect differences in the quality of vaccine delivery, in particular the quality of the cold chain and the precise age at vaccination.

The data set gathered during this study is virtually unique in tropical Africa. There is a high degree of consistency among the estimates of efficacy found in this study

and also between these estimates and other estimates of the efficacy of measles vaccines. In particular, the efficacy of standard vaccines observed in this clinical trial compares closely with the values found in developed countries. This result indicates that there is no reason to think that standard measles vaccines, when properly administered, are less efficacious in Africa than in the developed countries.

To our knowledge, there is no other published empirical study estimating vaccine efficacy after controlling for intensity of exposure to which these results could be compared. However, that intensity of exposure influences the estimate of vaccine failure makes sense. It suggests that accurate comparisons of vaccine failure require a proper description of exposure, a point that has been discussed extensively in the theoretical literature (12).

Controlling for exposure further validated the estimates. None of the vaccinated groups had a randomized control group of unvaccinated children, and in fact, it would not have been ethical to design a study with a control group of this kind. Although the control groups were similar to the vaccinated groups in many respects, their rate of exposure was 13 percent higher (95 percent CI 1.00–1.30, $p = 0.051$). Although small, this could bias the estimates of period efficacy. However, controlling for exposure allowed precise estimates of case-contact efficacy, which can be considered the most reliable estimate.

Controlling for intensity of exposure did not change the order of magnitude of the relative estimates of vaccine failure. A linear score of intensity of exposure was used, which translates into a proportional odds ratio of vaccine failure in the logistic regression. The choice of the linear score was justified by a preliminary analysis of the values of the relative secondary attack rates for three increasing values of the level of intensity of exposure, both for cases among unvaccinated children (1.00, 1.50, and 1.83) and cases among vaccinated children (1.00,

1.15, and 1.55). Although not perfect, the log-linear assumption was considered acceptable for the multinomial regression.

The efficacy of the standard Schwarz vaccines was higher in the clinical trial than after the national campaigns. The rate of vaccine failure after the national campaigns was 5.2 times greater than that observed in our clinical trial using the same standard vaccine. This result was expected, insofar as failures in the cold chain are common in large-scale campaigns. The efficacy of vaccines in national vaccination campaigns of Senegal compares closely with values found nearby in The Gambia (13).

Estimates of period efficacy were similar to those of case-contact efficacy. This result was expected, since multiple exposures were unusual during the study period (10.1 percent of cases), and the period of follow-up was relatively short. The small differences in exposure during the period of the study had virtually no impact on the period estimates, which were obtained by use of precise periods of exposure to risk within the susceptible population. This procedure leads to an unbiased estimate of vaccine efficacy as defined by a proportionate reduction in incidence at each exposure (10). This choice was justified by the very probabilistic nature of vaccine failure found in the effect of intensity of exposure. However, if efficacy had been defined as the proportion of the population that was fully protected, this procedure would lead to an overestimation of efficacy that increases with time. In this case, theoretical computations show that exposure for 3 years leads to a small overestimation of period efficacy: an observed efficacy of 98.0 percent would be equivalent to a theoretical efficacy of 97.7 percent, a small difference given the confidence interval of the point estimate.

Measles cases among vaccinated children were less likely to be confirmed than those among unvaccinated children, because in vaccinated children, the clinical effects of the disease were milder and the elevation of

antibodies lower (18). In fact, only 53.3 percent of the cases that occurred after failure of a vaccine were confirmed, compared with 67.4 percent of cases that occurred among unvaccinated children. This situation led to an artificially high estimate of vaccine efficacy among confirmed cases. The theoretical computations give an expected bias of 21 percent for vaccine failure, which remains consistent with the overall empirical findings. However, the differences between estimates of efficacy among all cases and among confirmed cases varied in each of the three vaccination series, depending on the proportion of cases confirmed in each group.

The comparison of the two trials using the standard Schwarz vaccine showed that 80 percent more failures occurred 10 years after vaccination (1981–1983) than occurred 2 years after vaccination (1987–1989). In the study of the duration since vaccination as a risk factor for vaccine failure, the risk ratio for 10 years after vaccination as compared with 1 year after vaccination was 2.71. However, none of these differences was statistically significant.

In the clinical trial setting, the failure rate of the high-titer vaccines was somewhat higher than that of the standard vaccines, even after exposure had been controlled for. The differences were not significant in this study, but they were found to be significant after the level of maternal antibodies at time of vaccination was controlled for (20). The failure rate of the high-titer Schwarz vaccine was higher than that of the high-titer Edmonston-Zagreb vaccine, an observation that matches the observed differences in seroconversion rates after administration of these two vaccines (29, 30). Because of the small numbers, the efficacy of the high-titer Edmonston-Zagreb vaccine between the ages of 5 and 10 months among children to whom it was administered at 5 months was not significantly different from zero ($p = 0.147$) when compared with the randomized control group that re-

ceived a placebo at 5 months (18). There was no case of vaccine failure in the high-titer Schwarz group between the ages of 5 and 10 months, and therefore, vaccine efficacy could not be computed for this age group. If the risk ratios for vaccine failure in national campaigns were equivalent to those found for the standard vaccine, then the failure of high-titer vaccines given at 5 months of age could be as high as 50 percent in general use.

In the randomized trial, both clinical efficacy and seroconversion were negatively correlated with the level of maternal antibodies at the time of vaccination. Another paper addresses this issue in detail (20).

The rationale behind the use of high-titer vaccines was earlier vaccination of infants to avert a number of measles cases that occur between the ages of 6 and 9 months. However, the higher failure rate associated with high-titer vaccines balanced the earlier protection. Assuming a constant incidence of measles of 0.1 case per person per year, susceptibility to measles starting at 4 months of age, and the values of clinical efficacy observed in this trial, a cohort of 1,000 children would experience 373 cases of measles by the age of 5 years if no one was vaccinated, 87 cases if all infants were vaccinated with the high-titer Schwarz vaccine at 6 months of age, 60 cases if all infants were vaccinated with the high-titer Edmonston-Zagreb vaccine at 6 months of age, and 57 cases if all infants were vaccinated with the standard vaccine at 9 months of age. Therefore, in theory, the high-titer strategy would not be optimal for preventing clinical measles between birth and 5 years of age. The situation would be even worse if all ages up to 30 years were taken into consideration. However, in practice, the decreasing efficacy might be compensated for by an increasing vaccination coverage usually associated with a lower age at vaccination in developing countries.

Furthermore, the high-titer vaccines are more costly to produce than the standard vaccine, a factor that lowers their cost-

effectiveness. Finally, the high-titer vaccines have been found to significantly increase children's risk of death within 3 years of vaccination (19). This finding was confirmed by two other studies and led to a change in the recommendations of the World Health Organization (31). This differs markedly from the standard vaccines, which have been shown to dramatically reduce children's risk of death in a similar environment (3). The results of this study emphasize the importance of studies based on a comprehensive surveillance of well-defined populations.

Although imperfect, vaccination with standard vaccines at 9 months of age remains a sound strategy. If well implemented with a high coverage rate, it could produce herd immunity and thereby reduce the incidence of disease before the recommended age at vaccination (9 months). Together with the appropriate management of measles cases, this strategy could in theory lead to satisfactory control of measles mortality (18). However, there is still a need for alternative strategies in order to protect children as soon as they become susceptible, for instance, with more immunogenic vaccines, or with several doses given at various ages. New and more efficient strategies could also open the way to global eradication.

ACKNOWLEDGMENTS

The study was funded by the Task Force for Child Survival, Atlanta, Georgia. The authors thank the Senegalese health authorities who supported the project, in particular Dr. Colonel Mame Thierno Sy and Dr. Fodé Diouf, and also Prof. Elizabeth Halloran, Prof. Richard Cash, Dr. Christine Costello, and Dr. Mary Adams, who provided detailed comments and critiques on the manuscript.

REFERENCES

- Henderson RH, Keja J, Hayden G, et al. Immunizing the children of the world: progress and prospects. *Bull World Health Organ* 1988; 66:535-43.
- Hayden GF, Sato PA, Wright PF, et al. Progress in worldwide control and elimination of disease through immunization. *J Pediatr* 1989;114: 520-7.
- Garenne M, Cantrelle P. Rougeole et mortalité au Sénégal. Etude de l'impact de la vaccination effectuée à Khombole 1965-1968 sur la survie des enfants. In: Estimation de la mortalité du jeune enfant (0-5 ans) pour guider les actions de santé dans les pays en développement. Paris, France: Editions INSERM, 1986;145:515-32.
- Koenig MA, Khan MA, Wojtyniak B, et al. The impact of measles vaccination on childhood mortality in Matlab, Bangladesh. New York, NY: Population Council, Programs Division, June 1990. (Working paper no 3).
- Preblud SR, Katz SL. Measles vaccine. In: Plotkin SA, Mortimer EA, eds. *Vaccines*. Philadelphia, PA: WB Saunders, 1988:182-222.
- Mast EE, Berg JL, Hanrahan LP, et al. Risk factors for measles in a previously vaccinated population and cost-effectiveness of revaccination strategies. *JAMA* 1990;64:2529-33.
- Orenstein WA, Markowitz L, Preblud SR, et al. Appropriate age for measles vaccination in the United States. *Dev Biol Stand* 1986;65:13-21.
- Van Ginneken JK, Muller AS. Maternal and child health in rural Kenya. London, England: Croom Helm, 1984.
- Measles immunization before 9 months of age. *Wkly Epidemiol Rec* 1990;2:8-9.
- Smith PG, Rodrigues LC, Fine PEM. Assessment of the protective efficacy of vaccines against common diseases using case-control and cohort studies. *Int J Epidemiol* 1984;13:87-93.
- Mehta CR, Patel NR. A network algorithm for performing Fisher's exact test in $R \times C$ contingency tables. *J Am Stat Assoc* 1983;78:427-34.
- Halloran ME, Haber M, Longini IM, et al. Direct and indirect effects in vaccine efficacy and effectiveness. *Am J Epidemiol* 1991;133:323-31.
- Hull HF, Williams PJ, Oldfield F. Measles mortality and vaccine efficacy in rural west Africa. *Lancet* 1983;1:972-5.
- Kenya PR. Measles and mathematics: "control or eradication?" *East Afr Med J* 1990;67:856-63.
- Coulibaly A, Motte J, Trolet C, et al. Importance de la rougeole et résultats de la vaccination antirougeoleuse dans un dispensaire rural de Côte d'Ivoire. *Actualités Médicales* 1990; 599-602.
- Porter JD, Gastellu-Etchegorry M, Navarre I, et al. Measles outbreaks in the Mozambican refugee camps in Malawi: the continued need for an effective vaccine. *Int J Epidemiol* 1990;19: 1072-7.
- Cutts FT, Smith PG, Colombo S, et al. Field evaluation of measles vaccine efficacy in Mozambique. *Am J Epidemiol* 1990;131: 349-55.
- Garenne M, Leroy O, Beau JP, et al. Efficacy, safety and immunogenicity of two high-titer measles vaccines: final report. Dakar, Senegal: ORSTOM, 1991.
- Garenne M, Leroy O, Beau JP, et al. Child mor-



- tality after high-titer measles vaccination: a prospective study in Senegal. *Lancet* 1991;338:903-7.
20. Garenne M, Leroy O, Beau JP, et al. High-titer measles vaccines: protection evaluation. *Arch Virol* (in press).
 21. Simpson RE. The period of transmission in certain epidemic diseases: an observational method for its discovery. *Lancet* 1948;2:755-60.
 22. Simpson RE. Infectiousness of communicable diseases in the household (measles, chickenpox and mumps). *Lancet* 1952;2:549-54.
 23. Bailey NTJ. The mathematical theory of infectious diseases and its applications. London, England: Griffin, 1975.
 24. Garenne M, Aaby P. Pattern of exposure and measles mortality in Senegal. *J Infect Dis* 1990;161:1088-94.
 25. Nkowane BM, Bart SW, Orenstein WA, et al. Measles outbreak in a vaccinated school population: epidemiology, chains of transmission and the role of vaccine failure. *Am J Public Health* 1987;77:434-8.
 26. Davis RM, Whitman ED, Orenstein WA, et al. A persistent outbreak of measles despite appropriate prevention and control measures. *Am J Epidemiol* 1987;126:438-49.
 27. Miller C. Live measles vaccine: a 21 year follow-up. *Br Med J* 1987;295:22-4.
 28. Rebiere I, Lévy-Bruhl D, Goulet V, et al. Estimation de l'efficacité de la vaccination anti-rougeoleuse à partir de l'enquête nationale d'évaluation de la couverture vaccinale menée en 1989, en milieu scolaire. *Bull Epidemiol Hebdo*, 1990;38:165-6.
 29. Whittle HC, Mann G, Eccles M, et al. Effect of dose and strain of vaccine on success of measles vaccination of infants aged 4-5 months. *Lancet* 1988;1:963-6.
 30. Markowitz LE, Sepulveda J, Diaz-Ortega JL, et al. Immunization of six-month-old infants with different doses of Edmonston-Zagreb and Schwarz measles vaccines. *N Engl J Med* 1990;332:580-7.
 31. Safety of high-titer measles vaccines. *Wkly Epidemiol Rec* 1992;67:357-64.

APPENDIX

Computation of theoretical efficacy from logistic regression

Notations:

SAR_v = secondary attack rate among vaccinated children

SAR_0 = secondary attack rate among unvaccinated children

TVE = theoretical vaccine efficacy

Logistic equation:

$$SAR_0/(1 - SAR_0) = \exp(a)$$

$$SAR_v/(1 - SAR_v) = \exp(a + b_v)$$

$$TVE = 1 - SAR_v/SAR_0$$

$$SAR_v/(1 - SAR_v) = \exp(b_v) \times SAR_0/(1 - SAR_0)$$

Therefore:

$$SAR_v/SAR_0 = \exp(b_v)/[(1 - SAR_0) + \exp(b_v) \times SAR_0]$$

$$TVE = 1 - \exp(b_v)/\{1 - SAR_0 \times [1 - \exp(b_v)]\}$$