EFFICACY, SAFETY, AND IMMUNOGENICITY OF TWO HIGH TITER MEASLES VACCINES

A study in Niakhar, Senegal

Final Report

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INSTITUT FRANCAIS DE RECHERCHE POUR LE DEVELOPPEMENT EN COOPERATION

UR Population et Santé

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FOREWORD

This report presents the methodology and main findings of the trial of two high titer measles vaccines conducted in Niakhar, Senegal from 1986 to 1990 by ORSTOM, Unité de Recherche Population et Santé. This report has been published as soon as possible after the end of the field work. It is a comprehensive report aiming at making results available to policy makers and to vaccine producers as quickly as possible, before formal publications are out.

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SUMMARY OF MAIN FINDINGS

A randomized vaccine trial was conducted in a rural area of Senegal (Niakhar) to study the safety, immunogenicity and efficacy of two high titer measles vaccines given at five months of age: Edmonston-Zagreb (EZ-HT) and Schwarz (SW-HT). Results were compared to the performance of the Standard (low titer Schwarz) vaccine given at 10 months.

The study was embedded in the national EPI program and based upon a comprehensive demographic and epidemiologic surveillance system of a rural population of about 25,000 people. New birth cohorts were recruited over time and were included in the study when they reached the appropriate age at vaccination. All children were prospectively followed for 16-39 additional months. Two sets of birth cohorts were considered separately: cohorts 01-16 randomized in three groups (EZ-HT, SW-HT, Standard) and cohorts 17-24 randomized in two groups (EZ-HT and Standard). The randomized groups were comparable in various social, familial and health characteristics. Due to vaccinations and to medical services provided during the study period, mortality of infants and children was significantly reduced during the study period.

Efficacy: both high titer vaccines protected against clinical measles. Efficacy was 89.9% for the EZ-HT vaccine (CI=74.7-95.9, p=1.1E-6) and 82.6% for the SW-HT vaccine (CI=59.0-93.4, p=1.2E-4). However, rates of vaccine failure were higher after high titer vaccines than after the Standard vaccine: 5.2 times more vaccine failures after the EZ-HT vaccine and 8.3 times more vaccine failures after the SW-HT vaccine. Results were confirmed by a case contact study and by values of efficacy of the Standard vaccine for older cohorts.

Safety and adverse reactions: among the first 16 cohorts, child mortality was significantly higher in the two groups vaccinated with high-titer measles vaccines than in the group assigned to the Standard vaccine. Relative risk of mortality was 1.80 (CI=1.18-2.74, p=0.007) in the EZ-HT group and 1.53 (CI=0.99-2.37, p=0.056) in the SW-HT group. Most of the effect occurred in the second and third year after vaccination and during the rainy season. There were no significant differences in mortality by sex. The last 8 cohorts were followed for a period too short to verify this effect. Morbidity was monitored only until age 12 months and there were no significant differences between the groups. Mild measles-like rashes occurred frequently after high-titer vaccines given at 5 months. Vaccination with high titer vaccines at 5 months was considered unsafe in these circumstances.

Immunogenicity: both high titer vaccines were immunogenic at 5 months. Among seronegative children, seroconversion rates were 98.6% with the EZ-HT vaccine (CI=95.9-99.9, P=0.0001) and 85.5% with the SW-HT vaccine (CI=78.5-93.2, P=0.0001). Immunogenicity of the EZ-HT vaccine was significantly greater than immunogenicity of the SW-HT vaccine. There was a significant increase in antibody titers among seropositive children after EZ-HT and SW-HT vaccine. However, there was no clear evidence of seroconversion among children with high levels of maternal antibodies (1000+ miu) in any of the vaccine group. Furthermore, the geometric mean titer of antibodies 5 months after the high titer vaccines was lower than 5 months after the Standard vaccine.

Conclusion: in this situation, the use of high titer measles vaccines at 5 months of age does not seem to be justified and alternative strategies for protecting children against measles at an early age should be investigated.

à Raphaëlle

RESUME EN FRANCAIS

Une étude randomisée a été conduite dans une zone rurale du Sénégal (Niakhar) pour étudier l'efficacité, l'inocuité et l'immunogénicité de deux vaccins à haut titre contre la rougeole administrés à 5 mois: le vaccin Edmonston-Zagreb (EZ-HT) et le vaccin Schwarz (SW-HT). Les résultats ont été comparés aux performances du vaccin standard (un vaccin Schwarz à bas titre) administré à l'âge de 10 mois.

L'étude a été réalisée dans le cadre du PEV national. Elle était basée sur un système de surveillance démographique et épidémiologique exhaustif d'une population rurale d'environ 25.000 habitants. Les cohortes de naissances étaient recrutées au fur et à mesure et inclues dans l'étude lorsqu'elles atteignaient l'âge de la vaccination. Tous les enfants étaient suivis prospectivement pendant une période allant de 16 à 39 mois. Deux groupes de cohortes de naissances étaient considérés séparément: les cohortes 1 à 16, randomisées selon trois groupes (EZ-HT, SW-HT, Standard) et les cohortes 17 à 24 randomisées selon deux groupes (EZ-HT and Standard). Les groupes randomisés avaient les mêmes caractéristiques socio-économiques et sanitaires. Du fait des vaccinations et des services médicaux fournis au cours de l'étude, la mortalité des enfants a été significativement réduite.

Efficacité: les deux vaccins à haut titre ont protégé contre la rougeole clinique. L'efficacité a été estimée à 89.9% pour le vaccin EZ-HT (CI=74.7-95.9, p=1.1E-6) et à 82.6% pour le vaccin SW-HT (CI=59.0-93.4, p=1.2E-4). Cependant, les taux d'échecs des vaccins à haut titre ont été supérieurs à ceux du vaccin Standard: 5.2 fois plus d'échecs vaccinaux après le vaccin EZ-HT et 8.3 plus après le vaccin SW-HT. Les résultats ont été confirmés par une étude cas-contact et par l'efficacité du vaccin Standard administré antérieurement à des enfants plus âgés.

Inocuité et effets indésirables: parmi les 16 premières cohortes, la mortalité a été significativement plus élevée dans les groupes ayant reçu les vaccins à haut titre que dans le groupe qui a reçu le vaccin Standard. Les risques relatifs de mortalité ont été estimés à 1.80 (CI=1.18-2.74, p=0.007) dans le groupe EZ-HT et 1.53 (CI=0.99-2.37, p=0.056) dans le groupe SW-HT. L'essentiel de la surmortalité est survenue au cours de la seconde et troisième année après la vaccination et a été concentrée au cours de la saison des pluies. Il n'y a pas eu de différence de mortalité selon le sexe. Les 8 dernières cohortes ont été suivies pendant une période trop courte pour vérifier cet effet. La morbidité, qui a été suivie jusqu'à l'âge de 12 mois, a été la même dans les trois groupes. Des éruptions similaires à celle de la rougeole ont été fréquemment observées après les vaccins à haut titre. La vaccination à 5 mois avec des vaccins à haut titre ne peut pas être considérée comme sans danger.

Immunogénicité: les deux vaccins à haut titre ont été immunogéniques à 5 mois. Parmi les enfants séronégatifs, les taux de séroconversion ont été de 98.6% avec le vaccin EZ-HT (CI=95.9-99.9, P=0.0000) et 85.5% avec le vaccin SW-HT (CI=78.5-93.2, P=0.0000). L'immunogénicité du vaccin EZ-HT a été significativement plus élevée que celle du vaccin SW-HT. Les titres d'anticorps ont été significativement plus élevés même chez les enfants séropositifs. Cependant, aucune séroconversion au sens strict n'a été observée après les vaccins à haut titre chez les enfants ayant des titres élevés d'anticorps maternels (1000+ miu). De plus, le niveau d'anticorps 5 mois aprés la vaccination a été plus faible chez les enfants ayant reçu les vaccins à haut titre que chez les enfants ayant reçu le vaccin standard.

Conclusion: dans ces circonstances, l'utilisation des vaccins à haut titre à l'âge de 5 mois ne semble pas justifiée et d'autres stratégies devront être recherchées pour protéger les enfants avant 9 mois.

AVANT PROPOS BY PIERRE CANTRELLE

En Afrique de l'Ouest, comme dans les autres régions du monde, un nom précis est donné à la rougeole, maladie habituellement bien identifiée par la population et distinguée des autres maladies éruptives. Cette facilité par rapport à d'autres pathologies permet des études fiables de la morbidité et la mortalité par rougeole au niveau des populations.

En Afrique de l'Ouest, cette maladie s'est ainsi révélée comme une cause majeure de morbidité et de mortalité. Sa gravité y est probablement plus élevée qu'elle ne l'était autrefois en Europe. La population était consciente de la gravité, considérant comme un permis de survie le fait d'avoir passé le cap de la rougeole. Les milieux médicaux aussi: par exemple en 1930, la rougeole était signalée comme un grave problème parmi les Touaregs. Dans les années 50, les rapports des services de santé du Burkina Faso, rassemblant les informations des Circonscriptions Médicales, signalaient "chaque année un lourd tribu est payé par la rougeole".

Mais le poids n'en était pas mesuré. En effet les statistiques du Service de Santé renseignent sur les causes de décès survenues à l'hôpital, mais ne représentent pas la mortalité du milieu rural. La maladie se passant à la maison, peu de cas étaient présentés à l'hôpital, et relativement peu de décès y survenaient, de sorte que la gravité était mal perçue des responsables du Service de Santé.

La mesure a été possible grâce à des enquêtes représentatives recueillant les déclarations des familles, et se limitant à certaines causes évidentes, notamment la rougeole.

L'enquête démographique de la Vallée du Sénégal en 1957-1958 a permis d'avoir pour la première fois un taux de mortalité par rougeole en milieu rural en Afrique. Devant son importance, la réaction de certains pédiatres a été de contester le fait, avec l'argument que "si c'était vrai, ça se saurait"!

Mais la confirmation fut apportée par l'enquête du Burkina-Faso en 1960 et au Nigéria. A ce moment, le vaccin nouvellement mis au point devenait disponible. Et à la demande du Ministre de la Santé du Burkina-Faso, des études préliminaires eurent lieu dans ce pays en 1961, avec le vaccin Edmonston B. Elles ont été suivies d'une campagne de masse de vaccination contre la rougeole au Burkina-Faso en 1962.

Le vaccin a été proposé au Sénégal en même temps qu'aux autres états de l'OCCGE. Après quoi, il a été administré au Sénégal en 1963 dans la région du Sine-Saloum, à Niakhar et à Tattaguine. Mais son inocuité n'ayant pas été jugée suffisante, le Ministère de la Santé y renonça d'autant plus qu'un nouveau vaccin, issu de la souche Schwarz, venait d'être mis au point. Une étude en fut réalisée dès 1965, limitée à la zone pilote de Khombole; puis en 1966, la zone d'enquête démographique du Sine-Saloum bénéficia d'une petite campagne de vaccination, précédant la première campagne de masse au Sénégal en 1967.

L'effet de ces premières campagnes a été spectaculaire, arrêtant les cours des épidémies et faisant chuter l'incidence de la maladie qui s'est traduit par une baisse de la proportion de consultations par rougeole dans les dispensaires. Mais c'est seulement au Sénégal qu'a été mesuré l'impact de la vaccination, non seulement sur la baisse de la mortalité du moment, mais aussi sur la survie des cohortes. La vaccination, en supprimant la maladie, a permis de montrer que l'impact de la rougeole était encore plus élevé que si l'on tenait seulement

compte des décès qui lui sont directement attribués. Il a été ainsi démontré qu'une action de santé de ce genre peut être décisive pour la baisse de la mortalité. Et ceci avec une seule vaccination qui assure une protection durable, en principe toute la vie. De plus, l'avènement de la vaccination contre la rougeole a changé la nature des déterminants de la maladie et de sa gravité.

Les notions de transmission et de prévention existaient-elle? Au Sénégal, à Khombole, on a constaté qu'une quarantaine était pratiquée spontanément par les familles lorsque l'épidémie survenait, afin d'isoler les enfants de la contagion. Cette mesure a pour conséquence de retarder l'âge de la maladie, et l'on sait que l'enfant devient relativement moins vulnérable à mesure qu'il avance en âge après 2 ou 3 ans. En milieu urbain, cette pratique étant plus difficile à appliquer, les risques de contage sont plus fréquents, d'où l'atteinte plus précoce de la rougeole.

Quant aux facteurs de gravité, ils portaient sur l'âge, sur les associations avec d'autres pathologies, la notion de cas secondaires/ cas primaires, et enfin le traitement et les soins traditionnels.

Depuis la vaccination, le seul déterminant est d'assurer cette intervention. En général, dès que la vaccination contre la rougeole a été proposée pour la première fois à une population en Afrique, elle a été acceptée sans réserve, car au niveau des mères comme de la communauté, tous en avaient vécu la gravité. Au constat de son efficacité; la vaccination a été considérée comme un nouveau pouvoir protecteur, à l'instar des protecteurs traditionnels, et sans doute plus puissants.

Mais, après la première campagne, le système de santé n'a pas pris les moyens de maintenir une couverture vaccinale suffisante an quantité et surtout en qualité dans les nouvelles générations. Au Sénégal, le résultat a été qu'après une période de quatre ans environ, la mortalité est revenue à son niveau antérieur. L'enquête de santé du Sine Saloum en 1982 l'a confirmé, de même que dans la zone d'étude du Sine, pendant la période 1983-1984. Cette évolution a été à peu près la même dans les autres pays d'Afrique Occidentale.

Le nouveau programme de vaccination, entrepris depuis 1986 sous l'égide de l'UNICEF, a connu un succès analogue aux premières campagnes vingt ans auparavant; c'est encore la série du Sine qui permit à nouveau de confirmer la chute de la mortalité par rougeole, ainsi que la série de l'état civil de la ville de Saint Louis. La question est maintenant de poursuivre de façon permanente le programme et le système mis en place va dans ce sens.

Mais l'étape décisive dans la lutte contre cette affection, sera l'éradication à l'échelle mondiale, comme il en a été pour la variole, dont le dernier cas a été relevé en 1979. C'est dans cette perspective qu'a été réalisée l'étude des vaccins précoces décrite dans les pages suivantes.

TABLE OF CONTENTS

List of annexes

List of other documents

INTRODUCTION

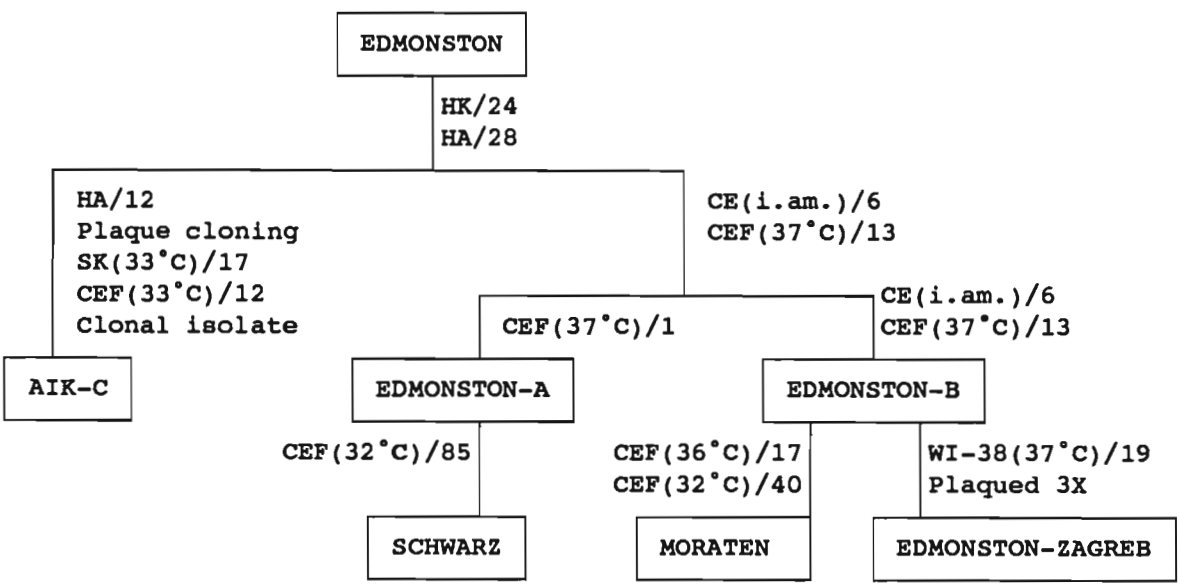
0.1 MEASLES VACCINE RESEARCH IN WEST AFRICA

Historical background

Measles was known for centuries as a major cause of death among children throughout the world. In tropical Africa, measles was ignored for a long time by colonial physicians. In their bibliography on population and health in the Senegambia region, Collignon and Becker (1989) identified only 3 references on measles prior to 1960, as compared to 151 references on Yellow-Fever. P. Cantrelle (1959) was among the first to draw attention to measles as a major cause of death among children in West Africa. Since then, measles has been recognized as a major public health problem in this region of the world and many efforts have been devoted to control measles mortality. However, measles mortality remains very high in West Africa for a variety of reasons.

The discovery of the measles virus by Enders in 1954 and the production of the first measles vaccines in 1963 resulted in several vaccine trials in West Africa. In Senegal, the first trial of the so-called Edmonston,B vaccine was conducted as early as 1963 in Tattaguine, a small town of central Senegal. This was a collaborative study between the Ministry of Public Health (service des Grandes Endémies), the Faculty of Medicine, Service des Maladies Infectieuses, Fann Hospital in Dakar and ORSTOM. That same year, a large vaccine trial was conducted in Burkina-Faso (Upper Volta at that time) in collaboration with the local Ministry of Public Health and the Centers for Disease Control (CDC). Results of these trials were disappointing: the Edmonston,B vaccine, a killed vaccine, was not safe. Adverse reactions were numerous, and the vaccine was producing severe clinical measles in a number of cases.

Chart 0.1 : Attenuation history of some measles vaccines



Source: WHO/EPI/GEN/88.11. Abbreviations: HK=human kidney, HA=human amnion, SK=sheep kidney, CE(i.am.)=chick embryo (intraamniotic cavity), CEF=chick embryo fibroblast, WI-38=human diploid cell line.

Two new vaccines, live and further attenuated, were produced a few years later the Schwarz vaccine (1965) and the Moraten vaccine (1968) (see chart 0.1). They were also tried in Senegal for the first time in 1966, in Niakhar and in nearby Khombole. Again this was a joint project of the Ministry of Public Health, the Faculty of Medicine and ORSTOM. This time the trial was successful. The further attenuated vaccines were found to be safe and effective.

Various estimates of measles vaccine efficacy were done at that time. The Khombole study showed a high efficacy of measles vaccines in a vaccinated village as compared with neighboring unvaccinated villages; furthermore measles vaccination was reducing child mortality by 26% when measles deaths accounted for only 16% of deaths (Garenne and Cantrelle, 1985).

The Schwarz vaccine was also tested in a variety of situations. Chart 0.2 displays measles vaccine trials that were conducted in West Africa over the last 30 years.

The window problem

Infants rarely contract measles before 4 months of age, because they are usually protected by transplacentally-acquired maternal antibodies. In less developed countries (LDCs), most infants become susceptible shortly after the age of 4 months. Measles case-fatality rates (CFR) are highest at younger ages, particularly between 4 and 12 months.

In developed countries low-titer, live, attenuated measles vaccines are safe, immunogenic, and effective when given in the second year of life. In LDCs, the profile of maternal antibodies is somewhat different (Black et al., 1986) and it is usually recommended that children be vaccinated at the age of 9 months (WHO, 1982). However, this strategy leaves open a window of high risk of death from measles between the ages of 4 and 9 months.

The Edmonston-Zagreb vaccine, a live measles vaccine from the Edmonston-B strain produced by the Institute of Immunology in Zagreb, Yugoslavia (Ikic et al., 1972) was found to produce a better immunologic response than standard vaccines even when given as early as 4 months of age (Whittle et al., 1984; 1988a, 1988b). Two possible explanations for the performance of this vaccine were proposed: the strain and the titer, often 10-100 times higher than that of standard vaccines. A series of recent vaccine trials compared the immunologic response and the adverse reactions after low, medium, and high titer Edmonston-Zagreb vaccines with those of other measles vaccines of the same titers (Aaby et al., 1988a; 1988b; Khanum et al., 1987; Gendrel et al., 1988; Tidjani et al., 1989; Markowitz et al., 1990; Halsey et al., 1991).

Chart 0.2 : Estimates of immunogenicity and adverse reactions in Africa

Country	Author	Year	Strain	Titer log_{10}	Age (mo)	N	% Sero-conversion	Safety and Adverse reactions
Burkina	Meyer	1962	EB	4.0 T	5-54	260	50-98 H	Fever+Rash
Burkina	Kalabus	1965	EB	2.6-2.9 T	9-60	379 +646	97-100 H	Rash 7 %
Cameroon	Guyer	1975						
Cameroun	Mouchon	1989	SW	3.0 T	6-10	89+85	84-90 H	
Gabon	Gendrel	1986	SW	3.4-4.5 T	3-7	52+37	29-45 H	
Gambia	Whittle	1984	EZ	3.5-4.1 P	-		73-100 H	
"	"	85-87	EZ	3.8-4.6 P	-	111		
		85-87	SW	4.0-4.6 P	-	105	79 H	
Gambia	Teller							
G.Bissau	Aaby	1985	EZ	4.6 P	-	234		
			SW	3.8 P		235		
Ivory Co.	Lhuillier	1988	SW	3.0 T	6-9	61+85	96-100 H	
Kenya	Machakos	74-81	SW					
Kenya	WHO	74-75	SW	3.3 T	4-11		60-100 H	
Nigeria	Ifekwun.	1980						
Nigeria	Morley	1962	EB			19	100 H	Rash 10 %
			SW			21	100 H	+ deaths?
Nigeria	Ruben	1973	SW	3.5 T	6-24		64-89 H	
Nigeria	Sherman	1967	EB	3.0 T	6-36		88-93 H	
			BK	3.0 T				
Rwanda	Ndikuyeze	1987	SW	3.0 T	8-19		63-90 E	Rash 2.5%
Sudan	Omer	1986	SW	3.0 T	3-30	149	42-100 H	
Tanzania	WHO	1977	SW	3.0	4-60		17-83 H	
Tanzania	Kimati	1981			6-21		44-91 H	
Togo	Budd	1965	EB			154	96 H	Rash 29.4%
Togo	Tidjani	1988	EZ	5.0 T	4-5	296	96 H	
"	"		AK	3.7 T	4-5	289	94 H	
"	"		SW	5.0 T	4-5	285	50 H	
"	"		SW	3.9 T	8-10	117	69 H	
"	"		AK	3.7 T	8-10	66	87 H	
Zaire	Kasongo	74-77						

Note: EB=Edmonston-B, SW=Schwarz, EZ=Edmonston-Zagreb, AK=AIK-C, BK=Beckenham. T= $TCID_{50}$, P=PFU, E=Elisa, H=HI.

0.2 MEASLES VACCINATION IN SENEGAL

After conclusive results of the 1966 studies, a major national measles vaccine campaign was conducted in 1967-1969 in Senegal (phase d'attaque). According to official records 682,901 children were vaccinated, representing 74.8% of the estimated 1 to 7-year-old population in 1968 (Cantrelle et al. 1985). Measles vaccination was later continued nationwide. Official publications suggest a high vaccination coverage. However, these figures are to be interpreted with caution. First they are not necessarily accurate, since some reports are missing from certain health posts; second, they mostly concern the urban areas and western Senegal; third, the size of the susceptible population that was vaccinated is unknown: children between ages 0 to 14 years were vaccinated, including children who already had measles and children who were already vaccinated once. Therefore, reliable estimates of vaccine coverage could not be computed directly from these data. Routine measles vaccination (phase d'entretien) was maintained at a relatively high level after 1970, with the potential of covering at least 75% of the susceptible population.

Measles vaccination was later included in the national Expanded Programme on Immunization (EPI) in 1978, together with other EPI vaccines (DPT, Polio, BCG, Yellow-Fever). Mass measles vaccination resumed in many places with the start of the "Primary Health Care" program. During the mid 1980's vaccination coverage dropped again, especially in rural areas.

A new EPI program began in October 1986, sponsored by UNICEF. This program was based on fixed post and mobile teams and a strong social mobilization during national weeks of vaccinations (opérations coup de poing). Measles vaccine coverage for the target population was estimated in July 1987 at 70% (children born from July 1, 1985 to June 30 1986). Since then, it is possible that vaccination coverage has dropped again, especially in rural areas, but reliable estimates are not available for comparison.

The declaration of measles cases is compulsory in Senegal. The quality of the registration of measles cases was probably not constant over time. However it gives a rough idea of disease incidence at the national level (Garenne et al. 1985). During the years following mass vaccination campaigns (1967-1969), measles had a much lower incidence: in 1970 the number of measles cases declared had dropped by 67.3 % of the mean number for the 5 years preceding the campaign (1962-1966). However, in the 5 years preceding the start of Primary Health Care (1973-1977) measles incidence was back at a level comparable to prevaccination years. After the 1978-1979 campaign, the number of reported cases had dropped again but only by 23.1%.

0.3 THE NIAKHAR STUDY AREA

There was also a long tradition of demographic research in Senegal in collaboration with the Bureau National du Recensement (BNR) and ORSTOM. Most of this research was conducted in the central part of Senegal and was associated with measles and measles vaccination studies. Outside of its participation in the Khombole demographic surveillance (1963-1969), ORSTOM was running prospective community studies (also called population laboratories) since December 1962, one in the department of Fatick, the other in the department of Nioro du Rip. The size of the population under study varied over time: three main periods can be considered, 1963-1966, 1967-1982, 1983-1989: they are summarized in the chart 0.3.

Chart 0.3 : ORSTOM Prospective Community Studies in Senegal :

Fatick (North West)	Nioro du Rip (South East)
Phase I : Sine-Saloum : December 1962 - February 1966	
all Niakhar arrondissement 65 villages 35,187 people in 1966	1/2 Paos-Koto arrondissement 135 villages 18,988 people in 1966
Phase II : Ndemene-Ngayokheme : December 1962 - February 1983	
all secco Ngayokheme 8 villages about 5,000 people subsample of previous area	all secco Ndemene 30 villages about 6,000 people subsample of previous area
Phase III : Niakhar : March 1983 - ongoing	
CR Ngayokheme + 1/2 CR Diarere 30 villages about 25,000 people extension of previous area 18 villages from phase I 8 villages from phase II	(terminated)

Figure 0.1 : Location of ORSTOM studies in Senegal

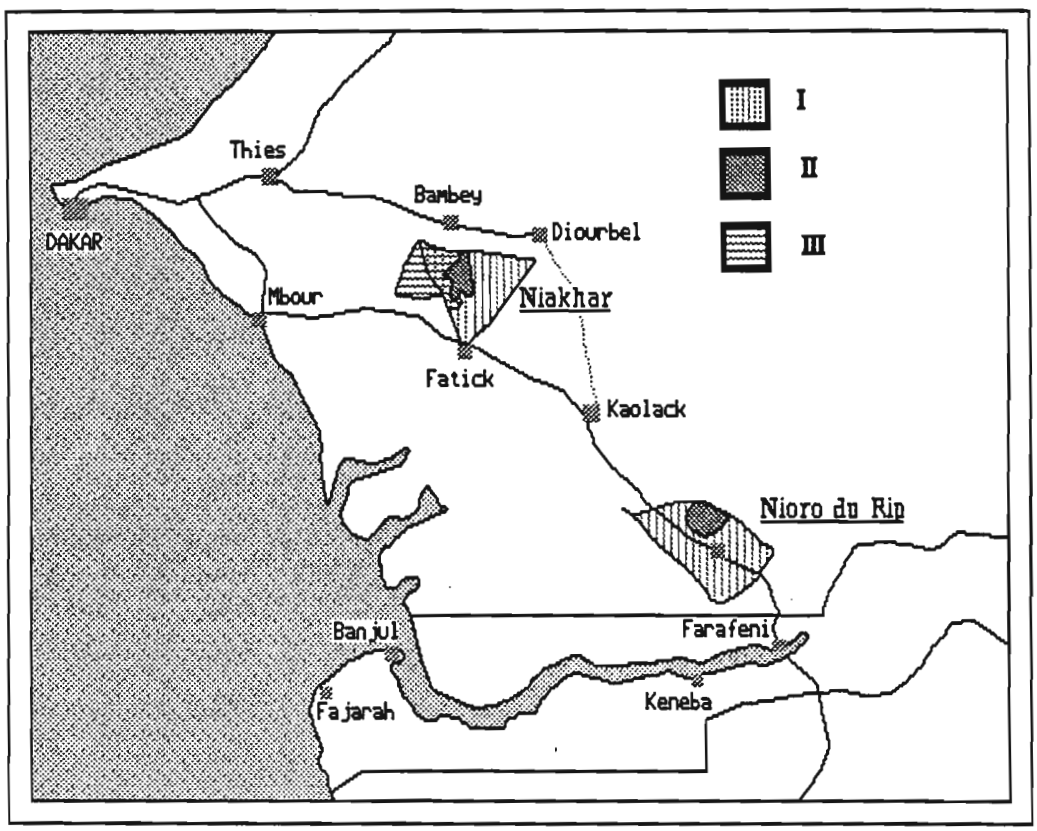
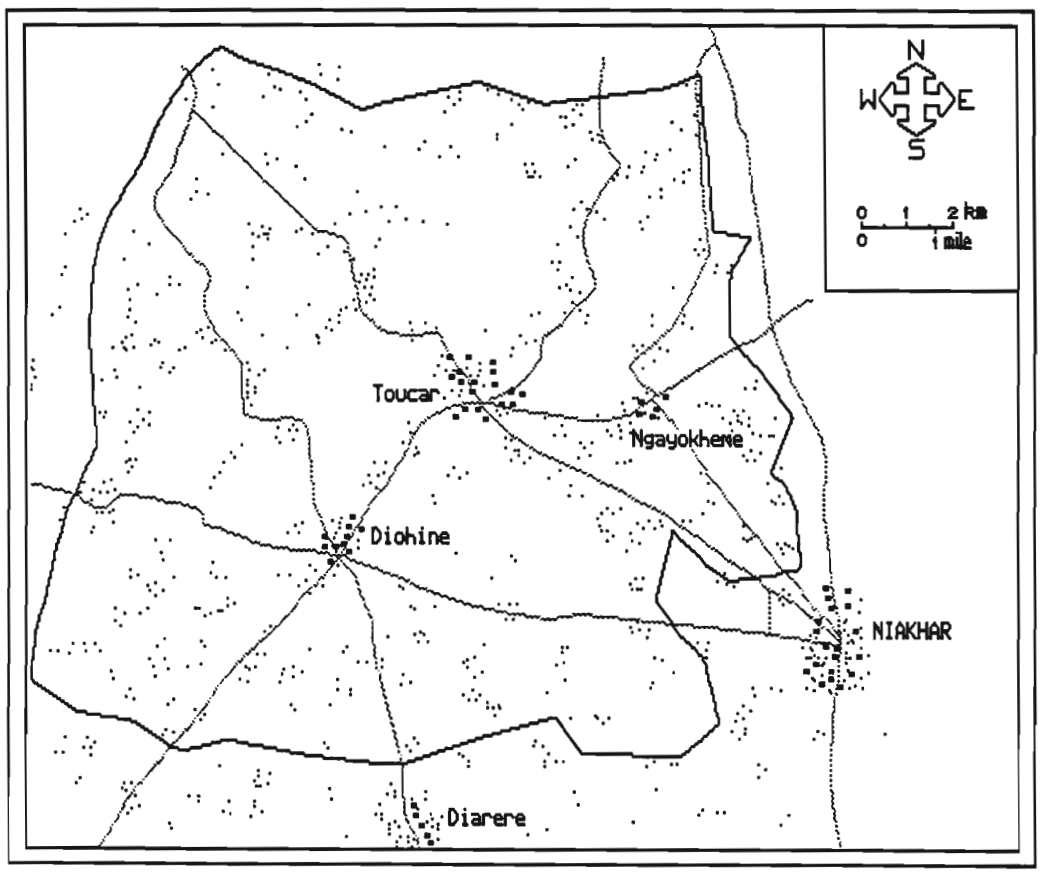


Figure 0.2 : Map of the study area.



Administrative divisions have changed over time in Senegal. They are based on: Regions (Région), Departments (Département) and Districts (Arrondissements). From independence until 1983 there were 8 regions. In 1984 two new regions were created within the former Sine-Saloum: Fatick and Kaolack. Fatick is the head of the Fatick region and of the Fatick department. The North West areas were always located in the department of Fatick, which was part of the Sine-Saloum Region until 1983 and is now part of Fatick region. The South East area was always located in the department of Nioro-du-Rip, which was part of the Sine-Saloum Region until 1983 and is now part of the Kaolack region.

Below district (arrondissement, a unit of 5000 to 50000 people) was "Seccos" before 1974. The second phase was based on the seccos of Ndemene and Ngayokheme, which were sub-samples of the former area. In 1974 "Communautés rurales" were created. The third study was based on an extension of the Ngayokheme area, encompassing the rural community of Ngayokheme and half of the rural community of Diarere.

Measles and measles vaccine information is available in all study areas. However, is it matchable with current files (Niakhar) only for the 8 villages of Ngayokheme since December 1962.

0.4 MEASLES INCIDENCE AND VACCINATION IN NGAYOKHEME 1963-1989

Data on measles incidence and measles vaccination were nearly complete for the 8 villages of the Ngayokheme area. They were not fully representative of the whole area since pilot vaccinations were conducted in the 8 villages in 1966 and special measles vaccination were conducted in 1981, 1982, 1983 again in the same 8 villages within the Dutch Primary Health Care Program with the help of the ORSTOM team. However they can be considered as an upper limit for vaccine coverage and a lower limit for measles incidence for the area as a whole.

Vaccines delivered and measles cases reported in the Ngayokheme study area are displayed in table 0.1 and in table 0.2. Vaccine coverage varied strongly with time. Birth cohorts best vaccinated were those vaccinated in 1966 (1963-1964 cohorts), in 1979-1983 (1978-1981 cohorts) and recently the 1985-1988 cohorts. These data do not fully reflect the effort of vaccination in cohorts, because they do not integrate the competing risks of contracting measles and of dying prior to vaccination.

Despite the relatively important effort of measles vaccination in this population, 41.2 % of the 0-14 population was still susceptible to measles in 1987-1989, not counting vaccine failures, and 49.2 % were protected by vaccination. A few other people age 15-29 years were also susceptible: this will be seen later when analyzing the age pattern of measles incidence, which ranges from age 4 months until age 29 years.

CHAPTER 1

METHODOLOGY

1.1 GENESIS OF THE PROJECT

This study had its origin in a series of circumstances. First, in the beginning of 1986, the Ministry of Public Health was preparing, with the help of UNICEF, a major push to the national EPI, in a poor shape at that time. Second, the ORSTOM team of "UR Population et Santé" based in Dakar (Michel Garenne, Oliver Fontaine, Jean-Pierre Beau and Odile Leory) was looking for a new major research project in Niakhar: the former project on malnutrition and mortality was ending in 1986 and there was an interest in vaccine efficacy and in the impact of measles vaccines on child survival. Third, there were contacts with Peter Aaby and Hilton Whittle who were getting the first results on the Edmonston-Zagreb vaccine in the Gambia and in Guinea-Bissau. P. Aaby had collaborated in a recent study on the epidemiology of measles in Niakhar [Garenne and Aaby, 1990]. It was felt desirable to undertake a formal vaccine trial based on large numbers, and the demographic and epidemiologic surveillance system already in place in Niakhar was considered particularly appropriate. Fourth, the Task Force for Child Survival sent a mission to Senegal, in April 1986, with CDC and APMP experts (Roger Bernier, Mr Giordano and Jacques Drucker) to look for a field site for a measles vaccine trial on high titer measles vaccines.

At that time, the efficacy of measles vaccines was debated and two factors were discussed: the strain and the titer. The CDC had gathered a recent meeting in Atlanta in 1986 to investigate the Edmonston-Zagreb vaccine as well as other vaccines unknown in the European and North American countries (Leningrad 16, AIK-C etc...). Among open issues, were the following:
a) does the strain matter for immunogenicity and efficacy? in particular was the Edmonston-Zagreb vaccine better than standard Schwarz or Moraten vaccines when given at the same titer?
b) does the titer of the vaccine matter for immunogenicity and efficacy?
c) are measles vaccines safe at a titer as high as 5.0 log10 $TCID_{50}$, such as the Edmonston-Zagreb vaccine? WHO recommendations were at least 3.0 log_{10} and current usage was around 3.6 log_{10}?

Contacts between the Task Force for Child Survival (TFCS), the Faculty of Medicine and ORSTOM, UR Population et Santé, were taken in Dakar and in May 1986 a first draft protocol was sent for review to the TFCS. The idea of the first protocol was to compare the efficacy of the Edmonston-Zagreb vaccine administered at 5 months against the efficacy of a standard Schwarz vaccine administered at 10 months. After in depth discussions with CDC experts it was decided:
a) to have 3 groups: Edmonston-Zagreb at 5 months, a Schwarz vaccine at the same titer as the Edmonston-Zagreb vaccine, also given at 5 months and a standard Schwarz at 10 months; furthermore a placebo should be given at 5 months in the third group to ensure a blind trial.
b) to add an immunogenicity study: this was considered safer in case there were not enough measles cases; this would also permit quicker results and a comparison of the two vaccines. The immunogenicity study was supposed to cover the first 5 cohorts.
c) to have a comprehensive safety study built into the protocol.

The final protocol was written and approved at a meeting of the investigators and TFCS experts (the Scientific Committee) in November, 1986 in Dakar. It was then submitted to the Ministry of Health for approbation. Approbation was delivered on July 26, 1987.

1.2 ORIGINAL RESEARCH PROTOCOL

The main points of the research protocol are explained here briefly. The protocol was to be fully integrated into the national EPI and implemented in the 30 villages of the Niakhar study area. From the beginning of the project, the vaccination team was in charge of the national EPI in the three local dispensaries of Ngayokheme, Toucar and Diohine, covering the whole population of the 30 villages. For the Ministry of Public Health the team was a mobile vaccination team (équipe mobile") although vaccinations were always conducted in a fixed post.

Objectives

The primary objective of the study was to evaluate the efficacy between age 5 and 10 months of the EZ-HT vaccine and of the SW-HT vaccine when administered at age 5 months.

The secondary objectives of the project were:
- to assess the adverse reactions to the injection of high titer measles live vaccines when administered at age 5 months.
- to evaluate the immunogenicity after high titer measles vaccination at 5 months.

The study was also designed to provide information for evaluating the impact of a new schedule of the EPI on survival of young children and on their morbidity and nutritional status, as well as information on the duration of the clinical protection after early vaccination with high titer vaccines.

Methodology

The study was designed as a randomized blind controlled clinical trial. Children were randomly allocated at birth to one of the three groups, by a micro-computer random generator: Group A, received the EZ-HT vaccine at 5 months, Group B received the SW-HT vaccine at age 5 months and Group C received a placebo at 5 months and a Standard low titer measles vaccine at age 10 months. Investigators and field workers did not know the type of vaccine each child received until the code was broken (June 1989).

Children were recruited at birth by the demographic surveillance system. They were vaccinated at age 3, 5 and 10 months. Vaccinations occurred once a month and children were grouped by monthly birth cohorts. For instance, a child born in January was vaccinated in April, June and November and so on. Age was computed in difference of months between month of vaccination and month of birth. This is not exact demographic age in months. Children in the 5 months group were in fact exact age 4.5 to 5.5 months old, since vaccination occurred usually in the middle of the month. Clinical efficacy was to be assessed through a comprehensive surveillance of all measles cases.

The study of adverse reactions was conceived at first as a record of all morbid episodes as they were declared by the family. In addition a full record of mortality was conducted, including the unvaccinated group. Later, a proper clinical examination by a physician of children vaccinated at 5 months was conducted, with emphasis on post vaccination rashes (see below).

Immunogenicity data were first scheduled to be obtained on the first 5 cohorts only. They were later collected on all cohorts (see below). Blood samples were routinely taken at the time of the 5 months and the 10 months sessions from children participating in the trial, except if the family objected. Additional immunogenicity data were to be obtained at the end of the study on all children who participated in the study. The data monitoring and safety committee evaluated the immunogenicity data of the first seven cohorts to determine whether sero-conversion rates were adequate or whether subjects needed to be revaccinated at approximately 10 months of age.

Parents were informed of the objectives and methods of the study and of their right to refuse to participate in the trial, and therefore to receive only the standard EPI vaccines; a few people refused any vaccination (see below 3.1). Outside of the EZ-HT and of the SW-HT vaccine, all other vaccines were those routinely administered in the National EPI: BCG, DPTP (Diphtheria, Pertussis, Tetanus, Inactivated Polio) and YF (Yellow fever).

1.3 CHANGES TO THE ORIGINAL PROTOCOL

1.3.1 Vaccine delivery

Four major changes were made to the original protocol following the advice of the Data Monitoring and Safety Committee. The first change was in vaccine delivery and in duration of the study. A first analysis of data was conducted in August 1988 and presented at a WHO meeting in Washington in September 1988. Results showed that the EZ-HT vaccine produced a better serological response than the SW-HT vaccine. These results corresponded to the results of the seven other studies presented at the meeting. The Data Monitoring and Safety Committee met in Dakar in October 1988 and recommended dropping the SW-HT vaccine (the B group). The Data Monitoring and Safety Committee met again in Dakar on June 28-30, 1989. In reviewing the available data, it recommended stopping the trial, after only 24 cohorts instead of 28 originally planned. However, vaccination of the population would continue with the EZ-HT vaccine at 5 months, when possible, and with the Standard vaccine at 10 months or more in other cases.

Chart 1.1 : Vaccine schedule, according to birth cohort (project children)

Group	3 months	5 months	10 months
I - Cohorts 01-16			
A	DPTP-1 + BCG	DPTP-2 + EZ-HT	DPTP-3 + YF
B	DPTP-1 + BCG	DPTP-2 + SW-HT	DPTP-3 + YF
C	DPTP-1 + BCG	DPTP-2 + placebo	DPTP-3 + YF + Measles
II- Cohorts 17-24			
A	DPTP-1 + BCG	DPTP-2 + EZ-HT	DPTP-3 + YF
C	DPTP-1 + BCG	DPTP-2 + placebo	DPTP-3 + YF + Measles

NB : the 3 months session was conducted at 8 months for the first 2 cohorts. (see table 3.6 for details).

Therefore, the effective vaccination protocol was (chart 1.1):

- for the first 16 cohorts (01-16), vaccinated at 5 months from August 87 until October 88 : 3 groups (A, B, C)
- for the next 8 cohorts (17-24), vaccinated at 5 months from November 88 until June 1989 : 2 groups (A, C)
- the last 5 cohorts (25-29), did not participate in the trial, although they were vaccinated during the last 5 months of the study; cohorts 26-29 were vaccinated at 5 months with the EZ-HT vaccine. Cohort 25 (children born in February 1989) did not receive the EZ-HT vaccine at 5 months in July 1989; it received the Standard vaccine at 10 months.

1.3.2 Revaccination of seronegative children

At the second meeting of the Data Monitoring and Safety Committee it was also felt that children belonging to groups A and B, who had received a high titer measles vaccine at 5 months and who did not have detectable levels of measles antibodies at 10 months should be re-vaccinated. All children from the first 16 cohorts who had no detectable antibodies at 10 months were then re-vaccinated in April 1989. They were randomly assigned to a group: either the EZ-HT vaccine or the Standard measles vaccine. A blood sample was taken at time of re-vaccination and 28 days later (see below 5.5).

1.3.3 Decay of antibodies

The third change in the protocol was the study of decay in measles antibodies after vaccination. At the second meeting of the Data Monitoring and Safety Committee it was felt that measles incidence was low (only 28 cases of all ages had been recorded at that time) and that more data on decay of antibodies over time was needed. Consequently, all children in the first 16 cohorts who were incompletely vaccinated and who came to at least one of the 5 or 10 months sessions were called back: their vaccines were completed (eg a third DPTP) and an additional blood sample was taken. Cohorts 01-04 were called in May 1989 (at age 24-27 months), cohorts 05-08 were called in June 1989 (21-24 months), cohorts 09-12 were called in July 1989 (18-21 months) and cohorts 13-16 were called in August 1989 (15-21 months). Among them, there were children vaccinated with one of the three measles vaccines and unvaccinated children. A last blood sample was taken at that time for the study of the decay of measles antibodies.

1.3.4 Adverse reactions

The fourth change in the protocol was for the study of adverse reactions. At the first meeting of the Data Monitoring and Safety Committee it was felt that the recording of morbidity from family declaration, although interesting, was not enough to document small adverse reactions such as post vaccination rashes. Hence, after each vaccination session following this meeting (sessions 10 to 24) the project physician was assigned a group of 15 children randomly selected among those vaccinated at 5 months. Each of these children were visited 5 times from day 1 to 28 after vaccination and carefully examined (see below 4.3).

1.4 THE DEMOGRAPHIC SURVEILLANCE SYSTEM

The whole study was based on the demographic surveillance system. In fact, official vital registration in the area was virtually useless: less than one third of births and less than 10 % of deaths were registered in Niakhar; furthermore, dates of birth or death were often wrong since the registration may have occurred months or even years after the event.

The demographic surveillance system existed in the new study area since March 1983 and in the old area since december 1962. Before this study, it was mainly based on a yearly census. Since January 1987, it has been based on weekly visits to households. Risks of missing events were extremely low during the weekly visits and furthermore censuses were conducted over the period. In December 1986 a formal census of the whole area was taken. In June of 1987 and 1988 light control censuses were taken by updating the list of residents and maternity histories for women. A formal census was again conducted in July 1989.

The study area was dispatched in 11 enumeration areas of about the same size. Each area was covered by one field worker. Each week, the 11 field workers visited each of the 1770 compounds of the study area and recorded all new demographic events: births, deaths, migration, changes in marital status as well as weaning. In addition they asked about any case of suspected measles and pertussis. Each suspected case was immediately reported to the physician. All events detected during the weekly visits were properly recorded on an event form. There was a special form for each category of event. Each of the field workers had the right to take a month of vacation each year. This was done month after month (first going in January, second going in February etc.). The twelfth field worker was utilized to replace his colleague on leave. He went on vacation the twelfth month. The demographic surveillance with weekly visits to households was continued over the 36 months of the project for the whole area, from January 1, 1987 until December 31 1989, without any discontinuity except for the few official holidays.

In addition, field workers routinely recorded the absences and the morbidity of all study children as reported by the mother or the family, from the first vaccination date (the 3 months session) until their first annual birthday (age 12 months).

The two supervisors had two weekly contacts with their field workers. They checked the work of the last 3 days, collected the event forms and randomly reinterviewed 2 compounds per field worker per week. Events forms were sent each week to Dakar, on Friday afternoon. They were checked again and coded prior to entry into the micro computer. Hence the population file was continuously updated in the computer and served as a basis for calling new birth cohorts for vaccination.

The key for the enrollment in the project was the early detection of live births. This was done systematically by following up pregnancies for women who were resident for a long period and by systematic questioning for women who recently settled, e.g. new wives. All together, for the 24 monthly birth cohorts, live births were reported to Dakar headquarters within a month in 96.4 % of cases, an additional 1.5 % the second month, and 1.0 % the third and fourth month. The 27 others (1.1%) were already too old to be enrolled in the project when notified. They were added to the statistics as children absent at the 5 months session.

1.5 EPIDEMIOLOGIC AND CLINICAL INVESTIGATION

As mentioned above, the field workers notified the field physician of all suspected cases of measles. In addition, strict monitoring of the dispensaries was also conducted at least once a week and almost every day in the case of an outbreak. Once a case was suspected, the physician went to the compound for a comprehensive clinical and epidemiological investigation.

At the first visit by the physician, an investigation was conducted in six steps:
a) the children age 0-14 living in the compound were listed, including residents temporarily absent and visitors; this was done systematically by asking all women living in the compound and later by matching with the field worker's list;
b) the history of contamination of the index case or cases was reconstructed, by questioning the mother or other family members. In general it was possible to find out where the index case was most likely infected. Secondary cases were usually found during next visits;
c) a clinical examination of all cases was conducted at time of the first visit as well as a clinical examination of all susceptibles (who never had measles).
d) a blood sample was taken for all cases and susceptibles;
e) all sick children were treated;
f) neighboring compounds with social contacts with infected children were visited in hope of early detection of new cases.

Infected compounds were revisited twice a week until the last case was fully cured, ie until desquamation had finished. Revisiting infected compounds implied:
a) updating the list of cases.
b) monitoring the clinical signs among cases not yet cured.
c) taking a blood sample for all cases about 28 days after onset of first symptoms.
d) treating sick children.

1.6 INFORMATION OF THE POPULATION

Prior to the vaccine trial, all governmental and health authorities as well as traditional authorities of the study area were visited and the methodology of the study was explained by the investigators. Then, all villages were visited by the field physician, who was often accompanied by one of the investigators. Meetings were organized with men and women under the authority of the head of the village. The aims of the study and the right to refuse or to withdraw at any time were explained to the people in words easy for them to understand. In addition, field workers had to explain again individually to all mothers the aims of the study and their rights at the time of vaccination. Mothers had to give an oral informed consent prior to having their children vaccinated. As it will be seen below (see 3.1) a relatively high proportion of mothers refused to participate in the trial (about 20 %).

1.7 MEDICAL SERVICES PROVIDED TO THE POPULATION

During the duration of the project, a special effort was made to provide the population with appropriate medical services, to the extent personnel and financial means permitted (chart 1.2). Medical services were integrated into the local system of primary health care as much as possible. Systematic use and promotion of essential drugs was continued during the study period. A list of these is provided in annex A-3. A separate study of use of medicines in the population was conducted in 1988.

A) Vaccinations

Free vaccination was provided not only to project children but also to all other children age and to adults who came on vaccination day to one of the three dispensaries. Free tetanus toxoid immunization was provided to all pregnant women who came for antenatal care as well as to all other persons who came for this purpose.

The vaccination sessions were conducted in the local dispensaries and vaccines were administered by the local nurses (infirmier) under the strict supervision of the vaccination team. This did not change the vaccination habits of the people and the standard national EPI program could continue after the end of the project without any disruption. During the vaccination sessions, free medical services were provided to the project children. In addition, standard fee consultations was provided to all sick people of all ages who came to the dispensary (see below).

B) Home visits

During his visits to the infected compounds, the physician treated free of charge all persons of any age who needed treatment. When required, people were referred to the nearest hospital, in general to Fatick, sometimes to Kaolack or to Dakar when necessary.

C) Dispensary consultations and antenatal care

In addition to their work in the field, the physicians provided consultations in collaboration with the local nurse once a week in each dispensary of the study area: Tuesday in Ngayokheme, Wednesday in Toucar and Thursday in Diohine. All people were properly treated when possible, others were referred to the nearest hospital. Sporadic antenatal care with a physician, about once a month, started in 1986. During the project antenatal services were provided regularly, on a weekly basis after 1987. From January 1987 there was one full time physician in Niakhar. In April 1988 he was assisted by a second physician who was in charge of pertussis cases investigation. In March 1989 a third physician joined who was in charge of the follow-up of pregnant women and tetanus toxoid immunization, and later participated in a study on AIDS and sexually transmitted diseases. A list of physicians who participated in the study is provided in annex A-5.

D) Detection and treatment of malnourished children

Malnourished children were systematically screened during vaccination sessions, home visits and dispensary consultations. In 1987 and early 1988 they were referred to Pikine (near Dakar) where ORSTOM UR Population et Santé runs a center for nutritional rehabilitation (Dr Jean-Pierre Beau). In August 1988 a small unit was opened in Toucar dispensary; the unit was closed in December 1988 and after this date children were either referred to Fatick where a new unit (CREN) was opened or to Dakar when needed.

E) Malaria treatment and prophylaxis

In order to facilitate the early treatment of malaria, anti-malaria pills (chloroquine) were given in small quantities (10 pills of 100 mg) to all mothers who brought a child for vaccination. Mothers received the necessary advice about

how to use the pills. Children with measles were also systematically given anti-malaria prophylaxis. All children or adults who were found to be sick during a home visit or in a dispensary were offered anti-malaria treatment. In addition, large quantities of chloroquine were distributed in the local dispensaries when there was a shortage of this drug. Some 80,000 chloroquine pills were distributed during the course of the project.

1.8 ORGANIGRAM

The project was a collaborative project with several institutions and researchers. The list of researchers and advisers is provided in annex A-5.

Scientific committee

The scientific committee (SC) met once in November 1986 to discuss and approve the protocol. A list of members who participated in the committee is provided in annex A-5.

Data monitoring and safety committee

The Data Monitoring and Safety Committee (DMSC) met four times at about 9 months intervals after the start of the project: in January 19-21, 1988, October 25-27, 1988, in June 28-30, 1989 and in June 1990. The DMSC was composed of representatives from participating institutions. A list of members is given in annex A-5.

Technical committee

The Technical Committee (TC) met every week during the entire period of the study, usually on Friday afternoon from 4 to 6 PM.

1.9 TIMETABLE

A timetable of the project is presented in chart 1.3. The study per-se lasted almost exactly 3 years in the field, from December 1986 until December 1989. However, the efficacy study was prolonged until August 1990, after the end of the third measles outbreak. The mortality study was prolonged until October 1990, after the last check during the third rainy season. About 5 years elapsed between the first draft protocol and the final report.

Most of the analysis refers to the period between August 1987 and December 1989: tables are labelled "Niakhar, 1987-1989". Mortality tables relating to the period from August 1987 to October 1990 are labelled "Niakhar, 1987-1990". Efficacy tables relating to the period from August 1987 to August 1990 are also labelled "Niakhar, 1987-1990".

Research Council based in Fajarah, the Gambia, provided laboratory facilities, supplies and personnel throughout the project.

Chart 1.2 : Medical services provided to the study population during the course of the project (in addition to the normal activity of the three dispensaries)

Date	Medical services and personnel
I Medical Services	
December 86-April 87	- free vaccination of children 0-23 months (national EPI campaign).
August 87-December 89	(during vaccination sessions) - free vaccination of new cohorts, born after February 1, 1987; - free vaccination of other children and adults; - free tetanus toxoid immunization of pregnant women or any person who needed one.
January 87-December 89	(in dispensaries, 3 times a week) - fixed fee consultation in dispensaries; - fixed fee antenatal visit+care; - free essential drugs when needed; - free medical care+drugs during home visits; - free referral to hospital when needed; - free referral+fixed fee treatment for malnourished children. - antenatal visits
August 86-December 87	- sporadic antenatal clinic
January 88-December 89	- systematic antenatal clinic, with TT immunization.
II Medical personnel	
January 87-March 88	- 1 full time physician + 1 part time physician
April 88 - February 89	- 2 full time physicians + 1 part time physician
March 89 - August 89	- 3 full time physicians + 1 part time physician
September 89 - Dec 89	- 3 full time physicians + 1 full time midwife

NB Fixed fee consultation was the self financing of the primary health care; the team provided drugs for free and gave the money to the local "comité de gestion".

Chart 1.3 : Timetable of the project

- April 1986 : first contacts between ORSTOM, the Ministry of Health, the Faculty of Medicine and the Task Force for Child Survival.
- June 1986 : first draft protocol.
- October 1986 : discussion of the draft protocol in Atlanta;
- November 1986 : meeting of the scientific committee; approval of the protocol.

- December 1986 : baseline census.
- January 1987 : composition of the team; full time physician arrives in Niakhar; the demographic and epidemiologic surveillance systems with weekly visits installed.
- February 1987 : registration of the first birth cohort.
- March 1987 : high titer measles vaccines received in Dakar.
- July 1987 : formal approval of the Ministry of Public Health.

- August 1987 : first 5 months vaccinations (cohort 01 and 02).
- January 1988 : first meeting of the Data Monitoring and Safety Committee
- September 1988 : WHO meeting on the EZ vaccine in Washington; first results on seroconversion presented (cohorts 01-07)
- October 1988 : second meeting of the DMSC; decision to drop the high titer Schwarz group made; implementation started in November 1988.
- June 1989 : third meeting of the DMSC; the code is broken; first results on efficacy presented; decision to stop the trial is made; decision to continue supporting the vaccination of the last cohorts until all children had their 10 months vaccination.
- September 1989 : expatriate physician (O. Leroy) leaves; field work and vaccination continued until December 31, 1989; a new team arrived for the Pertussis trial.
- November 1989 : last vaccination at 10 months (cohort 24); Principal Investigator (M. Garenne) leaves Senegal.

- December 1989 : Pertussis project started; Measles Surveillance and ascertainment will continue for 4 more years, supported by WHO.
- April 1990 : demographic data for the 1989 period entered; laboratory work completed for the vaccinated children.
- May 1990 : demographic data cleaning.
- July 1990 : end of the third measles outbreak.
- October 1990 : check on deaths among project children.

- February 1991 : mortality data presented at WHO, Geneva.
- March 1991 : census performed; a few errors in deaths detected.
- May 1991 : last corrections on deaths made.
- June 1991 : final report presented.

CHAPTER 2

STUDY POPULATION

This chapter briefly introduces the study population and the basic features of population dynamics which were the basis for the recruitment of birth cohorts and for the study of survival after vaccination. Details of the computations of age and person-years which are a key for most rates computed thereafter are provided in annex A-4. Most of demographic data were up-dated in April 1990, before the final results of the 1991 census were known.

2.1 DEFINITION OF THE RESIDENT POPULATION

The population under study was the resident population of the 30 villages listed in annex A-6. The details of the demographic surveillance system as well as the definitions used for the study are listed in the manual of instructions to the field workers. The definition of residence was the same as during the former study on malnutrition and mortality, 1983-1986: this period was used as a "baseline" for comparison of various demographic variables during the 1987-1989 period. The definition of residence was based on usual residence and the "6 months and rainy season" rule: people who moved out for more than 6 months and did not spend the last rainy season were considered as outmigrant; people who stayed for more than 6 months and stayed during the rainy season were considered as immigrant. Precise definitions are always arbitrary but various checks showed that the total population of the study area was known within a margin of approximately ± 1%.

2.2 POPULATION DYNAMICS

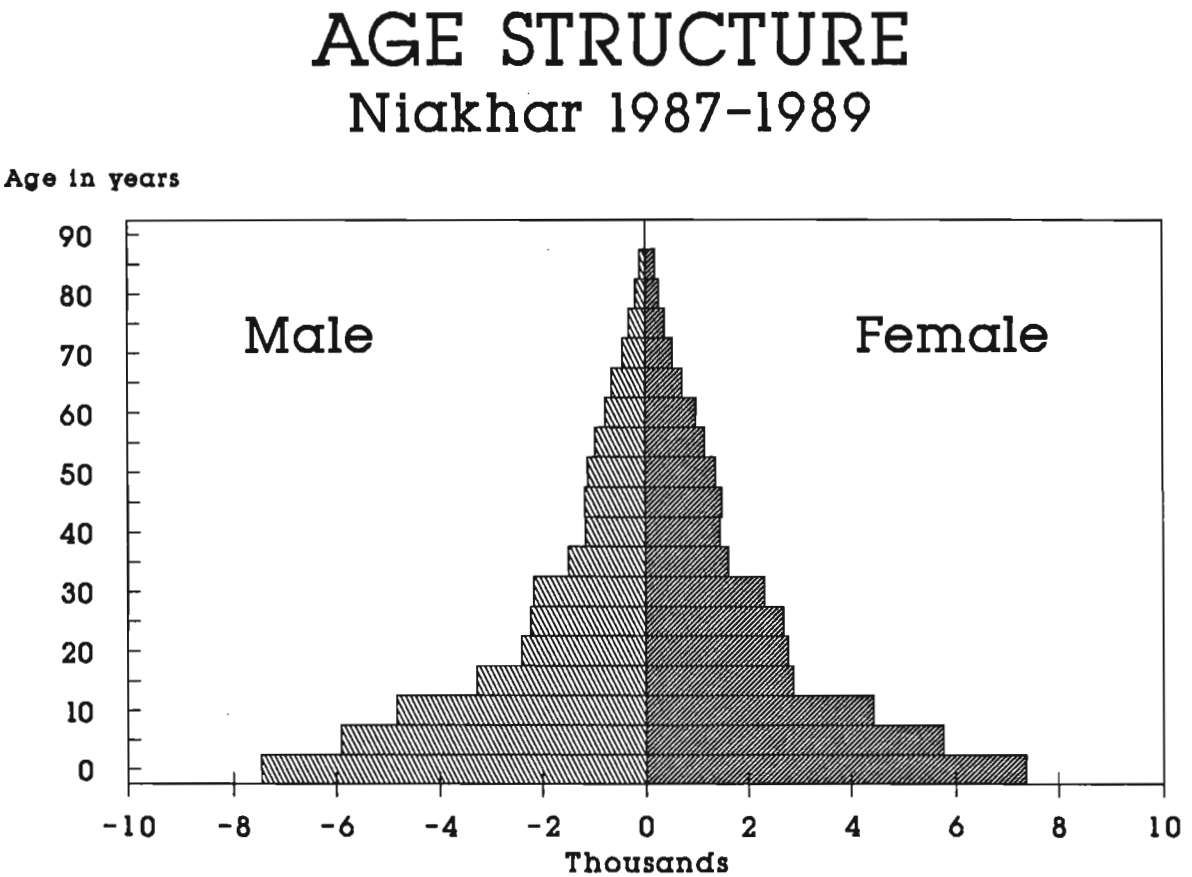
The period for the study of population dynamics covered three years, from January 1, 1987 to December 31, 1989. The resident population of the 30 villages of the study area accounted for 24,202 resident of all ages on January 1, 1987, just after the December 1986 census and for 26,356 resident of all ages on January 1, 1990. The total person-years lived was 75,342, that is an average population of 25,114 people.

Population growth was 28/1000 person-years over the study period which was more than during the baseline period (15/1000). Table 2.1 displays basic demographic rates and events over the 1983-1989 period. Over the three years of the study, there were 3713 live births, 1291 deaths, 2956 immigrants and 3224 outmigrants. The crude birth rate was on the average slightly lower than during the previous period 1984-1986. The crude death rate showed a marked decrease between 1984-1986 and 1987-1989. During the study period, immigration was higher and outmigration lower than before. A more thorough analysis of fertility and mortality is presented hereafter.

The age pyramid (figure 2.1) revealed the high fertility-high mortality situation. Most of the irregularities among the young adults of both sexes in the pyramid are genuine and due to a strong age specific pattern of migration.

There were marked seasonal variations in birth, death and migration rates (table 2.2). There were more births and deaths during the rainy season (July to October) and more in and out-migration at the end of the dry season which is the season during which marriages occur.

Figure 2.1


AGE STRUCTURE
Niakhar 1987-1989
Age in years
90
80
70
60
50
40
30
20
10
0
Male
Female
-10
-8
-6
-4
-2
0
2
4
6
8
10
Thousands

2.3 FERTILITY AND THE RECRUITMENT OF BIRTH COHORTS

Fertility is best assessed by computing the Total Fertility Rate (TFR), which gives a measure of fertility independent of the age composition of the population. This was done separately for males (fathers) and females (mothers) (table 2.3). Female age specific fertility rates were computed directly by dividing the number of live births to women in each age group by the person-years spent by the women in the same age group. TFR is the sum of the age specific fertility rates. Live births are counted here if and only if the mother was resident at time of birth.

Computations for male fertility raised a question of residence. The mother, and therefore the birth, could be resident but the father might not necessarily be resident; conversely a father who was resident could have children from a woman living outside of the study area. Here, the live births to non resident fathers (11.0 % of all live births) were allocated proportionately to the ages of other resident fathers; this compensated for births outside of the study area to fathers who were resident. After this correction, computation of male TFR was the same as for female TFR.

The three years of the study period were compared to the 1984-1986 period considered as a baseline. Both female and male fertility were markedly stable (figures 2.2 and 2.3): the female TFR fluctuated around 7.9 children per woman over life time, with a small variation of ± 2%; the male TFR fluctuated with the same variations around 13.0 children per man over life time. These fluctuations were smaller than those of the crude births rates, which means that a large part of the yearly fluctuations in the number of births was due to fluctuations in the number of susceptible adults. In any case, the yearly variations of the number of births were small and the reliability of the recording system remained stable over time.

Seasonal variations were far more pronounced. The number of live births per month, which determined the size of vaccination cohorts, varied from a low 71 (June 88) to a high 154 (November 88). The mean number of live births per month was 103 with a random standard deviation of 20 and an interval of confidence of [83-123]. Other fluctuations were not random and there were significant seasonal variations, with a peak at the end of the rainy season (September, October) and a low at the end of the dry season and beginning of the rainy season (June, July).

The sex ratio of live births was 104.6 (CI=100.1-109.2), which is consistent with former values of 105 found in this population as well as in other populations throughout the world. There was a ratio of 1/68 of twin deliveries and 1/4343 of triplet deliveries, which are also values consistent with other populations (table 2.4). 8.2% of all deliveries were still births.

Figure 2.2

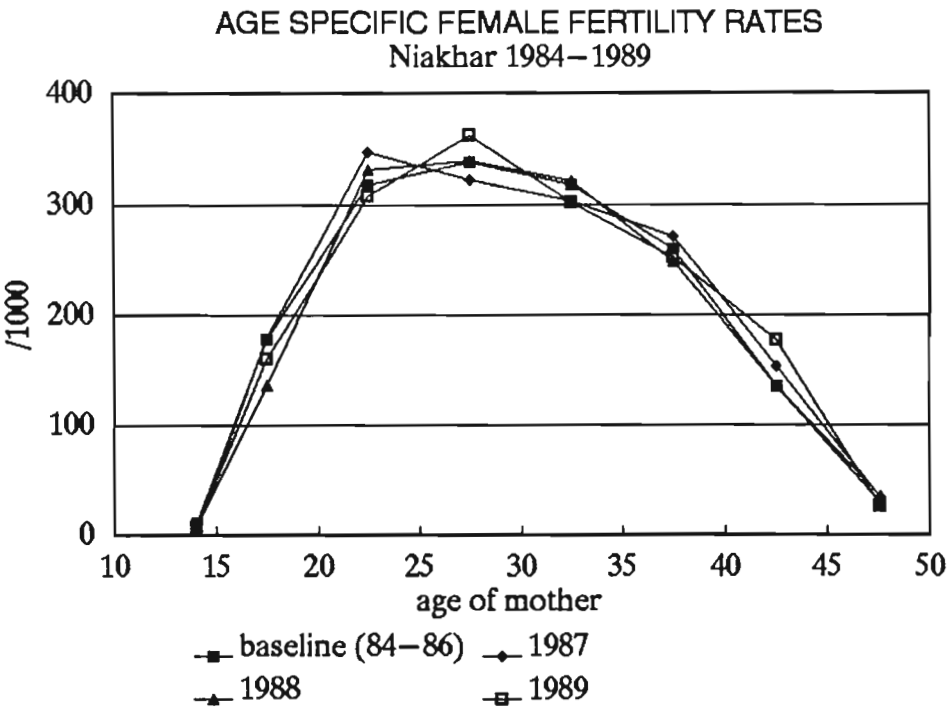
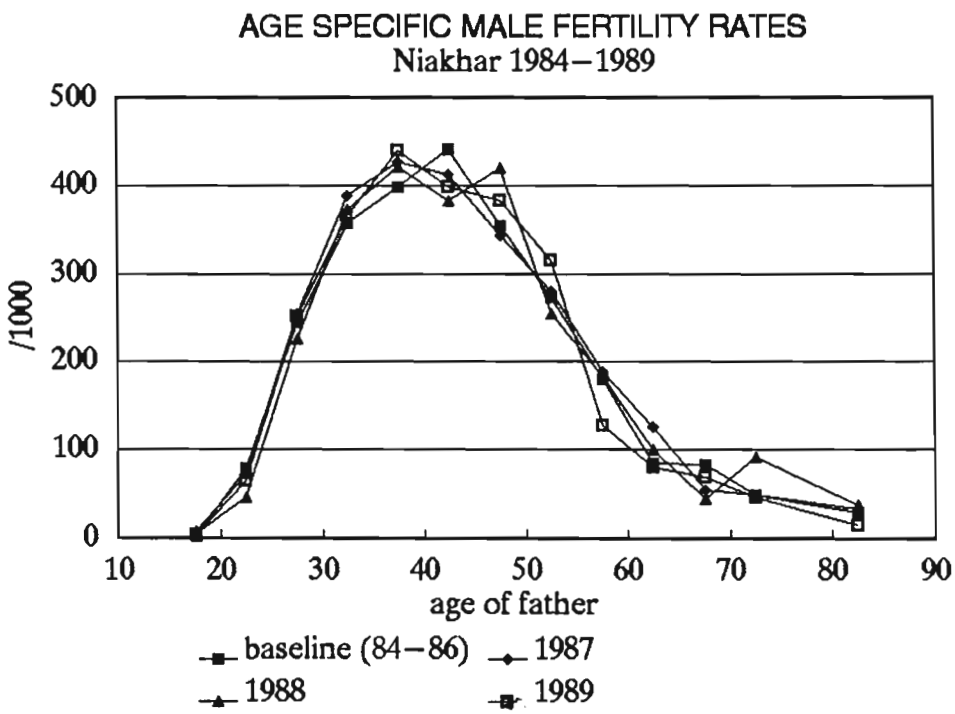


Figure 2.3



2.4 MORTALITY DECLINE

Mortality was lower during the 3 years of the study (1987-1989) than during the 3 preceding years (1984-1986). An abridged life table was computed for each sex (table 2.5). The life table was computed using standard formulae (Chiang, 1984). The starting point was age specific death rates (ASDR), computed directly by dividing deaths in each age group by person-years at risk.

Probably for the first time in the history of these villages, life expectancy exceeded 50 years for a significant period of time (51.9 for males and 52.5 for females). Infant mortality was 97.7/1000 for males and 108.3/1000 for females and child mortality age 1 to 5 was 135.0 for males and 141.2 for females.

When compared to the baseline period 1984-1986, mortality decline was noticeable at all ages (table 2.6 and figure 2.4). The crude death rate (CDR) in 1989 was 49% lower than the CDR in 84-86, i.e. mortality was reduced by half over the course of the study. Largest gains were obtained among children below age 5 years. This indicates that care provided by the project physicians was efficient. In fact mortality decline was more pronounced in 1988 than 1987 and greatest in 1989. This effect could be matched with the number of full time physicians in the study area: approximately 1 physician in 1987, 2 in 1988 and 3 in 1989 (see chart 1.2 for details of interventions). Although the ratio of people to physicians remained low by developed countries standards (8574 persons/physician in 1989) it was definitely higher than over the 84-86 period where only 1 physician was taking care of the whole department of Fatick which covers about 200,000 people.

Changes in mortality were significant in all age groups of infancy and childhood and virtually for all causes of death (table 2.7 and figure 2.4). In the neonatal period there was a reduction of 26%, probably due to better care and treatment of the newborn. The decline in neonatal tetanus mortality was not as marked as it could have been. This was probably due to two factors: 1) systematic vaccination of pregnant women started in 1987 only and was generalized in 1988 and therefore could not have a large effect on births before 1989; 2) it seems that tetanus mortality was lower than normal in 84-85 because of a marked drought in 83-84; this tended to diminish the overall effect of a marked neonatal tetanus mortality decline from 1987 to 1989 (- 55.1%). A significant effect of the rainy season on neonatal mortality has been documented elsewhere (Leroy and Garenne, 1988; Leroy and Garenne, 1990). A comprehensive study of neonatal tetanus is in process and will be published separately.

Decline in mortality due to other diseases preventable by vaccinations was close to full control. Decline in measles mortality was 100% for the post-neonatal period and 85.8% for children 1-4 years. Decline in pertussis mortality was 100% in all age groups. Better control of diarrhea and ARI mortality was achieved through systematic use of Oral Rehydration Therapy (ORT) and through the use of selected and appropriate antibiotics.

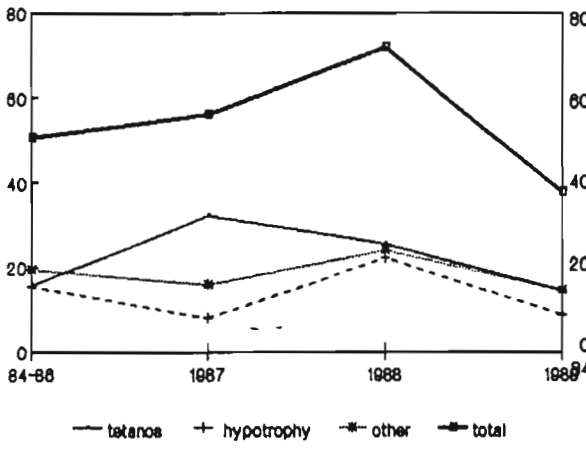
Maternal mortality was also reduced by half and other adult causes of death were reduced mostly through a good referral system to hospitals and help in treatment when necessary. A more detailed analysis of the control of mortality will be published separately.

Figure 2.4

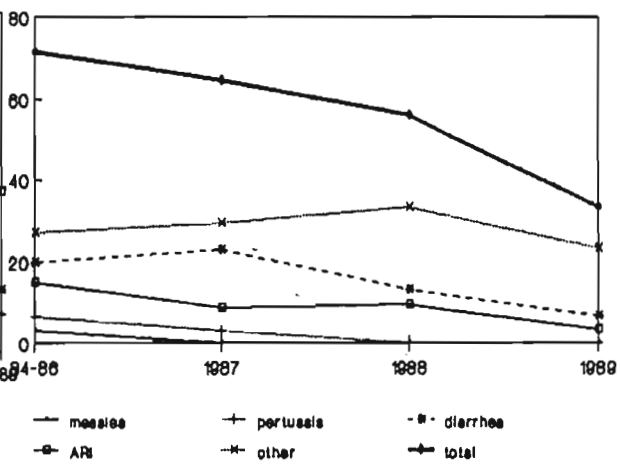
CHANGES IN MORTALITY

Niakhar 1987-1989

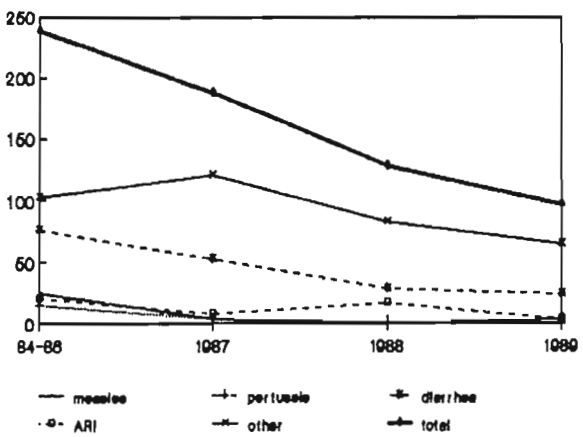
NEONATAL



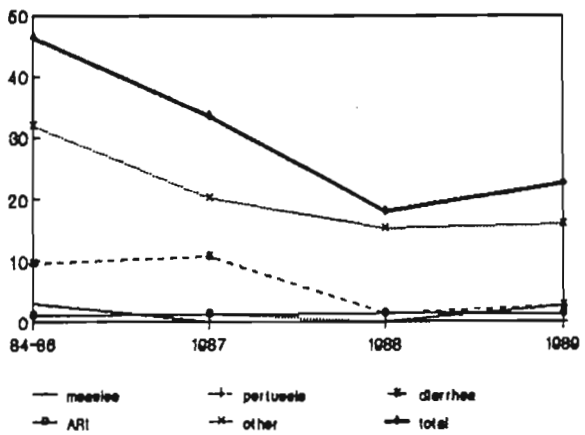
POST-NEONATAL



CHILDREN AGE 1-4



CHILDREN AGE 5-14



2.5 MIGRATION FLOWS

Migratory movements were difficult to compare with precision to previous periods since the method of data collection was not strictly the same, although the definitions were identical. Before this study, migration data were collected only once a year, at the time of the yearly census; hence all small term migration movements in and out between two censuses had no chance of being recorded, whereas this became possible with the weekly visits. However migration flows fluctuated between 108.9 and 156.3/1000 over the study period, a range of variation similar to that of the 1984-1986 period (104.8 to 150.4/1000). Migration played a relatively important role in the efficacy study and in the mortality study. In each case, the exact period of exposure to risk was computed to discount for the effects of migration.

2.6 PROJECT CHILDREN

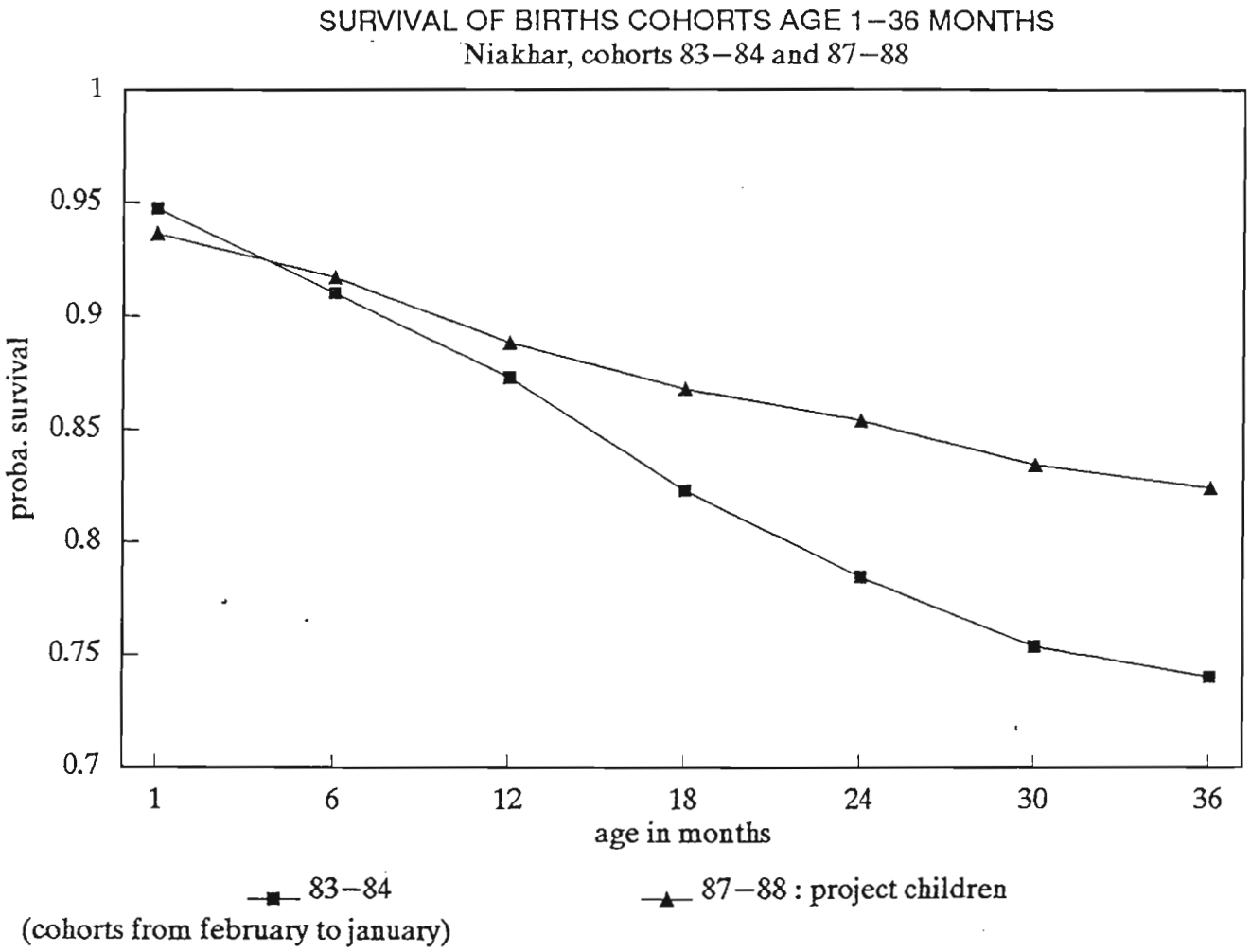
Children eligible for the study, called project children, were those born to mothers resident in the study area, from February 1, 1987 until January 31, 1989 (24 monthly birth cohorts). Children could be born outside of the study area, in Dakar for instance, but the mother had to meet the residence criteria at time of delivery. Children born within the study area but whose mother was not resident, were not counted as eligible for the study: they were considered as visitors; if they matched the residence criteria later on, they were counted as immigrants.

Table 2.8 displays the situation of each birth cohort on December 31, 1989. Children of the first cohort (01) were already 34 months old at that time and children of the last cohort (24) were 11 months old. On the average 14.2% of all live births had died by December 31, 1989 and 7.5% had emigrated.

Mortality of project children was compared to mortality of corresponding previous birth cohorts, born between February 1983 and January 1985 (table 2.9 and figure 2.5). These cohorts were not affected by this study between age 0 and 2 years since all of them were already two years old when the study started. Cohorts born between February 1985 and January 1987 were not considered for the comparison since they benefited from the study as well (they were less than 2 years old at start) and from the national EPI program for December 86 to March 87.

Results of the comparison of cohort mortality were as striking as those of period mortality. Probabilities of dying from 1 month to 36 months were reduced from 23.2% to 65.1% depending on the age group. Largest gains were at 12-23 months. However, this was not the case for neonatal mortality for the reasons mentioned above.

Figure 2.5


SURVIVAL OF BIRTHS COHORTS AGE 1–36 MONTHS
Niakhar, cohorts 83–84 and 87–88
1
0.95
0.9
0.85
0.8
0.75
0.7
proba. survival
1
6
12
18
24
30
36
age in months
83–84
(cohorts from february to january)
87–88 : project children

2.7 SUMMARY OF MAIN FINDINGS

Fertility was stable over the period, with marked seasonal and random variations. The average size of the monthly birth cohorts was 103 children, which was close to the value predicted by the protocol.

Mortality was reduced by 49% over the study period, when compared to the 1983-1986 baseline period. The most striking decline occurred for children below age 5 years, outside of the neonatal period, and for the diseases that were the target of the vaccination project, measles and pertussis. Pertussis mortality was under total control and measles mortality close to total control. The decline in other causes was attributed to the efficient work of the study physicians who provided high quality care, and were available about 5 days a week. The decline was proportionate to the number of physicians working full time in the study area. Strong improvement in child survival over those three years was a major achievement of this study.

Migration flows during the study period were comparable to those of the baseline period.

CHAPTER 3

VACCINATION

3.1 VACCINES

Vaccine batches

Vaccines other than the trial vaccines were provided by the Ministry of Public Health. Most of them were donated by UNICEF. They were collected from the regional pharmacy in Kaolack about twice a year. Details of batch numbers and dates of acquisition are provided in annex A-2. Trial vaccines were provided directly by the producers: the Institute of Immunology, Zagreb, Yugoslavia, for the EZ-HT vaccine and Institut Mérieux, Lyon, France, for the SW-HT, the Standard measles vaccine and the placebo. The trial vaccines were identical to the ones used in the Mexico trial (Markowitz et al., 1990).

Two batches of the EZ-HT vaccine were received directly from Zagreb. The first batch (81/3) was received in February 1987 and the second (137) in January 1989. The first batch was used for cohorts 01 to 21 and the second batch for cohorts 22 to 24 and 26 to 29; cohort 25 did not receive it because of a confusion in the batch numbers: after checking in early July 89, we thought that we had a low titer vaccine, and we did not use it at the July 1989 session; but this proved to be incorrect and the batch was used at the August session for cohort 26 and thereafter until November 1990, when the excess mortality effect was detected.

One batch of SW-HT vaccine was received directly from Lyon, in March 1987. The use of the SW-HT was discontinued after October 1988 when the immunogenicity of the vaccine was found to be too low. Two batches of Schwarz standard vaccines and two batches of placebo were received in March 1987 and in March 1989. The first batches were used until the April session of 1989 and the second batches thereafter. The placebo was a standard vaccine preparation without the active particles. It was also produced by Institut Mérieux, France. All trial vaccines and the placebo were single dose vaccines. They were in similar containers with a standard label on them: A, B, C and D.

Vaccine storage

Vaccines were stored in a cold room at 4°C, at ORANA, Dakar. This room was checked regularly, once a month, by the manufacturer. There was no evidence of any change in temperature over the 30 months. Vaccines were transported in UNICEF large cold boxes from Dakar to the field station in Niakhar, once a month, on the Monday of the vaccination week. Vaccines were taken in supplies larger than needed and vials that were not used were taken back on the Friday of the vaccination week in the same conditions. At the Niakhar field station, vaccines were stored in the solar refrigerator which had an outside thermometer and a permanent registration of internal temperature. For the vaccination days, vaccines were taken in small UNICEF cold boxes. Trial vaccines were in individual vials. Other vaccines came in 10 or 20 doses vials. Live vaccines were reconstituted at time of use. Individual vials of reconstituted measles vaccine were never kept for more than a few minutes. Other vials of reconstituted vaccines (10 or 20 doses) were kept cold for about one hour.

Vaccine potency

After each vaccination session a sample of each measles vaccine was brought back to Dakar, deep frozen and then sent to Fajarah M.R.C. laboratory for analysis of potency. Various analyses were performed over time, including plaque formation and tissue culture infection. Hence results are expressed in PFU or in TCID50 and are not strictly comparable. A conversion rate can be applied for converting PFU in TCID50 depending on the vaccine strain according to the following chart 3.1:

Chart 3.1 : Conversion factors, according to method of potency determination

Vaccine strain	Adsorption method PFU / $TCID_{50}$	Ratio PFU / $TCID_{50}$
-	theoretical	0.69
Moraten	S / S	0.60
Schwarz	P / P	2.5
Schwarz	P / S	10.0
Edmonston-Zagreb	P / P	1.0
Edmonston-Zagreb	P / S	17.0

Source : Institut Pasteur-Mérieux.
P = virus adsorbed onto performed monolayers
S = virus adsorbed in dilute cell suspension.

Furthermore the tissue culture techniques were changed over time and later results were not directly comparable to others. In any case, results showed that there was no decrease in potency of any vaccine, even after 24 months of storage at 4°C (see annex A-7). Mean values for the EZ-HT vaccine averaged consistently 5.4 $\log_{10}$ pfu, the SW-HT vaccine 5.4 $\log_{10}$ pfu and the Standard vaccine 3.7 $\log_{10}$ pfu. Very high values for the EZ-HT vaccine at the beginning were probably due to excessive sensitivity of the cultures to the EZ virus.

Vaccine administration

Vaccinations for the trial were fully integrated in the national EPI. Vaccines were given at the local dispensaries by the local nurse, using the tools provided in late 1986 by UNICEF for the mass vaccination campaigns. Syringes and needles were reusable and sterilized in UNICEF pressure cookers.

Measles vaccines were injected subcutaneously in the left upper arm. BCG was given intra-dermatically in the right upper arm. DPTP vaccines were given deep subcutaneously in the left thigh. Children who did not come at the 5 months session but came at the 10 months session or later received measles and yellow-fever mixed in the same syringe. Children who came at the 5 months session (project children) received measles and yellow-fever separately, even in the placebo group that received measles and yellow-fever vaccines the same day; in this case yellow-fever was injected in the right thigh.

3.2 VACCINATION SESSIONS

Vaccination sessions were organized each month, usually in the week closest to the 15 of the month, sometimes a week earlier or later for convenience such as avoiding a holiday or a local festival. The vaccination team and the vaccines came from Dakar to Niakhar on Monday. There were three vaccination days: Tuesday in Ngayokheme, Wednesday in Toucar and Thursday in Diohine. The unused vaccines and the blood samples were kept cold and taken back on Friday to Dakar.

Calling infants

Two weeks before each vaccination session a list of children eligible for vaccination was printed by the computer. Two copies of the lists were given to the field workers. The first list was used by the field worker as a reminder. The second list was cut in small pieces used to convoke children (convocation), one for each child. The week before the vaccination session, at the time of the weekly visit, the field workers gave the convocation. Therefore, the family knew a few days in advance that the child was to be vaccinated, which day and in which dispensary. People were asked to come on their own if they could. Days of vaccination were chosen in agreement with market days. Tuesday was a market day in Ngayokheme, Wednesday was a market day in Toucar and Thursday was a market day in a village north of Diohine, Mbafaye. For each vaccination day people had many opportunities of finding a cart for transportation. If they did not come on their own, a car was sent from the dispensary to pick them up at home. This was done systematically for villages more than 4 kilometers away from the dispensary. Two or three cars were used for picking-up children, depending on the number of eligible children. There were 50 to 150 children vaccinated at each session day, depending on the dispensary, the number of cohorts eligible and the number of children who showed up although not convoked. The vaccination day started early in the morning and lasted until late at night, with about 30 minutes for lunch in the middle of the day.

The line of flow

Two other copies of the list of eligible children were also printed: one for the supervisor and one for the drivers. On vaccination day, the team arrived at the dispensary early in the morning. A line of flow was organized. First the mother had to check-in at the registration desk. One of the supervisors was sitting at that desk with his own list of eligible children. He had the tasks of registering the attendants, preparing the vaccination card, keeping the driver's list updated and sending the driver to pick-up missing infants village by village. Usually people came with their own convocation; in case they did not, the supervisor had to check the name and identification in his own register. Children not convoked were also welcome and identified the same way. These were older children, visitors or children who had missed an earlier session. After the first desk all infants were properly identified and all had a national vaccination card prepared. Children who participated in the project had a stamp put on their health card. The stamp warned that the child was in a vaccine trial and that he was not supposed to be re-vaccinated outside of the trial until July 1, 1989. However, a few children were vaccinated elsewhere (see below 3.4).

Anthropometry

The second desk in the line of flow was anthropometry. All children were weighted on a SECA 10 grams precision scale, measured on a locally constructed length board (2 mm precision) and had their arm circumference measured with an insertion tape (Talc, UK) with a 2 mm precision. Anthropometric measurement was written on a separate sheet, in the order in which children came in the

dispensary. Weight was also written on the national vaccination card and on the growth chart.

Clinical examination

The third desk was the clinical examination. A comprehensive clinical examination was conducted for each child. Emphasis was on any contra-indication to vaccination, any disease to be treated and malnutrition. Contra-indications were any evolving systemic infection for live vaccines and any history of seizure for DPTP. At each session, there were a few cases of contra-indication, usually high fever from various origin, malaria, pneumonia or other diseases of infancy. History of seizure was rare at that age. Sick children were treated when possible and brought back home or referred when necessary. Most common cases of sickness were: diarrhea, eye infection (conjunctivitis), ear infection (otitis media) and skin diseases. These were treated for free. Cases of severe malnutrition were referred to the nutritional rehabilitation center that ORSTOM "UR Population et Santé" was running in Pikine near Dakar at the beginning of the trial; after August 1988 children were referred to the centers that were opened in Toucar and in Fatick; mothers whose children were mildly malnourished were given feeding advice with the help of a local interpreter.

Vaccine identification

The fourth desk in the line of flow was the vaccine identification. This desk was manned either by the Bioforce or by one of the investigators. A register similar to that of the registration desk was available, printed by the computer with the vaccines that the child should receive. For measles vaccines, when the child was eligible, a letter was printed on the register, A, B, C or D. For other vaccines, the name of the vaccine was also written (BCG, DPTP, YF). The computer also printed whether the child was to have a blood sample taken or not. The name of the child was checked again at that time by calling his name to the mother to avoid any error, especially in the case of twins. However, a few mistakes were made: 5 cases of errors in identification were found at this point, out of 1606 children vaccinated at 5 months, usually because mothers mixed their cards after their arrival at the admission desk.

Blood sample

Blood samples were taken at this time from eligible children, usually the 5 and 10 month-old (fifth desk). Detachable stickers were used and the same number was stuck on the microtainer and in the register. Over the 24 sessions, a small proportion of women (5.0%) refused to have the blood sample taken. Most of them accepted the vaccination but a few decided at that time they did not accept it and left.

Vaccination

The last desk of the line of flow was the vaccination desk. Vaccines other than measles vaccines for the project came in 10 or 20 doses vials, prepared in advance and ready to use. Measles vaccines for the project came in individual vials. They were prepared by the person in charge of the vaccine identification desk which was close to both the blood sampling desk and the vaccination desk. The vaccine to be given, A, B, C or D, was given with the infant health card to the nurse in charge of the vaccination. Errors were very unlikely, although we noticed 3 cases of mixing vaccines over the 2965 children who came at 5 or 10 months. Project vaccines, A, B, C and D, were counted day by day: with the exception of the above noted cases, the count was correct. This does guarantee

a high degree of certainty to have administered the proper vaccines. However, it would have been easier to have had each measles vaccine vial given a sequential number and have written down the number on the register for later cross-checking.

Sometimes, a woman started the line of flow and later disappeared, usually after anthropometry where the waiting list was longer, or because she was afraid of the blood sampling she could see from the open door. These were called "évadées" (escaped) and usually identified at night when matching the admission register with the vaccine register.

All vaccinations performed by the team were transcribed into the dispensary register and a monthly report was sent to the Fatick Circonscription Médicale.

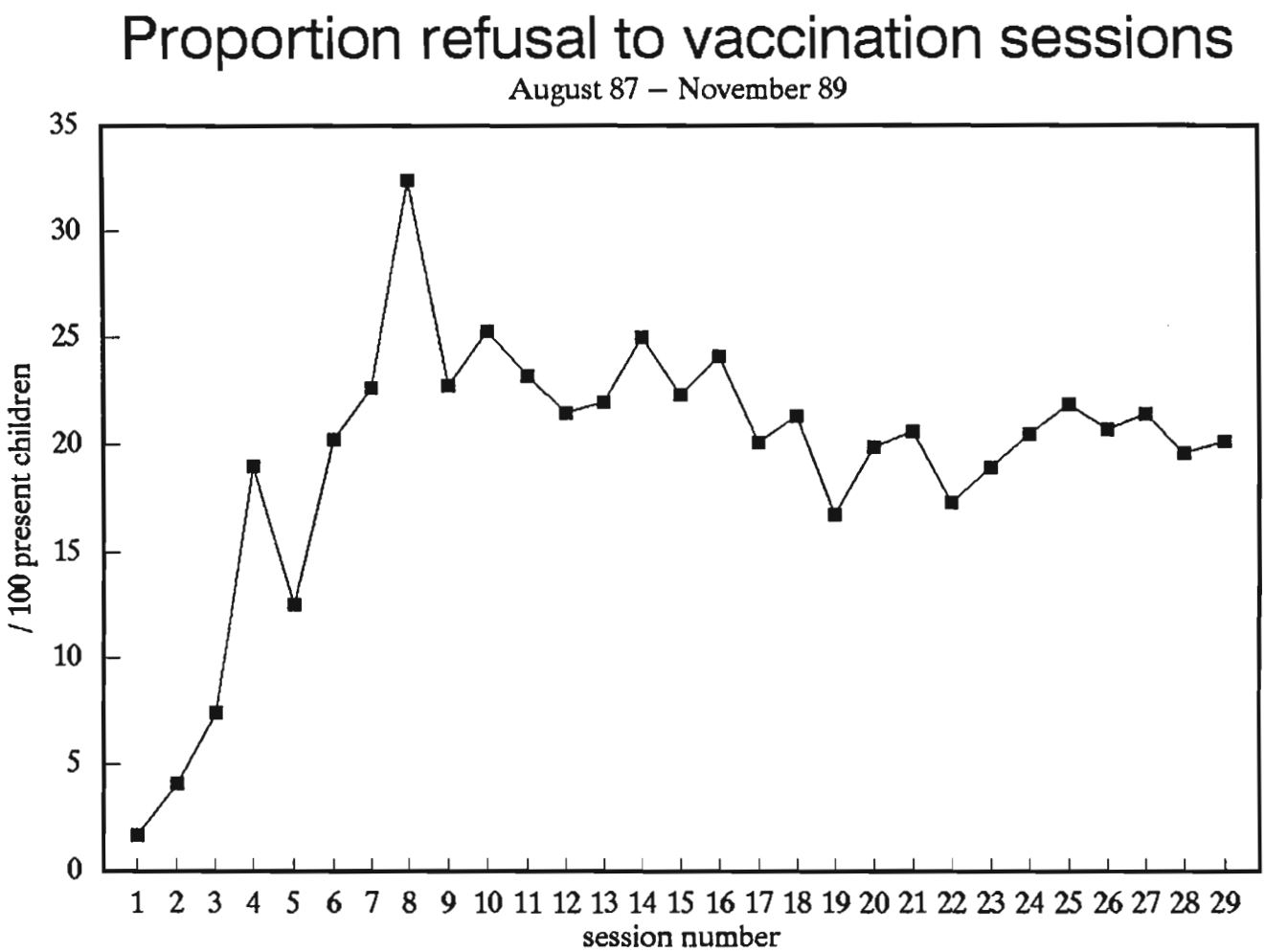
3.3 ATTENDANCE AT VACCINATION SESSIONS

Attendance at vaccination sessions was first classified by residence and participation in the study. Persons who were not resident in the study area were not counted. They appeared only in the dispensary register and statistics. Children belonging to the 24 cohorts, called "Project Children" were classified into "convoked" that is called for the 3, 5, 10 months vaccination sessions or for the later revaccination session and "not convoked" that is children who came by themselves outside of the scheduled sessions. Other children or persons who were vaccinated were classified as "other".

Project children whose age matched the vaccination session (3, 5, 10 months) could be resident, dead or emigrated at time of the session. If resident, they could be present at the session, absent from the village or present in the village but refused to come (refusal), whatever the reason for not coming. Children who came at the session but were not vaccinated because of contra-indication were treated as present. Children who did not complete the line of flow but registered at the registration desk (évadés) were treated as refusal. Children who were not convoked were separated into project children and others. Mortality and migration of project children was discussed earlier (see chapter 2).

Over the 29 sessions the proportion of refusal (refusal / refusal + present) averaged 19.9%. This proportion was lower at the beginning: 4.6% for the first 3 sessions, increased sharply after to peak at the eighth session (32.4%) and later stabilized around 20% (table 3.1; figure 3.1). There were three main reasons for refusal to attend the vaccination session when mother and child were in the village. The first reason was refusal to participate in the study, sometimes associated with systematic refusal of blood sampling and of any vaccination. A second reason was personal inconvenience, usually a family ceremony at home or within the village, often a funeral ceremony. A third and important reason was rumors against the project. These rumors were investigated during the first year of the project. They were based on irrational ideas, usually coming from one person, often associated with blood sampling (they are selling the blood of our children; they are sending the blood to cure old Europeans who are sick etc.). Rumors spread mostly within the extended family, first in the same village but also among other members of the family living in other villages. Rumors dissipated as fast as they started and there was no case of systematic refusal of the study over the 26 sessions, except in a few families in two neighboring villages, Sob and Diokoul. These were villages were the ORSTOM team has been known for the longest period and where we had several friends. However these were also villages where blood was taken in bad circumstances in 1968 for a nutrition study and it seems that the memory of these regrettable events was retained over the years.

Figure 3.1


Proportion refusal to vaccination sessions
August 87 – November 89
/ 100 present children
0
5
10
15
20
25
30
35
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
session number

Villages which were included in another vaccine trial against hepatitis B in 1978-1979 also had bad memories of blood sampling. However, the fact that we took only small amount of blood (0.5 ml) and that this was done openly in a room where everybody could see what was going on, greatly helped to overcome apprehension.

Among children who were not convoked, who accounted for 11.9% of the total number of vaccinated children, the majority (52%) were project children who were coming late (rattrapage); others (48%) were older children or adults who needed their vaccination series to be completed or visitors who took the opportunity to be vaccinated.

Attendance at the 5 months vaccination session was even higher than the average: 82% (table 3.2). Among cohorts 01-16, 1015 children participated in the study, 336 in the EZ-HT group, 322 in the SW-HT group and 357 in the Standard group; among cohorts 17-24, 576 children participated in the study, 292 in the EZ-HT group and 281 in the Standard group (table 3.3). Among children who came at 5 months, a majority came back at 10 months and therefore could participate in the immunogenicity study: 67.9 % among cohorts 01-16 and 78.0% among cohorts 17-24 (table 3.4). By December 1989, 80.8 % of resident children were vaccinated against measles, 82.9% among cohorts 01-16 and 79.6% among cohorts 17-24 (table 3.5).

3.4 AGE AT VACCINATION

In the regular schedule, children were to be vaccinated at 3, 5 and 10 months. The 3 month session was delayed at 8 months for the first 2 cohorts. In fact the trial started in August 1987, with the first 2 cohorts eligible for the 5 months vaccination session already too old for the 3 months session (table 3.6). They were vaccinated in October and November 87, at 8 months instead of 3 months and received BCG and DPTP-2. Cohort 03 was vaccinated at 4 months instead of 3. All other cohorts 04-24 were vaccinated at 9-17 weeks, or 3.0 months on the average (standard deviation: sd=0.36).

To be included in the project, a child had to attend the 5 months session. Outside of the first cohort which was vaccinated at 6 months in August 1987, all the others were vaccinated at 5 months, age being counted in difference of months. 5 months, in difference of months, was roughly equivalent to 20-24 weeks of age. However some were vaccinated earlier and some later. Table 3.6 displays the distribution of age at the 5 months vaccination session by birth cohort. Ages lower than 20 weeks were those born late in the month who were vaccinated in a session set up early in the month; ages higher than 24 weeks were those born early in the month who were vaccinated in a session set up late in the month. For cohorts 02 to 24, 89.7% of the children were vaccinated between 20 and 24 weeks, 7.4% before 20 weeks and 2.9% at 25 weeks; the first cohort was vaccinated at 24-28 weeks. This rather small age range was important to consider since the level of maternal antibodies decreased rapidly over this period and 20 weeks was the threshold below which vaccines have a much lower uptake. This point is discussed further below (see 5.8). For cohorts 02-24, the mean age at vaccination was 5.0 months (sd=0.35); for cohort 01 the mean age at vaccination was 6.0 (sd=0.30).

The 10 month session was conducted as scheduled for all cohorts, in general between 41 and 46 weeks of age. The mean age at vaccination was 10.0 months (sd=0.35). Project children who were not convoked could receive their measles vaccine at any age after 10 months.

The interval between the 5 months and the 10 months sessions also had a

small range (table 3.7). This interval is important for the study of immunogenicity since antibodies decay with time, as well as for the study of efficacy since not all children were exposed to the exact same length between the two sessions. Except for the first cohort for which it was 3.7 months (16 weeks), the interval between the 5 months and the 10 months sessions was 5.0 months (sd=0.26) with a range from 20 to 24 weeks. There was no difference among the vaccination groups.

3.5 INCLUSION AND EXCLUSION RULES

To be included in the study a child must:
- have been born to a resident mother between February 1, 1987 and January 31, 1989;
- have attended the clinic at 5 months for vaccination and have parental agreement to participate;
- not have had any contra-indication to measles vaccination, i.e. evolving infectious disease, history of convulsion, previous measles infection or previous measles vaccination;
- not have been revaccinated with another measles vaccine between 5 and 10 months.

Children who accidentally did not receive the scheduled vaccine were also excluded (chart 3.2).

Chart 3.2 : Cases of exclusion among 2470 children of the 24 birth cohorts

No longer resident (dead or outmigrated):	277	(11.2 %)
Not present (absent or refusal) :	587	(23.8 %)
Contraindications to vaccination :	11	(0.4 %)
Errors in identification (5), vaccine (2)	7	(0.3 %)
Participants	1588	(64.3 %)
Total	2470	(100 %)

3.6 REVACCINATION

In two separate instances, children were called back after the 10 months session to be revaccinated. In the first instance, children who were vaccinated with one of the high titer vaccines who were seronegative at 10 months were revaccinated with either the EZ-HT vaccine or with the Standard vaccine. There were 49 children for whom this was the case, of whom 37 came for revaccination (session 22). Children were randomly allocated to a group: 14 received the EZ-HT vaccine and 23 received the Standard vaccine (chart 3.3).

Chart 3.3 : Status of seronegative children called at session 22 for revaccination with a measles vaccine (cohorts 01-16)

Residence status	Previous vaccine at 5 months EZ-HT	SW-HT
Emigrated/dead	0	4
Absent/refusal	2	6
Present : EZ-HT	1	13
Standard	4	19

All children of cohorts 01-16 who were incompletely vaccinated after the 10 months session, were also called back systematically, by groups of 4 cohorts, from session 23 to session 26 (chart 3.4). Other children were revaccinated in May 1990.

Chart 3.4 : Calendar of cohorts called back for completing EPI vaccination

Cohorts	Session	Age range (in difference of months)	N
01-04	23	24-27	79
05-08	24	21-24	51
09-12	25	18-21	45
13-16	26	15-18	48

3.7 SUMMARY OF MAIN POINTS

Attendance at vaccination sessions was high: 80.1 % of present children. Few women refused the blood sample at time of vaccination (5.0 %). Outside of firm refusal to participate in the study, cases of refusal were often due to personal inconvenience; others were due to fears of vaccines based on various rumors circulating in the study area.

Altogether, 1589 children of the 24 births cohorts were vaccinated at age 5 months and therefore could participate in the study.

Age at vaccination was kept within a narrow range (sd=0.35 months) around 3.0, 5.0 and 10.0 months, with the exception of the first 3 cohorts.

Randomization between the three groups was fair and there was no evidence of any bias at this level.

37 children from cohorts 01-16, who were seronegative at age 10 months, were revaccinated with either the EZ-HT or the Standard vaccine.

223 children from cohorts 01-16, who were incompletely vaccinated after the 10 months session, were revaccinated at sessions 23 to 26.

CHAPTER 4

SAFETY

The safety of the high titer measles vaccines was investigated with three indicators: mortality, morbidity and specific adverse reactions. Therefore, this chapter is divided into three independent parts. Mortality was investigated until October 1990. Morbidity and adverse reactions were investigated until December 1989. The analysis of nutritional status was integrated into the morbidity part.

PART I : MORTALITY

The study of mortality after early vaccination with high titer vaccines was part of the original protocol. It was expected that early vaccination against measles would prevent deaths and therefore improve child survival. In addition, mortality was considered as a safety check because cases of severe measles were reported after earliest vaccinations in the 60's with the Edmonston-B vaccine, even though this was a killed vaccine. When first results of mortality differences were found significant, in the Spring of 1990, it was decided to do further checks on the data: one was done in the Fall of 1990 and another one at the time of the 1991 Census. Results presented here integrate all deaths reported at the 1991 Census that occurred prior to October 1990.

4.1 LIFE TABLE RESULTS

Computations

Mortality was computed separately and differently in the various age groups. From birth until the 5 months vaccination session and between the 5 months and the 10 months vaccination sessions information on child survival was complete: whether the child was alive or dead at the exact day of the scheduled session was known. Therefore, probabilities of dying were computed directly by dividing the number of children dead at the date of the vaccination session by the total number of children at risk at the beginning of interval in the same cohorts.

After 10 months, the survival of the child was known only until the end of observation, at which children's age ranged from 21 to 44 months. In this case, computations were done by computing a monthly life table. Cases were removed from analysis (censored) when they outmigrated or when they reached the end of the study.

Comparisons between vaccine groups

Three kinds of comparisons could be made according to vaccine group:
1) From birth to 5 months, according to the 3 groups randomized at birth.
2) From 5 to 10 months or from 5 months until the end of the study, according to the three randomized groups that received the EZ-HT, the SW-HT and the placebo at 5 months; children who did not participate in the study were counted separately.
3) From 10 months until the end of the study, according to the three randomized groups that received the EZ-HT, the SW-HT and the Standard at 10 months; other children were counted separately, even when they received a Standard vaccine after 10 months.

The four children who accidentally received a vaccine that was not scheduled were excluded from the analysis. There were no deaths among them.

Mortality from birth to 5 months

Since vaccination groups were allocated at time of birth, it was possible to compute mortality by vaccination group although children were not yet vaccinated. This was done to check whether randomization was fair, that is if there was no selection bias associated with vaccination groups.

Results appear in table 4.1. For the 24 cohorts participating in the study, mortality from birth until the 5 months session averaged 81.4/1000, 64.4/1000 in the neonatal period (0 to 27 days) and 18.2/1000 from 28 days until the day of the 5 month session. There were no significant differences between the three groups, which indicates that randomization was equitable.

Mortality from 5 to 10 months

For mortality between 5 and 10 months, results were less homogenous (table 4.2). The EZ-HT group consistently had the lowest mortality (23.8/1000 for cohorts 01-16 and 6.8/1000 for cohorts 17-24). The SW-HT had the highest mortality among cohorts 01-16 (46.4/1000). However, none of those differences was significant, even when the 24 cohorts were cumulated. The non-participant group had a mortality similar to the placebo group.

There was also no evidence of any clustering of deaths within the 6 weeks after the vaccination at 5 months in any group. Among the causes of death of children who died within 6 weeks after the 5 months vaccination session, there were in the EZ-HT group: 1 diarrhea, 1 hydrocephaly, 1 unknown; in the SW-HT group: 1 diarrhea, 1 unknown; in the Placebo group 2 cases of diarrhea; in the non-participant group 1 pneumonia. Here also no pattern emerged.

Chart 4.1 : Cumulated mortality after 10 months, by group and cohort.

Vaccine group	Death rate / 1000	RR	95 % CI	T	P (2 tail)
Cohorts 01-16					
EZ-HT	147.7	2.50	1.52 - 4.13	3.537	0.0004
SW-HT	102.1	1.73	1.00 - 2.98	1.915	0.0560
Standard	59.0	1.00 (ref)			
Not participant	89.6	1.52 (NS)			
Cohorts 01-24					
EZ-HT	127.8	1.94	1.26 - 2.99	2.847	0.0044
Standard	65.8	1.00 (ref)			
Not participant	90.6	1.38 (NS)			

Figure 4.1

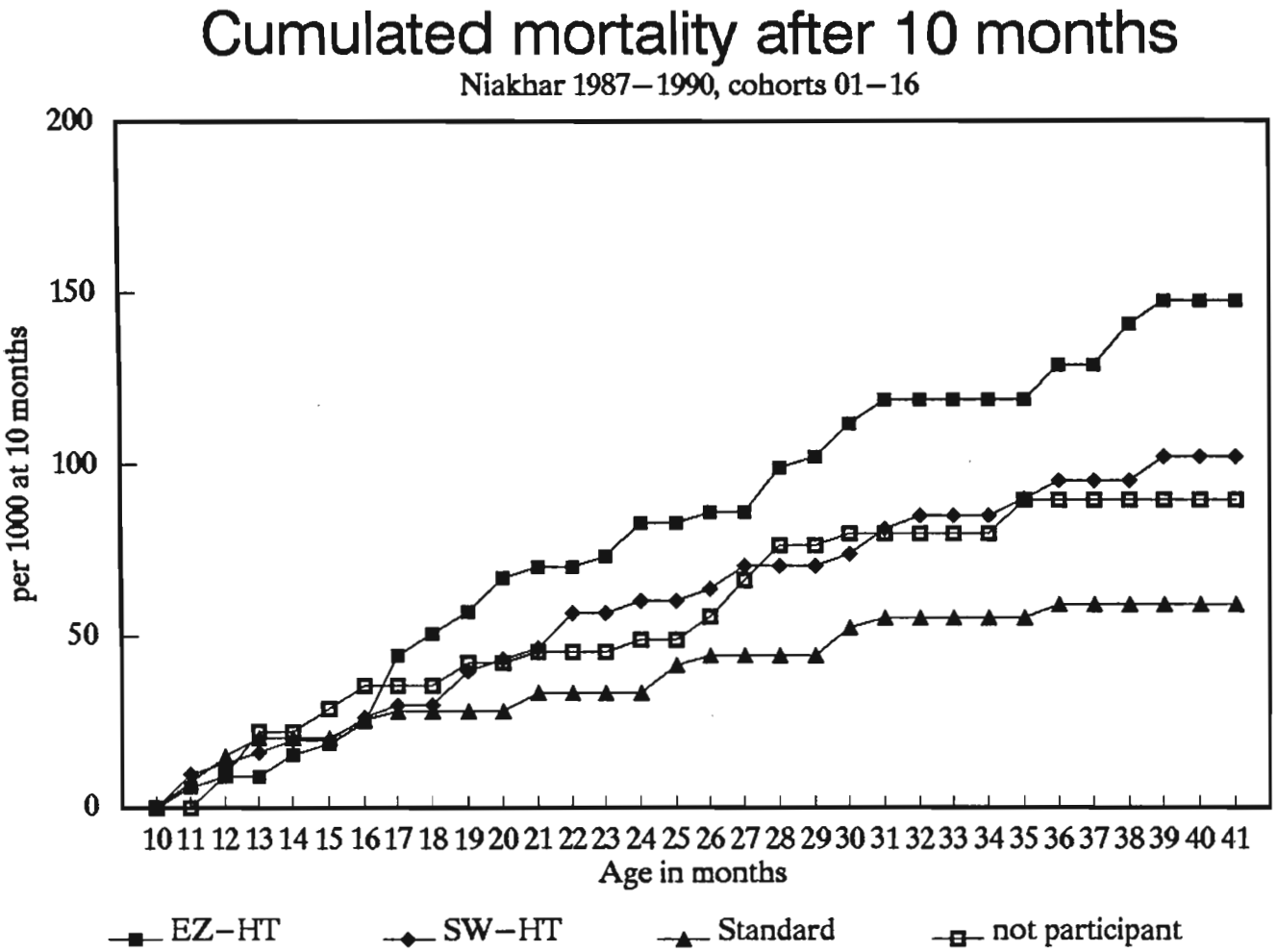
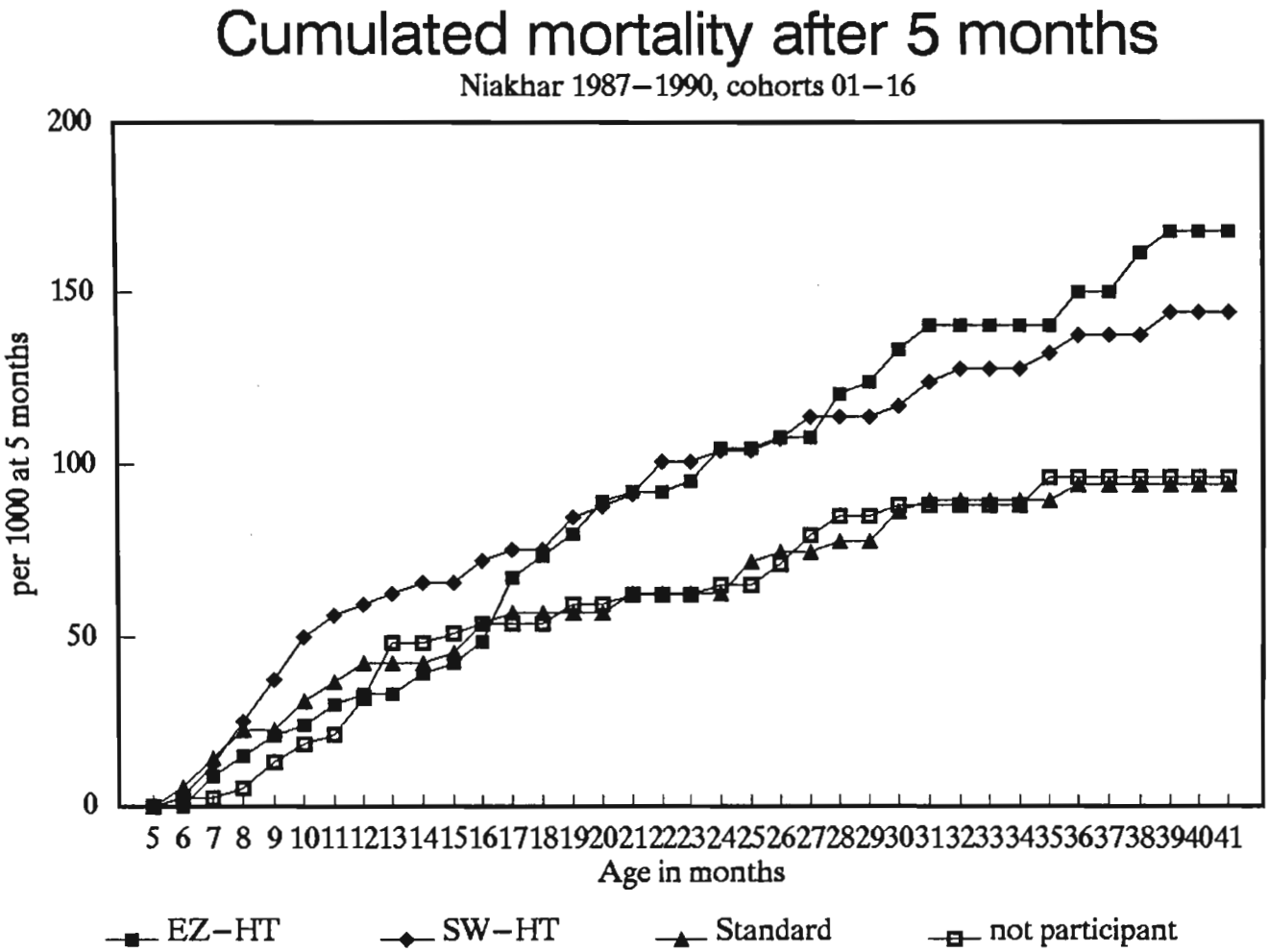

Cumulated mortality after 10 months
Niakhar 1987–1990, cohorts 01–16
200
150
100
50
0
per 1000 at 10 months
10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41
Age in months
EZ–HT
SW–HT
Standard
not participant

Figure 4.2


Cumulated mortality after 5 months
Niakhar 1987–1990, cohorts 01–16
per 1000 at 5 months
200
150
100
50
0
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41
Age in months
EZ–HT
SW–HT
Standard
not participant

Mortality after 10 months

Results of the life table analysis of mortality after 10 months are presented in table 4.3 and summarized in chart 4.1. There was a marked excess of deaths between 10 months and the end of the study in the two groups that received high titer vaccines at 5 months (figure 4.1). For cohorts 01-16, the EZ-HT group had a 2.50 higher mortality than the Standard group (CI=1.52-4.13, P=0.0004) and the SW-HT group had a 1.73 higher mortality (CI=1.00-2.98, P=0.0560). Even when results were grouped with cohorts 17-24 there was still a highly significant excess mortality in the EZ-HT group: RR=1.94, CI=1.26-2.99, P=0.0044. Mortality in the non-participant group was not significantly different from mortality in the standard group.

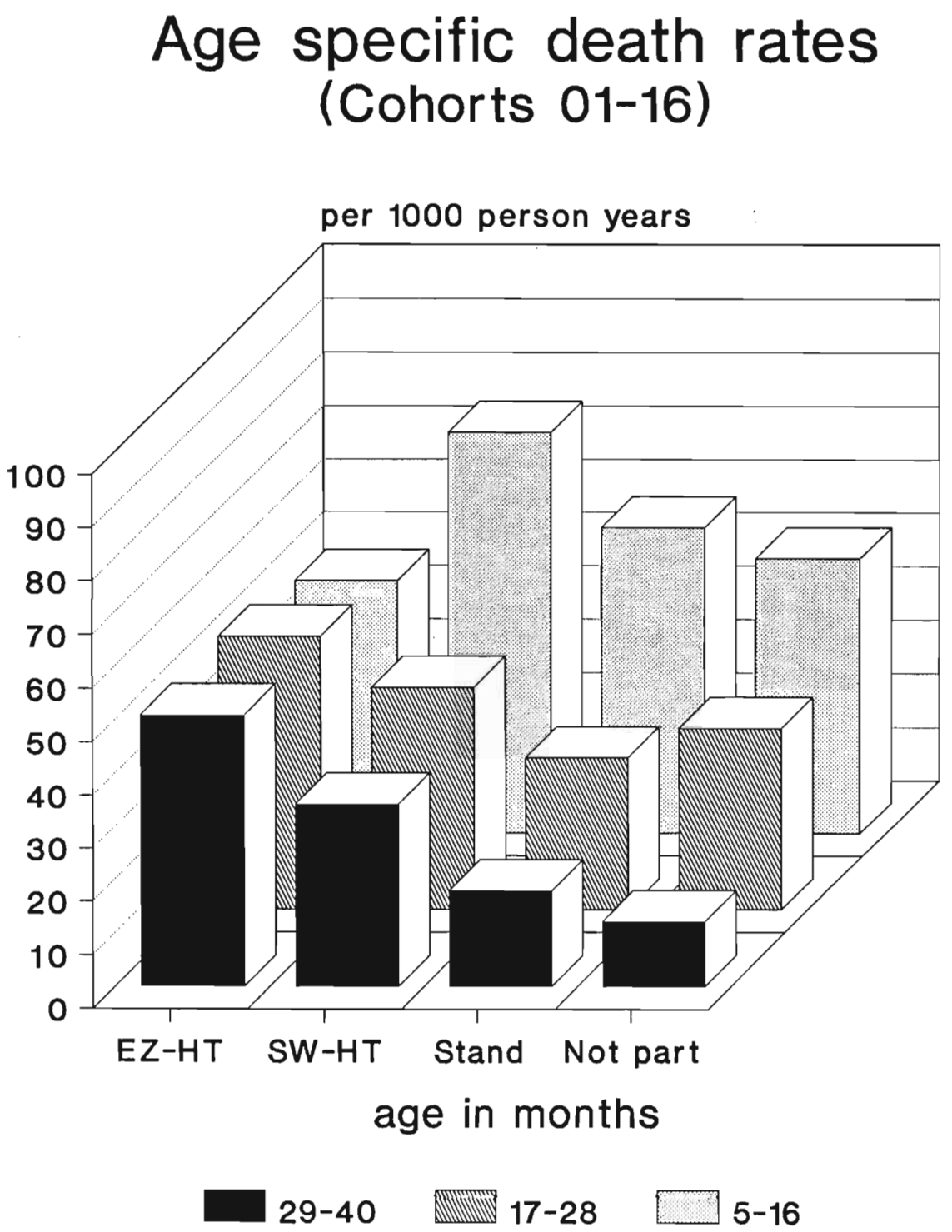
Mortality after 5 months

The life table analysis was repeated starting at 5 months for the three randomized groups, whether or not children in the Placebo group at 5 months received the Standard vaccine at 10 months. Results are displayed in table 4.4 and figure 4.2 and summarized in the following chart 4.2. Here again, the two groups receiving the high titer vaccines had an excess mortality when compared to the Standard group: RR=1.80, CI=1.18-2.74, P=0.0070 in the EZ-HT group; RR=1.53, CI=0.99-2.37, P=0.0564 in the SW-HT group. The group that did not participate had a mortality similar to that of the standard group. When grouped with the last 8 cohorts, mortality was higher in the EZ-HT group (RR=1.41), but the difference was no longer significant (P=0.0756).

Chart 4.2 : Cumulative mortality after 5 months, by group and cohort.

Vaccine group	Death rate / 1000	RR	95 % CI	T	P (2 tail)
Cohorts 01-16					
EZ-HT	168.2	1.80	1.18 - 2.74	2.706	0.0070
SW-HT	144.0	1.53	0.99 - 2.37	1.911	0.0564
Standard	94.0	1.00 (ref)			
Not participant	96.2	1.02 (NS)			
Cohorts 01-24					
EZ-HT	141.8	1.41	0.97 - 2.05	1.778	0.0756
Standard	100.5	1.00 (ref)			
Not participant	95.0	0.95 (NS)			

Figure 4.3


Age specific death rates
(Cohorts 01-16)
per 1000 person years
100
90
80
70
60
50
40
30
20
10
0
EZ-HT
SW-HT
Stand
Not part
age in months
29-40
17-28
5-16

4.2 ANALYSIS OF EXCESS MORTALITY

Since all excess mortality was concentrated at older ages and therefore among the first 16 cohorts, this analysis focuses on factors of mortality among cohorts 01-16.

Randomization

Analyses were undertaken to determine whether the vaccine groups were comparable (table 4.5). The 3 groups were similar with respect to the following variables: age of mother, mother's literacy, size of residential compound, distance to dispensary, past mortality of older children of the same mother, proportion of outmigrants, overall death rate in compound during the study period, and mortality in the randomized groups from birth to 4 months. Children in the non-participant group were from families with a similar background, but they lived in compounds with a higher overall death rate.

In addition, average age at vaccination, weight, height, and circumference of the mid-left-upper-arm of children from the 3 vaccine groups were similar at age 5 months (table 4.6).

Clustering of deaths

To verify whether any unexpected event could have accounted for the excess mortality, such as an undetected epidemic, deaths were distributed by month and village (table 4.7). There was no evidence of unexpected clustering of deaths according to date or place of residence. There was a marked excess of deaths in the rainy season (July to October) in all groups and in the large villages (V6, V19, V21, V22).

Causes of death

The demographic survey routinely recorded information on causes of death, that were later interpreted in "probable causes of death", using the so-called "verbal autopsy technique". The method has been presented elsewhere (Garenne and Fontaine, 1986). Children apparently died of common diseases of childhood (table 4.8). In the EZ-HT vaccine group, there was a high number of deaths attributed to kwashiorkor (9 cases) and to viral diseases other than measles (5 cases). Five out of 6 dysentery deaths and 8 out of 10 deaths due to acute respiratory infections were in the SW-HT group. The only accidental death and the only death attributed to measles were among the non-participants. The frequency of other diseases and unknown causes of death was similar in the four groups.

Age Pattern

The number of deaths was comparable among the three groups during the first year after vaccination (table 4.9). It became higher in the groups that received the high titer vaccines only in the second and third years (figure 4.3). Relative risks of death after 17 months were 2.76 in the EZ-HT group (CI=1.40-5.42) and 1.90 in the SW-HT group (CI=0.92-3.91).

Earlier data from the same population showed that 17 to 41 months of age was a period of high risk for children, in part associated with a peak of severe malnutrition (Cantrelle, 1974; Garenne, 1981; Garenne, 1982; Garenne et al.

1987).

Sex differences

There was no significant difference in mortality by sex in any of the groups: the relative risk of death (females/males) was 1.20 in the EZ-HT group (CI=0.68-2.10, P=0.497), 1.14 in the SW-HT group (CI=0.62-2.10, P=0.636), 0.64 in the standard group (CI=0.31-1.31, P=0.195), and 1.16 (CI=0.60-2.24) among the non participants (P=0.640). Baseline data, going back to 1963 in the same population, showed no difference in mortality by sex beyond the neonatal period. However, most of the effect of excess mortality between the high titer vaccine groups and the Standard group was among the females (the differences between the male groups were not significant). This could be explained by the random fluctuations in the sex ratio of deaths among the groups, none of which was significant: due to random fluctuations, there were more female deaths in the high titer vaccine groups and less in the Standard group.

Seasonality

Mortality had a strong seasonal component, death rates being much higher during the rainy season (table 4.9). Most of the excess mortality was concentrated in the rainy season. Relative risks of deaths in the rainy season, as compared to the dry season were 7.67 in the EZ-HT group (CI=3.73-15.78), 3.90 in the SW-HT group (CI=2.03-7.50), 2.56 in the Standard group (CI=1.26-5.18) and 2.89 (CI=1.46-5.59) in the Non-participant group.

The pattern of deaths according to the season of vaccination was more mixed. There was an excess of deaths among children vaccinated in the rainy season in the EZ-HT group and in the corresponding cohorts of the non participant group; on the contrary, there was an excess of deaths in the SW-HT group and in the corresponding cohorts of the Standard group. Although these differences were statistically significant, we could not find a reasonable explanation for these inconsistencies and these differences were considered to be due to random fluctuations.

Multivariate analysis

To simultaneously analyze the net effect of these different variables, two types of multivariate analyses were carried out. The first procedure was a Cox proportional hazard model. This model assumes that the relative risk of deaths among the groups remains constant over time. This assumption was not fulfilled because of the strong seasonality of deaths: a child vaccinated at 5 months in January did not have the same risk of death at 12 months, in the middle of the rainy season, than a child vaccinated in August. Note that the magnitude of the perturbation, from 2.5 to 7.7 largely exceeds the magnitude of the relative risks investigated (1.5 to 1.8). Despite the fact that the fit was poor, results were consistent with the univariate analysis (table 4.10). The EZ-HT group had a relative risk of death of 1.70 (P=0.0204) and the SW-HT group had a relative risk of death of 1.51 (P=0.0778). Other variables (sex, season of vaccination, age at vaccination) had no significant impact. Due to the structure of the model, age and season could not be introduced as covariates.

A second model was developed to include the age and season effects. Periods of exposure to mortality were decomposed into periods of 4 months corresponding to the 3 seasons of the year: July to October (rainy), November to February (dry-cool), and March to June (dry-hot). Separate models were tested for each vaccine group. Results of the effect of the vaccines remained stable when controlling

for other variables: age, sex, age at vaccination, season, season of vaccination, measles antibody titer at 5 months, and seroconversion between 5 and 10 months of age. The EZ-HT vaccine had an odds ratio of 1.53 (P=0.0204) and the SW-HT vaccine an odds ratio of 1.49 (P=0.0778) (table 4.11). The coefficient of the rainy season was always high and significant and was greater in the two vaccinated groups. Sex, level of antibodies at 5 months, and seroconversion between 5 and 10 months of age were not significant in any group.

Conducting the same multivariate analyses by vaccine group revealed that the coefficient of age in the EZ-HT group was close to zero, whereas it was significantly negative in the other groups. This finding indicates that mortality remained consistently high in the second and third year after the EZ-HT vaccine, whereas in other groups death rates declined with age as expected. The failure of mortality rates to decline as is customary with aging of children is an area of future concern.

Simulations

The logistic model did not simultaneously integrate all the information on survival. Although both the Cox model and the Logistic model gave similar results with different hypotheses, it was felt important to directly evaluate the effect of any possible bias in the samples and to obtain testing procedures that could at the same time control for age, period, cohort and sex effects. This was done by developing a Monte Carlo simulation model. The mortality experience of each child was simulated directly beginning at 5 months until the end of the study. Hypotheses were the following:

a) the monthly probability of dying declined with age;
b) mortality was the same in each vaccine group;
c) mortality was 3.1 higher during the rainy season;
d) there were no sex differences in mortality.

1000 samples for each vaccination group were generated on a personal computer. Results (table 4.12a) revealed that by the mere effect of differences in the composition of the groups one could expect 6.7% less deaths in the EZ-HT group and 10.4% less deaths in the SW-HT group than in the Standard group: biases in the sample would tend to diminish actual differences in the mortality. Testing directly the differences between the logarithms of the observed and expected deaths in the EZ-HT group produced again consistent estimates of the relative risk: RR=1.65, CI=1.14-2.39, p=0.008; in the SW-HT group, estimates of the relative risk were: RR=1.48, CI=1.02-2.15, p=0.041.

The simulations also allowed direct testing of various events (table 4.12b). In particular, sex differences were again found to be not significant. The only significant event, other than the total number of deaths, was the high proportion of deaths in the rainy season in the EZ-HT group (P=0.012).

4.3 DISCUSSION

Comparison of statistical procedures

Differential mortality between the groups was tested by eight different statistical procedures: life table, death rate, probability of death, age standardized death rates, linear logistic regression, proportional hazards, log-rank tests and simulations (table 4.13a and b). They showed a consistent level of significance of mortality differences with respect to the standard vaccine group (p=0.007 to 0.024 for the EZ-HT group and p=0.041 to 0.094 for the SW-HT group).

Consistency of the data

The consistency of the data, both in the groups vaccinated with high titer vaccines and in the groups not given the high titer vaccines was striking. The probability of concurrent occurrence of at least 50 deaths in the EZ-HT group and at least 42 deaths in the SW-HT was very low ($p<0.0001$). Since the high titer vaccines produced by two different companies had similar effects, it is unlikely that the excess mortality was due to a production defect such as contamination.

Level of mortality in the Standard group

The possibility of abnormally low mortality in the Standard group was considered but ruled out by the data analysis. Since 1963, there has been a long term trend of declining mortality at age 5 to 41 months. Because of medical services provided during the project, overall mortality was reduced between 1987 and 1989. Extension of the trends predicts a mortality of 91/1000 during the study period, versus the empirical value of 93/1000 found in the standard vaccine group. Furthermore, the level of mortality among the non-participants was similar to the level of mortality in the Standard group.

Measles incidence

The finding of an excess mortality in the vaccinated groups was possible because 1) the incidence of measles was low during the study period (68 cases among the study children), 2) the measles case fatality rate was also low as a result of intensive medical care provided during the project. The only child who died from measles was away from the study area and was a non-participant in the study.

Effect of censoring outmigrants

The fact that children who migrated out of the study area were counted as removed (censored) at the time of their move did not affect the results. An attempt to find those who died after outmigration indicated that including them would not have affected the results. There were 11 deaths: 3 in the EZ-HT group, none in the SW-HT group, 1 in the standard group, and 7 in the non-participant group, which included most of the outmigrants. The difference between the EZ-HT and the standard group would have been even larger (20 deaths) if deaths among migrants had been included.

Other cohorts

Later cohorts also were vaccinated with the EZ-HT vaccine at 5 months: cohorts born between June 1988 and January 1989 were randomized and cohorts born between March 1989 and May 1990 were not randomized. It is too early to judge the mortality of those cohorts, but mortality in the EZ-HT group, although lower than in previous cohorts, thus far has not declined with age.

Prevalence of HIV

The prevalence of HIV infection was low in the study area: only 2 out of 401 project children sampled at age 3 months were found to have HIV antibodies

and none of them died. A sero-prevalence of 0.5% was found among pregnant mothers of the study area. Thus HIV infections could not have played a role in this study.

Biological plausibility

Short term effects of live virus vaccines on child immunity have been observed, but their association with mortality has not been documented (Gandra and Scrimshaw, 1961; Baer et al. 1981; Hirsh et al. 1981). In a recent study in the Niakhar area, a low response to yellow-fever vaccination was found when given in association with the EZ-HT vaccine (personal communication of Dr Gonzalès). A measles vaccine was found to have an effect on weight in India (Kielman, 1977).

The wild measles virus has severe adverse short term effects on immunity and nutritional status of children, in particular on nitrogen metabolism (Wilson et al. 1961) and vitamin A (Oomen, 1958). In addition, the wild measles virus can have long-term effects, such as subacute sclerosing panencephalitis (Choppin, 1981).

There was no reason to suspect excess mortality after measles vaccination in the study area: earlier findings in the study area and in a nearby area showed that survival was better among children vaccinated with a standard measles vaccine, even when given before 6 months of age (Garenne and Cantrelle, 1986). Therefore we suspected the high titer to be primarily responsible for the effect.

Excess mortality became significant for the first time in the Spring of 1990, several months after the last child completed the vaccination series. However, children who participated in the study had a mortality not higher than preceding cohorts and children who did not receive the high titer vaccines had a better chance of survival than preceding cohorts (table 4.14). Overall, the population benefitted from the project in terms of survival.

PART II : MORBIDITY, NUTRITIONAL STATUS AND ADVERSE REACTIONS

4.4 MORBIDITY

Morbidity was recorded routinely by the field workers from the date of the first convocation (the 3 months session) until the first birthday. Signs and symptoms were recorded on a morbidity sheet and then coded at the end of each episode. All morbid episodes reported by the mother for children present in the study area were registered and coded, whatever their nature.

Computations

The main parameter used in this analysis is "incidence", the ratio of new episodes to person-years at risk. Periods at risk were computed by discounting periods during which a child was not present in the compound and during which no morbidity record could be made, usually when the child travelled outside of the study area for a couple of weeks. Details of computations appear in table 4.15. Children spent on the average 4.8% of their time outside of the study area, which induces a minor correction in estimates of incidence.

Morbidity is more difficult to record than mortality. This can easily be shown by comparing the number of episodes recorded by each field worker (table 4.16). The two most productive field workers (# 1,2) recorded 2 to 3 times more episodes than the two least productive (# 10,11), and 28% more than the average. This gives a magnitude of the inaccuracy of the data, in lieu of which correcting for absences appears to be of minor importance.

A list of major morbid episodes appears in table 4.17, with their frequency expressed as the number of episodes per person-years at risk for 3 age groups: 3-5 months, 5-10 months and 10-12 months. Here again 3, 5 and 10 are the exact dates of the vaccination session and 12 months is the exact birthday. The analysis by group will emphasize diarrhea, fever, cough and skin rashes since these are the most sensible symptoms for our purpose.

There were no difference in any of the 4 major symptoms between the vaccination groups. The study was restricted to the first 16 cohorts (table 4.17, table 4.18). A more detailed study of the frequency of morbid episodes within 21 days after the 5 months and after the 10 months vaccination session did not reveal any significant difference either. The analysis was pursued by sex (table 4.19) but again no clear pattern emerged that could match the mortality findings.

4.5 REPORTS OF CONVULSIONS

Lastly, all mother's reports of convulsions were investigated, with special attention to the four weeks after vaccination. Again, no clear pattern emerged. Most convulsions within 28 days after vaccination were after the 10 months session (table 4.20). There was a high number of convulsions after 28 days after the 5 months vaccination, both in the EZ-HT and in the placebo group.

A case of severe encephalitis of unknown origin was reported and treated in Dakar, at Fann and Le Dantec hospital. This was the case of a 12 months old boy who received the EZ-HT vaccine at 5 months. He had a series of convulsions for several days until he was seen for the first time by a physician and referred to Dakar. He went blind for about 8 months, after which he recovered gradually

part of his sight.

Another case of severe convulsions leading to death was reported. A girl, was vaccinated at 5 months with the EZ-HT vaccine. She developed high fever 2 days after vaccination and convulsions of unknown origin 6 days after vaccination. She was seen once by a physician, but left the study area the following day and died 11 days after vaccination. The cause of death was unknown.

4.6 NUTRITIONAL STATUS

The nutritional status of children was assessed at each vaccination session, using measures of weight, height and arm circumference. A comparison of the anthropometric measurements of children who died after the EZ-HT vaccine with those of other children did not reveal any association (table 4.21). This indicates that there was no evidence of an interaction of the EZ-HT vaccine with nutritional status, either at time of vaccination, or at 10 months. However, children who died after the SW-HT vaccine was administered to them had a consistently lower anthropometry than the mean population, at 3, 5 and 10 months. The difference was significant only for one measurement at 3 months. Although this effect would require a thorough examination, it suggests that there may have been a selection of malnourished children among the ones who later died after receiving the SW-HT vaccine.

4.7 ADVERSE REACTIONS

After the second meeting of the Data Monitoring and Safety Committee it was agreed that the recording of morbidity from mother's declaration was insufficient and that a specific examination by a physician of a sample of children within the next two weeks after vaccination should be conducted. This was done for birth cohorts 10 to 24 (April 88 to June 89).

A double sampling procedure was used for this procedure. The first step was to prepare a random list of eligible children, by dispensary. This was done by computer before the vaccination session. All eligible children were assigned a random number, then ranked. The second step occurred after the vaccination: the first 5 children effectively vaccinated on each dispensary list were selected, a total of 15 children. Then, each of these children were seen 5 times, on the next 3 Fridays and 2 Mondays after the vaccination session. Since vaccination sessions were conducted on three different days, children vaccinated on Tuesday were seen on day 1,4,8,11 and 15, children vaccinated on Wednesday were seen on day 2,5,9,12 and 16, children vaccinated on Thursday were seen on day 3,6,10,13 and 17. Most of the days after vaccination were covered except day 7 and 14. Children who still had a rash after the last day were seen for a longer period, until the end of the rash.

Emphasis was put on rashes. Children have many skin rashes at this age. There is a high incidence of 2.6% episodes within 15 days reported by the mothers and of 9.8% episodes seen by the physician, or 3.8 times more (table 4.22a). The physician may have missed short episodes since he came only every 3 or 4 days. One of the most common skin rashes was miliaria. Miliaria bears some similarity with mild measles rashes: it is a papular generalized rash often starting on the face and followed by desquamation. Measles rash in natural measles occurs 8 to 16 days after contamination. Hence all measles like rashes which occurred during the second week after vaccination could be interpreted by the physician as measles-like rashes. The physician was blind to the type of vaccine received, therefore it was possible for him to interpret a miliaria as a measles-like rash in the placebo group if by chance it occurred at the right time. And in fact this did happen.

Post vaccination measles like rashes were defined as a papular rash, which occurred about 8 to 16 days after vaccination, started on the face, invaded symmetrically all or most of the child body within a few days and followed by desquamation. 22 measles-like rashes were found in the sample of 224 children examined by the physician, 10 out of 87 children in the EZ-HT group (11.4%), 6 out of 35 children in the SW-HT group (17.1%) and 6 out of 102 children in the placebo group (5.8%). There were more rashes classified as measles-like in the SW-HT (P=0.0420) and in the EZ-HT group, although the difference was not significant (P=0.1672) than in the placebo group (table 4.22b).

We propose to interpret this result the following way. Measles like rashes were a genuine effect of high titer measles vaccine given at 5 months since the incidence was higher in the vaccinated groups than in the placebo. But among these, there was a proportion of rashes which were in fact miliaria rashes occurring at the expected time and which did not have anything to do with measles. If this is true there was a proportion of 5.8% false observations in each group (this is the figure from the placebo group), which corresponded to the true incidence of skin rashes in this population over a 8 days period. Hence, we estimated the proportion of adverse reactions to be: 11.3% (=17.1-5.8) in the SW-HT group and 5.6% (=11.4-5.8) in the EZ-HT group. These results roughly match the results from the Mexico study (Markowitz et al. 1990).

In addition, the physician also examined any episode of diarrhea or fever during the five visits. There were no significant differences between the three groups, as was the case for the incidence of the same diseases reported by the mothers.

4.8 SUMMARY OF MAIN FINDINGS

Vaccination with the EZ-HT and with the SW-HT vaccines at 5 months does not appear to be safe. There was an excess of mortality among children who received high titer vaccines when compared to those who did not.

Most of the excess mortality was concentrated in the second and third year after vaccination between ages 17 and 41 months, which are also ages of peak mortality in this population. The excess mortality was also concentrated in the rainy season which is also a high risk period.

There were no significant differences by sex, by age at vaccination or seroconversion status.

The recording of morbid episodes by the field workers, as reported by mothers was poor. No pattern of differences between vaccination groups emerged from the analysis.

According to available data and to our interpretations, the EZ-HT vaccine given at 5 months seemed to produce a measles like rash in about 5% of cases and the SW-HT in about 10% of cases. These rashes were mild, they occurred within the second week after vaccination and lasted for a few days; they were followed by a mild desquamation. These rashes were usually not noticed by the mother or if noticed they were not attributed to vaccination since they were similar to common skin rashes of young children of the same age.

CHAPTER 5

IMMUNOGENICITY

Immunogenicity was not a main objective of the study at first, but its importance became greater over time when measles incidence remained abnormally low in the general population. In the original protocol, only the first 5 cohorts were supposed to be part of the immunogenicity study, but in fact all 24 cohorts had blood taken at the 5 and 10 months vaccination session and all of the first 16 cohorts were fully analyzed for comparison of the two vaccines.

5.1 BLOOD SAMPLING

Blood was drawn from children just before vaccination at the 5 and 10 months sessions for all children of the 24 cohorts. In addition, blood was drawn at the 3 months session for volunteer children of three cohorts (05, 06 and 07) and at the 8 months session for the first 2 cohorts (01, 02). Blood was also taken from project children of other ages when coming for other vaccinations, whatever the antigen they received. In particular, this was the case for children of the first 16 cohorts who were called back from May to August 1989 to complete their vaccination series. A specific study of seroconversion was conducted for children of the first 16 cohorts who did not have detectable antibodies at 10 months after vaccination at 5 months of age and who were revaccinated in April 1989 (see below 5.7). Altogether 3409 blood samples were taken at the time of vaccination, 125 before 5 months, 1513 at 5 months, 157 between 5 and 10 months, 1270 at 10 months and 344 after 10 months. The following chart (5.1) summarizes the main points of the blood sampling strategy at the time of vaccinations:

Chart 5.1 : Blood sampling strategy at time of vaccination

Date of sampling	Cohorts involved
August 1987 - November 1989	Cohorts 01 to 24, at 5 and 10 months; project children if not convoked, any age
September - November 1987	Cohorts 05, 06, 07 at 3 months (volunteers)
October - November 1987	Cohorts 01, 02 at 8 months (volunteers)
April 1989	Cohorts 01-16, if seronegative at 10 months (prior to revaccination)
May 1989 - August 1989	Cohorts 01-16, called back for vaccination

Oral informed consent was obtained from all mothers before blood was drawn. A small proportion of mothers refused to have their child's blood taken at the time of vaccination: 6.3 % for the 24 cohorts called at either the 5 months or the 10 months sessions. Their children received the same care and the same vaccines as the others. This proportion varied slightly over time with a peak for cohorts 09-12 and 17-20 (table 5.1). There were marked differences between villages and dispensaries. In Ngayokheme, a dispensary where 9 villages were

vaccinated the refusal rate was 19.8%; in Toucar, where 10 villages were vaccinated, the refusal rate was 5.6%; in Diohine where the remaining 11 villages were vaccinated, the refusal rate was low: 0.9%. The villages where the highest rates of refusal were registered were also those that had some former bad experience with blood drawing (see above 3.3).

Blood samples were taken by a laboratory assistant with several years of experience in Senegal. He was of Sereer origin and was able to communicate amicably with mothers to make them feel at ease. Blood was drawn from the left hand mid finger, using a sterile lancet. Blood was kept in a siliconed separator microtainer (Microtainer inc.). About 0.5 ml of blood was taken each time, less if the child was crying too much or if the mother complained. Microtainers were centrifuged the same night at the Niakhar field station for about 10 minutes at 7000 t/mn. They were later frozen in the solar powered freezer at about -14°C. They were brought back to Dakar frozen and stored at -14°C until they were shipped to MRC laboratory in Fajarah, every other month or so.

5.2 LABORATORY PROCEDURE

42 batches of blood samples were analyzed between August 1987 and April 1990 (table 5.2). The delay between blood sampling and serum analysis averaged 80 days with minimum and maximum values of 18 to 579 days (standard deviation=72 days). There was no correlation between the level of antibodies and the delay between blood sampling and serum analysis, which indicates that the samples were properly stored and frozen. Details of the laboratory procedure are explained in annex A-7.

5.3 INTERPRETATION OF HI ANTIBODY TITERS

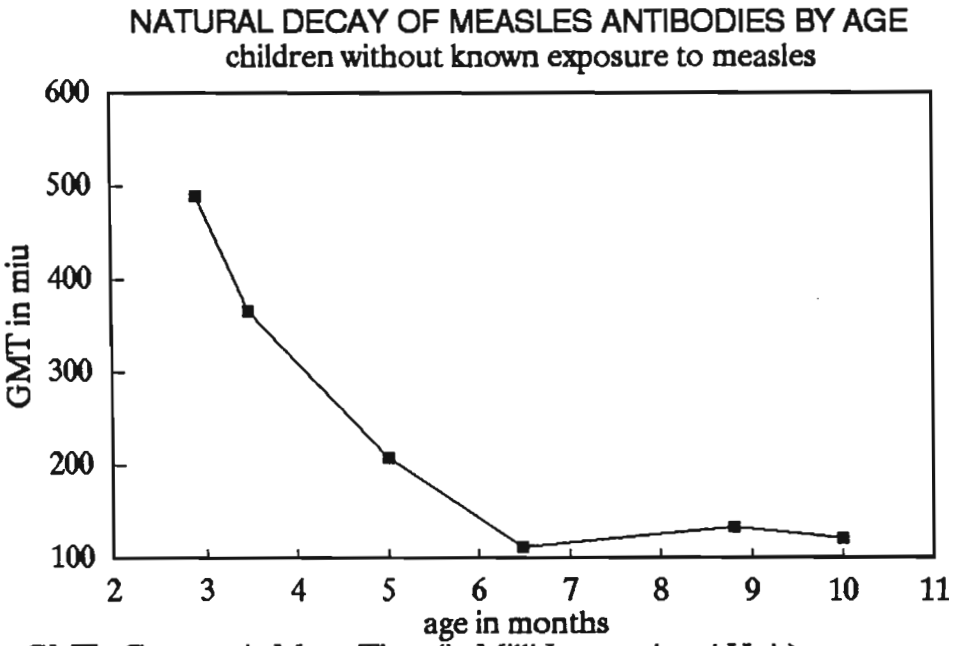
Among the 3409 blood samples taken at time of vaccination, 165 were analyzed twice (4.8%): 59 samples from the first cohort were reanalyzed because they showed a low titer; 28 placebos meeting the criteria for seroconversion were reanalyzed and 78 others for various reasons.

Except for the case of the first cohort, there was a high correlation between the two analyses: 0.707 to 0.837 (table 5.3). There was, however, a systematic bias of close to one dilution (0.896) between the two analyses, with a tendency of higher titers at second analysis. The study of the 106 samples other than the first cohort showed that in only 66% of cases, titers were equivalent, that is no more than one dilution off the previous value (table 5.4). This standard error, normally found with the HI method, must be taken into account in the interpretation of any study of seroconversion. One way of handling the problem is to add the variance due to the method to the sampling variance using the formula:

Total variance = Method Variance + Sampling Variance

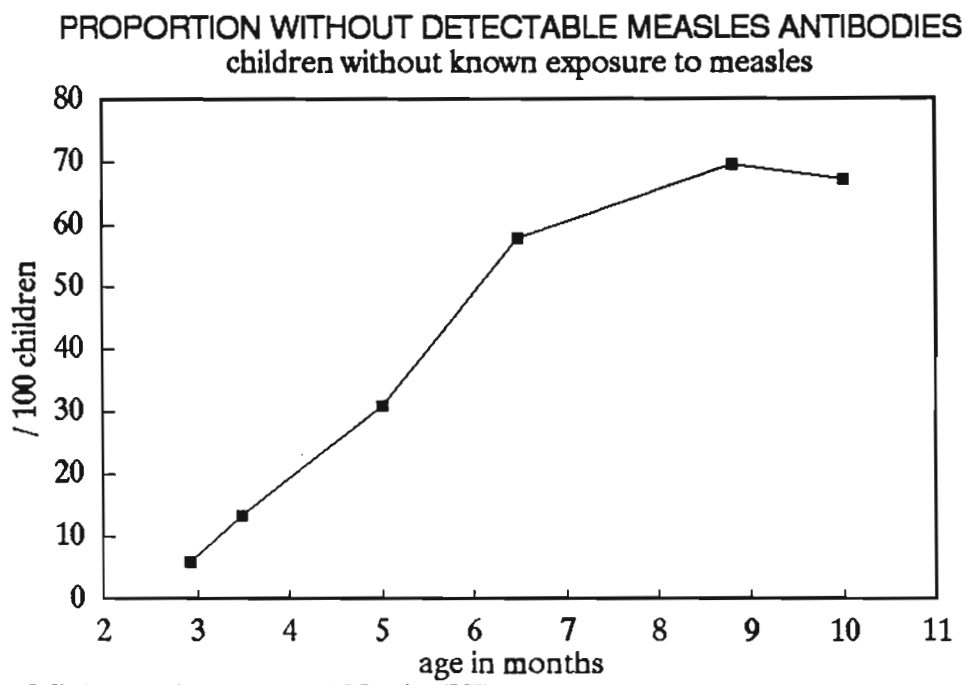
The case of the first cohort was puzzling: there was no correlation between the two analyses and results from the first two cohorts, sampled and analyzed at the same time, were discarded. This is why most tables are based on cohorts 03-16 only.

Figure 5.1



GMT : Geometric Mean Titer (in Milli International Unit)
Minimum detectable : 125 miu

Figure 5.2



Minimum detectable : 125 miu (HI)

5.4 NATURAL DECAY OF MATERNAL ANTIBODIES

The natural decay of maternal antibodies could be studied cross-sectionally by comparing the Geometric Mean Titers (GMT) by age at time of blood sample. Although this was not a longitudinal study, results revealed a strong pattern (table 5.5 and figures 5.1 and 5.2). The GMT averaged 490 miu at 10-13 weeks and declined rapidly until the first birthday. The proportion of children without detectable antibodies increased rapidly from 6.1% at 10-13 weeks to about 70% at age 9 months. The GMT among the seropositive children had a more complex pattern with decreasing titer from 10 to 33 weeks which then increased significantly. This was probably due to a selection of fewer children with higher titers. In any case it seemed that a small proportion of children had a significant level of measles antibodies for quite a long time beyond age 12 months. Therefore, vaccine failure could be expected in this population, even when children were vaccinated around their first birthday. At 5 months vaccination (18-25 weeks), 68.8% of children had a detectable level of measles antibodies, with a GMT of 356 miu.

5.5 IMMUNOGENICITY OF VACCINES

The serological response to vaccines was studied by comparing the levels of measles antibodies between the vaccines and the placebo, and directly between the vaccines. Results were based on 535 children who came to the 5 and 10 months sessions, who were immunized with the EZ-HT vaccine or the SW-HT vaccine or received the placebo at 5 months, who belonged to cohorts 03-16 and who had not had measles prior to age 10 months and were not known to have been exposed to measles in a compound of the study area (table 5.6).

Proportions of children with a detectable level of antibodies and GMT were comparable among the three groups at age 5 months, which indicates that randomization was fair. At age 10 months, both vaccine groups had significantly higher titers and a lower proportion of seronegative children than the placebo group. Furthermore, the EZ-HT vaccine had significantly higher titer (P=3.0E-06) and a lower proportion of seronegative children (P=3.7E-06) than the SW-HT vaccine.

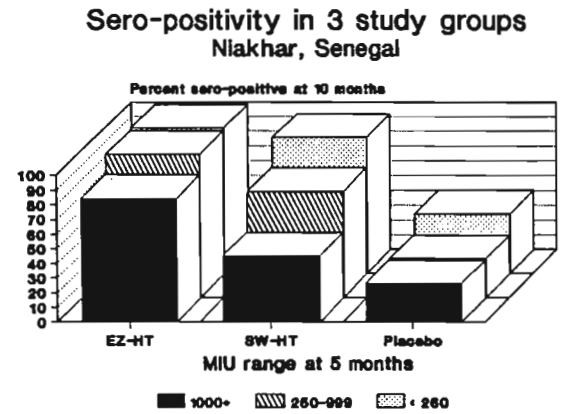
Three definitions of the serological response to vaccines were compared:

- sero-positivity, defined as at least 125 miu at 10 months
- sero-response, defined as at least the same titer, if >=125 at 5 months, or >=125 miu, if <125 at 5 months.
- sero-conversion, defined as at least a four fold increase in GMT if >=125 or >=250 miu, if <125 at 5 months.

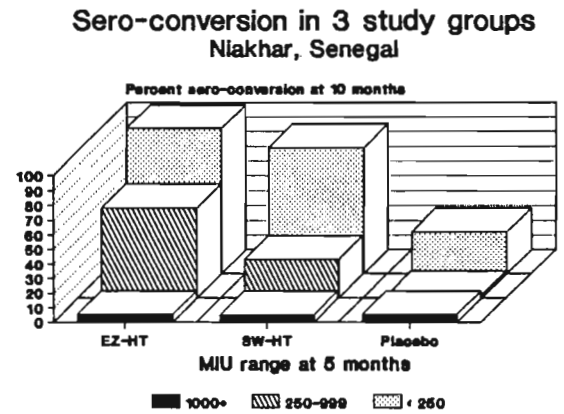
In the three cases, the EZ-HT vaccine performed far better than the SW-HT vaccine, and results were highly significant (see figures 5.3, 5.4 and following chart 5.2). The proportion of children without detectable antibodies at age 10 months was 5.9 times greater in the SW-HT group, and the proportion of children who did not meet the seroconversion definition was close to 50% as compared to 29% in the EZ-HT group. Even the GMT among seropositive children was higher in the EZ-HT group.

High titers (above 16,000 miu) were found in the two vaccine groups (table 5.7). This may be partly due to a strong response and partly to the standard error due to the method. In the earlier analysis of the method error it was found that the same sample was tittered once 512,000 and once 16,000 miu.

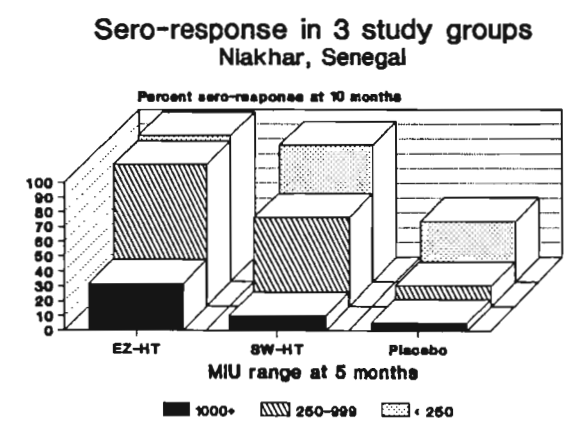
Figure 5.3 : comparison of immunogenicity of HT vaccines



Sero-positivity : at least 125 miu



Sero-conversion : 4 fold increase



Sero-response : at least same titer

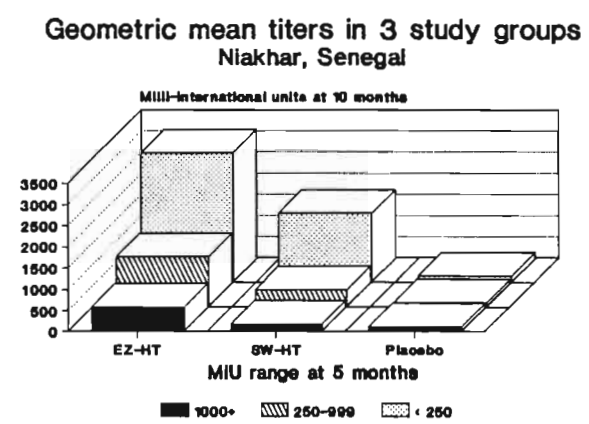
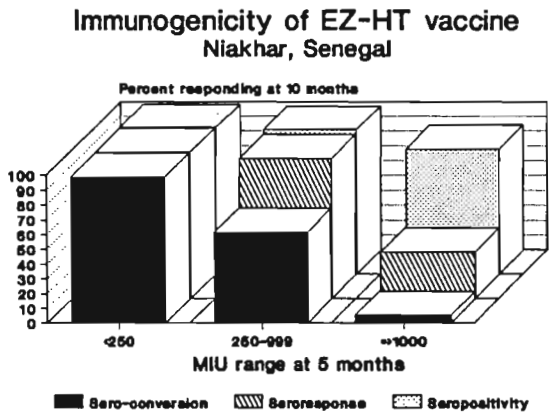
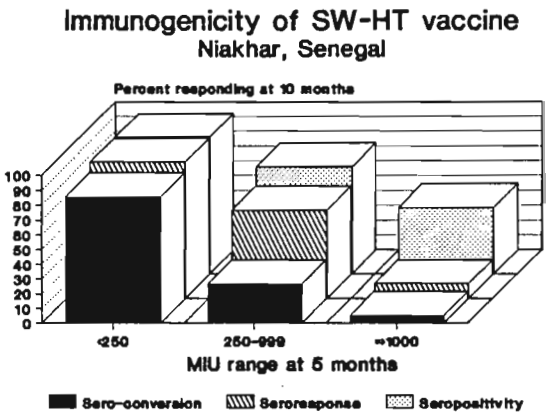


Figure 5.4 : comparison of definitions of immunogenicity





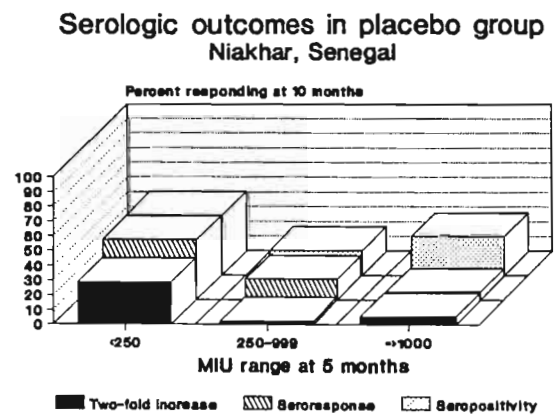


Chart 5.2 : Statistical tests for the comparison of the immunogenicity of the EZ-HT to that of the SW-HT vaccine.

GMT at 10 months	T = 4.599	P = 6.0E-06 *
GMT if >=125 at 10 months	T = 1.969	P = 5.0E-02 *
Sero-positivity	Z = 4.951	P = 7.4E-07 *
Sero-response	Z = 4.546	P = 5.4E-06 *
Sero-conversion	Z = 3.837	P = 1.2E-04 *

A small proportion (13.2%) of children who received the placebo at age 5 months had an apparent increase in titer which met the criteria for sero-conversion. This could again be easily explained by the method error. Among the 106 samples analyzed twice, 33 (31.1%) would fall into this category, although they were exactly the same samples.

5.6 ANALYSIS OF IMMUNOGENICITY

Level of antibodies at age 5 months

Among the main factors of immunogenicity was the level of antibodies at time of vaccination. Table 5.8 compares the immunogenicity of the vaccines according to the level of antibodies at age 5 months. For children with less than 250 miu at 5 months, seroconversion was 98.6% in the EZ-HT group and 85.5% in the SW-HT group. For children with 250-999 miu at 5 months, seroconversion was 61.6% in the EZ-HT group and 26.4% in the SW-HT group. There was no clear evidence of seroconversion after high titer vaccines when the level of antibodies was above 1000 miu. However, the percentage of seropositive children at age 10 months was significantly higher than in the placebo group.

Factors of immunogenicity

Several other factors could account for differences in immunogenicity, in particular age per se (in weeks, between 18 and 25), sex and nutritional status. Furthermore, to check if any trend in the potency of the vaccine was visible, a variable "cohort" was introduced; a control was also established on the season at which the child was vaccinated. Immunogenicity was studied using a "Multinomial Logit Regression" when the dependent variable was dichotomous (e.g. sero-positivity, sero-conversion, sero-response) or a standard "Multinomial Regression" when the dependent variable was the Log(GMT).

Extensive computations were performed using various models as well as other variables. No effect of sex or nutritional status at either age 5 or 9 months was found significant; various interactions among significant variables were also tried without success. Only significant results are presented here.

The effect of the vaccine and of the level of antibodies at 5 months appeared overwhelming in the three main models (table 5.9). In addition, there was a small significant independent effect of age at vaccination for sero-conversion and sero-positivity, but not for sero-response.

Comparison of the two vaccines

The behavior of the two vaccines was analyzed separately in other models. For sero-positivity, the EZ-HT vaccine seemed to be more sensitive to the level of antibodies than the SW-HT vaccine; however the SW-HT vaccine was more sensitive to age when controlling for level of antibodies (table 5.10). When GMT was used as the dependent variable, the EZ-HT vaccine seemed more robust to changes in age at vaccination and in level of antibodies (table 5.11). In this case, the EZ-HT vaccine group revealed a significant positive effect of cohort. This suggests that the immunogenicity of the vaccine did not diminish over time, although it remained for nearly two years. In addition, there was a significant effect of season in the EZ-HT group only: the GMT was lower for children vaccinated during the rainy season. This last observation requires further research on the possible interaction between the vaccine and general immunity, which is poor during the rainy season.

Decay of antibodies after vaccination

At the time this analysis was performed, only 104 blood samples from children above the age of 10 months were available, 41 in the EZ-HT group, 32 in the SW-HT group and 31 in the Standard group (table 5.12). Another 166 samples had already been taken but not yet tittered. This is, however, enough information to perform a first comparison of the decay of antibodies after the three vaccines. Most of the samples were taken around age 16 months, before a revaccination (children who were revaccinated because they were sero-negative at 10 months were not included here). The GMT in the EZ-HT group (1402 miu) was still higher than in the SW-HT group (859), but the decline in levels of antibodies seemed more pronounced and the proportion without detectable antibodies increased to 19.5%. There was virtually no decline in GMT in the SW-HT group between 10 and 16 months.

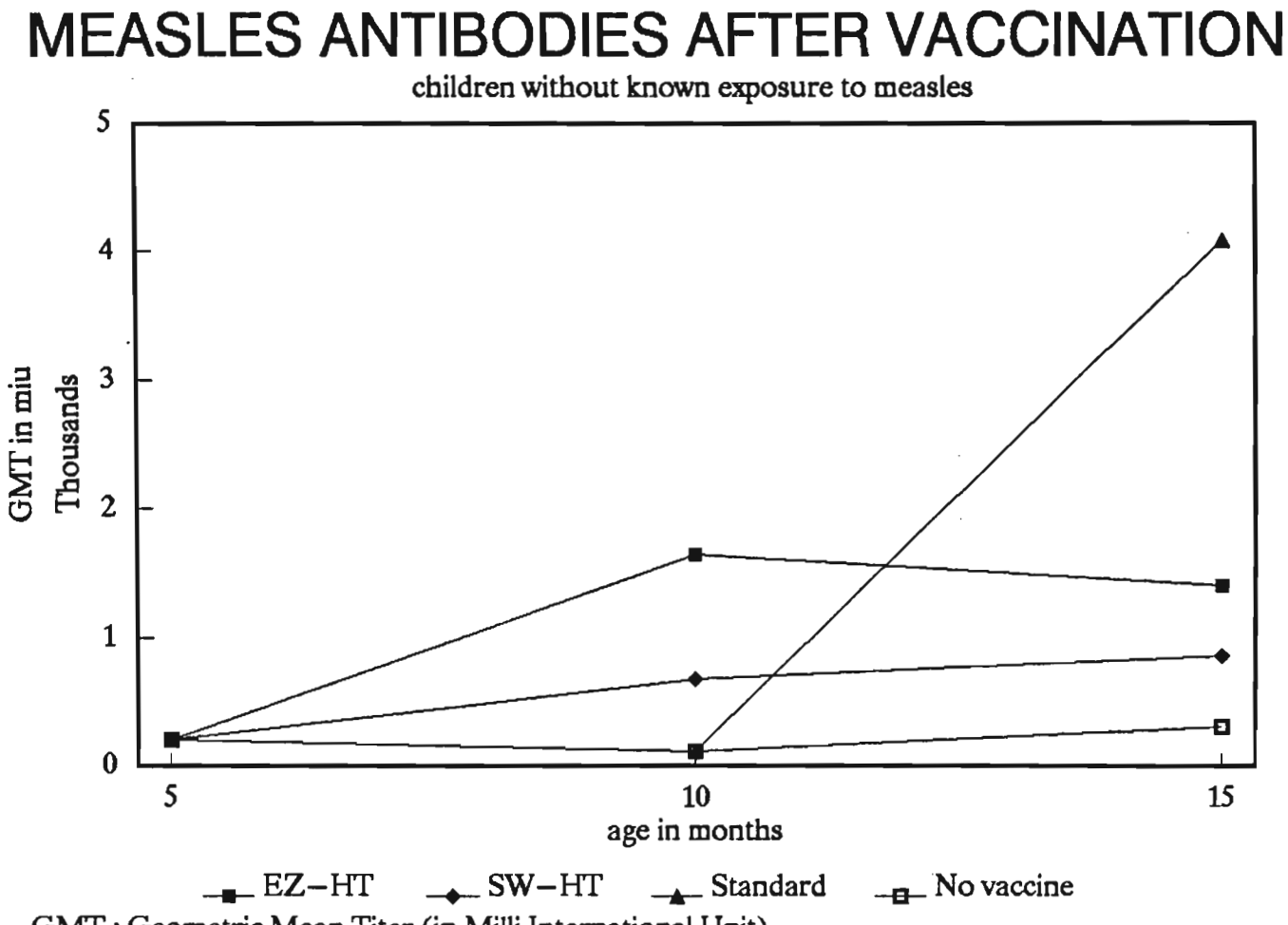
Children who were vaccinated with the Standard vaccine at age 10 months had much higher levels of antibodies 6 months after vaccination (4090 miu) than any other group, and also much higher than the EZ-HT or the SW-HT group at age 10 months (figure 5.5). A similar result was recently reported (Whittle et al., 1988). This raises serious questions concerning the value of the immunogenicity of high titer vaccines given at 5 months.

5.7 RESPONSE AFTER REVACCINATION OF SERO-NEGATIVE CHILDREN

Among children vaccinated at age 5 months with either the EZ-HT or the SW-HT vaccine, 49 children did not have a significant level of antibodies at first analysis. They were called back for re-vaccination in April 1989. At the second meeting to the DMSC it was decided to randomize these children and to revaccinate them with either the EZ-HT or the Standard vaccine.

Among the 49 children, 4 were dead or had outmigrated, 8 refused to come or were absent and 37 participated. They were revaccinated according to the scheme displayed in chart 3.2. Results of the revaccination were not yet available when this report was completed.

Figure 5.5



GMT : Geometric Mean Titer (in Milli International Unit)

5.8 MORTALITY AND SERO-CONVERSION

In an earlier article, Aaby et al. (1988) found that children who did not seroconvert after measles vaccination had a higher risk of dying than others. This was not the case in this study. Deaths among the 535 who entered in the seroconversion study were broken-down by vaccine, sero-conversion, sex and age at death. There was no significant difference between children who died and survivors (table 5.13). Extensive survival analysis was conducted on the same children, but nothing else of significance was learned except what was shown earlier (see 4.1), i.e. the EZ-HT group had a higher mortality.

5.9 OPTIMAL AGE FOR VACCINATION

Estimates of the optimal age for vaccination could be derived by comparing the expected proportion of children who would seroconvert or seroraspond, by age at vaccination. This was done by multiplying the expected rates and seroconversion and seroresponse for each level of antibodies (from table 5.8) by the distribution of antibodies at this age (from table 5.5). The expected immunogenicity increased sharply with age from age 3 to 6 months and reached a plateau after age 7 months (table 5.14, figure 5.6). These results indicate that the optimal age for vaccination with high titer vaccines would be 6-7 months, and not 5 as was chosen for this study.

5.10 DISCUSSION

We found very difficult to compare the values of seroconversion after high titer vaccines with the results of earlier studies (chart 0.2). Seroconversion varies very much with age, titer and strain, as well as with the definition used, in particular with the laboratory method and the threshold used. Our results for the EZ-HT compare well with results of the Mexico and Togo trials.

5.11 SUMMARY OF MAIN FINDINGS

- Both the EZ-HT and the SW-HT vaccines were immunogenic when given at 5 months.

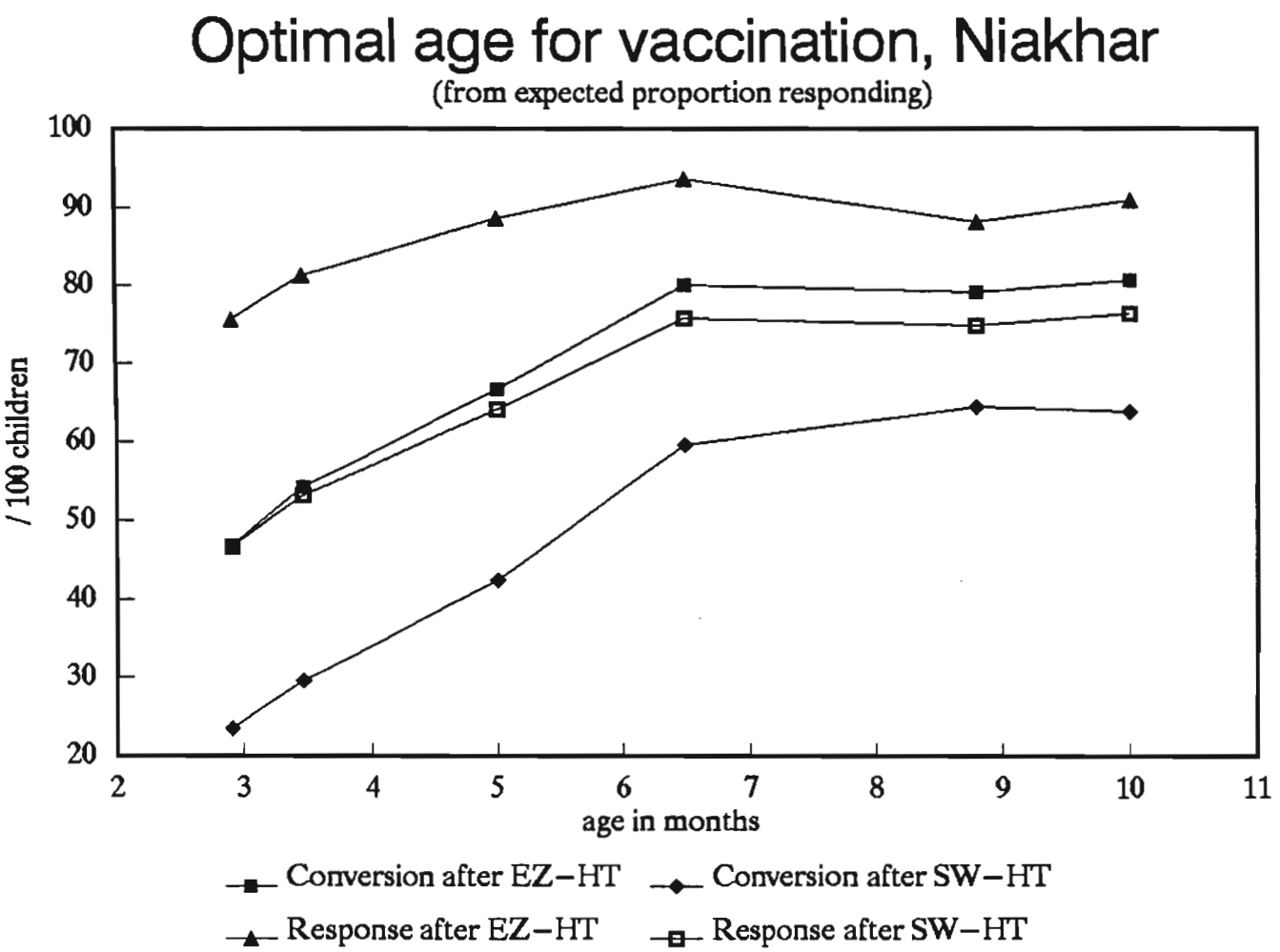
- The EZ-HT vaccine induced a higher response than the SW-HT vaccine. Differences between the two vaccines were highly significant. For instance there were only 3.7% of children with no detectable antibodies at 10 months in the EZ-HT group, as compared with 22.0% in the SW-HT group and to 67.6% in the placebo group.

- The evidence that the EZ-HT vaccine passed the barrier of high levels of maternal antibodies (e.g. 1000+ miu) was poor.

- None of the high titer vaccines given at age 5 months seemed to produce a level of antibody response comparable to the Standard vaccine given at 10 months.

- levels of antibodies present after the EZ-HT vaccine seemed to decline faster than after the SW-HT vaccine; but this effect would require confirmation with more data and at various points after vaccination.

Figure 5.6


Optimal age for vaccination, Niakhar
(from expected proportion responding)
/ 100 children
100
90
80
70
60
50
40
30
20
2
3
4
5
6
7
8
9
10
11
age in months
Conversion after EZ–HT
Conversion after SW–HT
Response after EZ–HT
Response after SW–HT

CHAPTER 6

MEASLES: EPIDEMIOLOGY AND CASE DEFINITION

This chapter is devoted to the case definition of measles. The case definition is based on all epidemiological, clinical and serological evidence that was gathered during the course of the study. The chapter is divided into 3 main sections: epidemiology, clinic and serology. Cases were investigated each time there was a suspicion of a clinical case in a family. There was no systematic attempt to investigate subclinical measles, although some observations were made during the course of the study (see below). Therefore, estimates of sensitivity and specificity of clinical and serological criteria are dependent upon parental recognition and upon suspicion of clinical measles in a family by the investigators.

Two analyses were performed separately: one in early 1990, which included cases until December 1989. Tables referring to this period were labelled 1987-1989. Other cases were found in the first part of 1990. They were included in some of the analyses. Tables referring to that period were labelled 1987-1990.

PART I : EPIDEMIOLOGY OF MEASLES

6.1 RESIDENCE CRITERIA

Residence

Residence criteria for the general demographic surveillance are detailed in the manual for field workers. They were based on the following main rules.

Were considered as outmigrant:

- people who left the study area without intending to return;
- people who left the study area for more than 6 months or who did not spend the previous rainy season in the study area, even if they intended to return;

Were considered as immigrant:

- people who came to the study area with the intention of staying;
- people who spent more than 6 months in the study area or who spent the last rainy season in the study area, even if they had no intention of staying.

Special rules for visiting husbands, seasonal workers and students were given to the field workers.

Presence

People who spent the previous night in the compound were considered present in the compound on a given day. Herders, usually young boys age 8 to 14, who received their meals from the compound but who lived and slept in the bush with the animals were considered as residents but considered separately. Others were considered absent. For measles investigation, only presence status at time of first investigation in the compound was recorded. This slightly biases the case-contact ratio: a child could be exposed to the index child but no longer be present a few days later when the first investigation was conducted, and therefore not counted as a contact; conversely, a child could be absent at the first investigation and could return later and become infected by secondary cases and therefore be counted as a case. However these cases were rare.

In addition to these standard rules of residence and absence, various provisions were made for the efficacy study and for the case contact study (see chapter 7 for details).

Project children

Project children were those born between February 1, 1987 and January 31, 1989 to a mother resident in the study area at time of birth. Project children were considered outmigrating if their mother or the person in charge of them outmigrated after the birth. Once outmigrated, project children were not re-inserted into the file used for the efficacy analysis even if they returned; they were however reinserted in the general demographic file. There were no cases of children who left and returned prior to the 10 months vaccination session. Children entered the file at time of birth, they entered the study at time of the 5 months vaccination session and they left the study either at the end of the study, or at death if they died during the study, or at time of outmigration if they outmigrated before the end of the study.

Residence status for measles cases and contacts

All measles cases that occurred in the resident population within and outside the study area and cases that occurred in visitors within the study area were considered. Measles cases and contacts can have three residence statuses:
1) Resident, Present in the study area (RP): these are cases and contacts among the resident population who were present in the study area at time of the outbreak;
2) Resident, Absent from the study area (RA): these are cases among the resident population, who were absent from the study area at time of the rash; they were usually contaminated during travel outside the study area or during a stay in another village or city;
3) Visitor, Present in the study area (VP): these are cases and contacts among the non resident population who were present in a compound of the study area at time of the outbreak.

For the efficacy study, all residents were considered. Residents could have only two possible residence statuses at time of a measles outbreak in a compound: Present (within study area) or Absent (outside study area). For the case-contact study, only those present were considered for cases and contacts, since knowledge of their exposure status was needed (table 6.1). Residents absent at time of an outbreak in the compound were discounted from the contacts. Therefore, depending upon the residence and the presence statuses, and the infection, five situations were considered for the analysis. They are summarized in the following chart 6.1:

Chart 6.1 : Residence statuses

Residence status	cases	contacts
Resident, present	RP	
Resident, absent	RA	-
Visitor, present	VP	
Efficacy study	RP+RA	-
Case/contact study	RP+VP	RP+VP

6.2 MEASLES OUTBREAKS IN THE STUDY AREA

Before the vaccine trial

Prior to the 1987 mass vaccination campaign, short breaks of measles lasting a few months occurred every year in the study area. The national mass vaccination campaign ran from October 1986 to April 1987. At that time an outbreak of measles was in course in the study area; it continued throughout the dry season and the last case of this outbreak occurred on May 24, 1987. This was the last case for almost a year. However, four other cases occurred between June 87 and April 88 among resident children absent from the study area: they occurred in Dakar on August 2 and 15, November 15 and December 4, 1987.

During the vaccine trial

The first vaccinations of the project started on August 11, 1987, about 10 weeks after the last case of the previous outbreak was recorded in May 1987. From August 1987 until August 1990 three measles outbreaks occurred in the study area; in addition, isolated cases occurred among residents absent from the area. The reason cases outside of the study area occurred at about the same time as the cases inside the area was because index cases in an outbreak were always imported from outside, usually from Dakar. It was epidemics in Dakar or other cities in the country that produced outbreaks in the study area: there was no continuous transmission of measles within the study area (table 6.2).

First outbreak

The first outbreak began on May 2, 1988 in Godel-Mbelpil, a small hamlet in the Western part of the study area. The index case was a 5 year old girl who had been to a wedding ceremony on April 18 in Thiadiaye, a nearby town. Only 5 compounds in the same village and 19 cases were infected and the last case occurred on August 3, 1988. In addition, there were 8 other cases among residents outside of the study area during the same period and another isolated case in another village: Toucar.

Second outbreak

Then, measles transmission ceased until November 6, 1988, when a case occurred in Ngangarlame-Pindalang: this was an 11 year-old child for whom no certain source of contamination could be found. Transmission resumed and lasted until June 26, 1989, at which time it stopped again; in addition another compound was infected from outside on July 7, 1989. Altogether, 20 villages, 48 compounds and 122 cases were infected in the study area during the second outbreak. Measles was present throughout the country and 39 resident children were infected elsewhere, mostly in Dakar, during the same period.

Third outbreak

Transmission resumed on August 19 and 21, 1989 in two different villages simultaneously: a 4 year old girl living in Gadiak-Dafeme was infected in a nearby hamlet (Ngassiak) and a 20 month-old girl from Ngangarlame-Khakhal, coming from Dakar where she slept in the same bed as another girl with measles. The outbreak spread to 11 neighboring villages and peaked in November when it hit the school of Gadiak. 119 compounds and 407 cases were infected and the third outbreak lasted until July 14, 1990.

Exposure periods

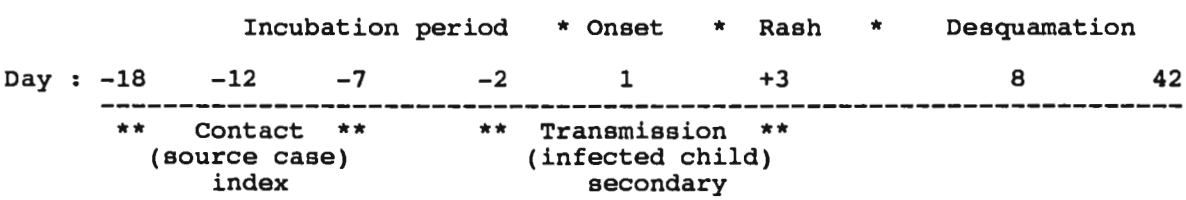
Since the code was broken in June 1989, computations before opening the code included roughly the first two outbreaks (a few cases occurred after the code was broken). Exposure to measles after vaccination at 5 months ran from August 25, 1987 (14 days after the first vaccination with high titer vaccines) to August 15, 1990, a month after the last case of the third outbreak. Most tables in this chapter refer to these three years.

Pattern of disease transmission in outbreaks

The pattern of disease transmission was rather atypical when compared to previous years. Firstly, the size of the first two outbreaks was small: previous outbreaks during the 1983-1986 period accounted for 300 to 600 cases; this was obviously the effect of the vaccine coverage. Secondly, the seasonality was rather different from previous years: the dry season peak was less pronounced, because the transmission of measles was seriously disrupted by the 1987 vaccination campaign. Thirdly and most surprising, the secondary attack rate in compounds was low (54.8% versus close to 100% in previous epidemics). The identification of the reasons for this pattern would require further investigation that is beyond the scope of this report.

6.3 PATTERN OF TRANSMISSION

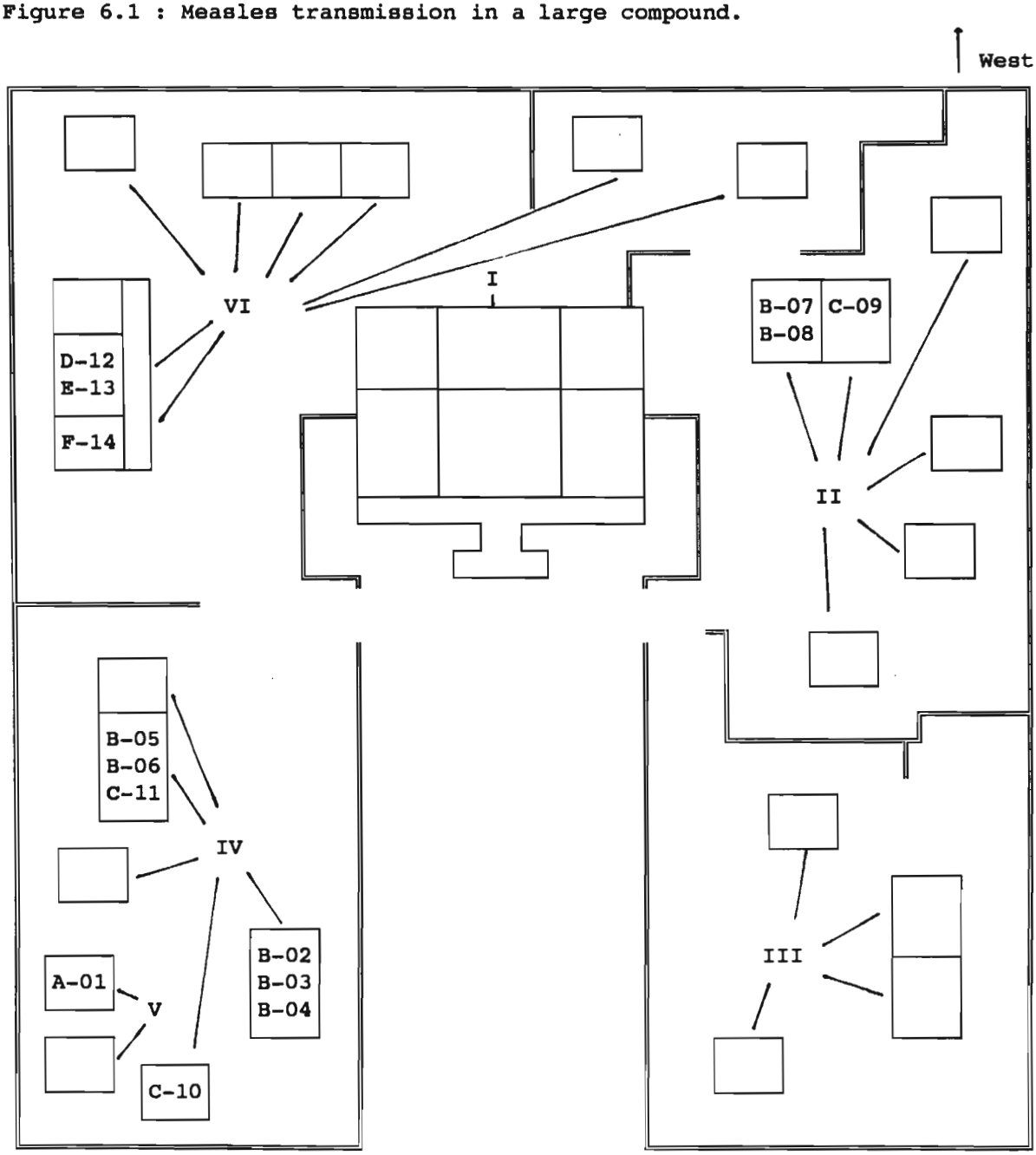
Measles transmission has a standard pattern that has been well described for centuries. The length of the incubation period averages 12±3 days. The child may transmit the virus from 2 or 3 days before rash to 1 or 2 days after the rash. The delay between a source case and an infected case averages 12.5±5.5 days (7 to 18). In this study, when a case was followed by another case occurring 7 to 18 days later, with evidence of social contact during the susceptible transmission period, the first case was considered the source case of the later.



Transmission within the study area

Measles transmission within the study area was carefully monitored at the village and compound level. In most compounds the source of contamination of the index case was identified with a good degree of likelihood since usually only a few possibilities existed and among them one was likely and the others were unlikely in the normal interval of incubation. This was due in particular to low incidence of the disease. Furthermore, people were often able to infer the source of contamination since they pay a great attention to disease transmission. However their information was always checked for consistency because they had a tendency to consider first the closest contact, even when the interval was too short or too long.

Figure 6.1 : Measles transmission in a large compound.



Generations		Sex and age of cases				Symbols	
A	(1) 20 December	01= M 3		08= F 3		═══	fence
B	(7) 30 December	02= F 2		09= M 7			
C	(3) 13 January	03= M 4		10= M 8		▭	hut
D	(1) 31 January	04= F 7		11= M 1			
E	(1) 13 February	05= M 8		12= M 6			
F	(1) 27 February	06= F 6		13= M 6		——> IV	eating at kitchen IV
		07= F 5		14= M 2			

Over the 1987-1989 period, 48.9% of the index cases in a compound were infected in the village, during games with other infected children or exposure during a visit or a ceremony in another compound; in addition 20.0% were infected during short term travel outside of the study area, 12.2% in school and 5.6% at a local dispensary; in 4.4% of cases the source of contamination was unknown (table 6.3).

Transmission within compounds: generations

The pattern of disease transmission within the compound was also closely monitored, as exposed elsewhere (Garenne and Aaby, 1990). An index child can infect up to 20 other children living in the same compound. During the first two outbreaks a maximum of 14 children infected was recorded in the same compound. In large compounds, transmission was complex and usually there were several generations of cases. An example of a very large compound of 95 residents in which 14 measles cases occurred between December 12, 1988 and February 27, 1989 is displayed in figure 6.1: 6 generations of cases could be distinguished: the index case, a 3 year old boy who was a visitor from Bambey, a nearby town, infected 6 other children in the same kitchen (second generation), who in turn infected 4 other children again in the same kitchen (third generation). Later, there were three other generations of one child each, in another kitchen at about 13 to 14 days interval each.

In all compounds investigated during the study period, details were obtained on living patterns and disease transmission. Each case was classified according to the kitchen (Ngak) he was eating from and to the hut he was sleeping in. An index of intensity of exposure which measured the social proximity to the source case was defined as: (1) if the source and the infected cases did not live in the same compound, (2) if in the same compound but not in the same kitchen, (3) if in the kitchen but not the same hut, (4) if in the same hut. The source case was identified as the "most likely" in the previous generation, ie the child with the highest social proximity in the previous generation. The interval between two successive generations was 7 to 18 days, 12.2 on the average. This was due to the variance in the duration of the incubation period and in the period of infectivity of a child (table 6.4 and 6.5).

There was little doubt that successive generations were properly identified because most of the time there was a time lag of about 10 days between two successive generations; 7-18 days seems to be a good cut-off to separate the same generation from successive generations. Our definition of the source case may have some arbitrary component in extreme situations, but even comparing the date of onset of a secondary case with the date of onset of the first and the last case in the previous generation did not change the general picture and extreme situations (<7 or >18 days between secondary case and first or last case of the previous generation) could be explained differently (same generation or three different generations).

There were on the average 1.10 cases in the first generation (10% of co-index cases), 2.08 cases in the second generation and 1.90 in the third generation. Only three compounds had more than 3 generations, with 1 case in each of the generation of rank higher than 3. The secondary attack rate diminished with the rank of the generation. This is probably due to a selection of large compounds, in which the secondary attack rate is lower because social proximity is lower.

Altogether, secondary cases accounted for 60.8% of all cases, a typical feature of measles transmission in West Africa. This pattern has given the team the opportunity to investigate clinical measles at the onset of the disease in most secondary cases.

6.4 DEMOGRAPHY OF MEASLES

Incidence, age and sex pattern

Incidence of measles was relatively low over the study period: on the average 10.5/1000 person-years lived by children age 0-14. It was highest in the 5-9 years age group (the unvaccinated population) and below 10 months, before vaccination of all groups (table 6.6, figure 6.2). These figures did not take into account the exact time spent at risk, ie they did not discount for vaccinated children and for children who already had measles. The age pattern of measles incidence was strongly influenced by the vaccinations and was markedly different from previous years. Incidence was slightly higher for females, as was observed earlier on, although vaccine coverage was the same for males and females.

Case fatality

Mortality from measles was markedly low over the study period and much lower than during previous years (figure 6.3). Only 5 deaths were recorded, four girls, age 22 months, 23 months, 5 years and 6 years and one boy who was 20 months old. There were no deaths below age 1 year, whereas in previous years this age group had the highest Case Fatality Ratios (CFR). The CFR for all ages was 15.8/1000 in 1988-1989, i.e. 73.1% less than during the previous 1983-1987 period (table 6.7). The strongest mortality decline was in infancy (100%) and in early childhood, age 1 to 4 years (53.5%). Details of the measles deaths are given in annex A-1.

The major achievement of a low case fatality ratio was due to the close follow-up and careful treatment of each case from the first visit by the project physician. Standard treatment was the following:

- systematic antiparasitic treatment, for intestinal worms (Mebendazole) and malaria (Chloroquine);
- systematic treatment of fever (Aspirin);
- systematic treatment of conjunctivitis, keratitis and stomatitis with antiseptic (Aureomycin, Iduviran and Pyralvex);
- treatment of acute lower respiratory infection (ALRI) with antibiotics (Cotrimoxazole, Ampicillin, Ceporexin);
- treatment of diarrhea episodes with Unicef Oral Rehydration Salts (ORS);
- treatment of nutritional deficiencies: Protein-Energy-Malnutrition (PEM) with a high energy mixture (oil-sugar-yoghurt) and anemia with iron pills;
- treatment of other diseases at home when possible; in particular otitis and laryngitis;
- referral to a hospital for emergency treatment when needed, in particular:
  + croup
  + acute bronchopneumonia
  + any neurological complication
  + any hemorrhagic form
- referral to an ophthalmologist in cases of post measles keratitis.

Figure 6.2

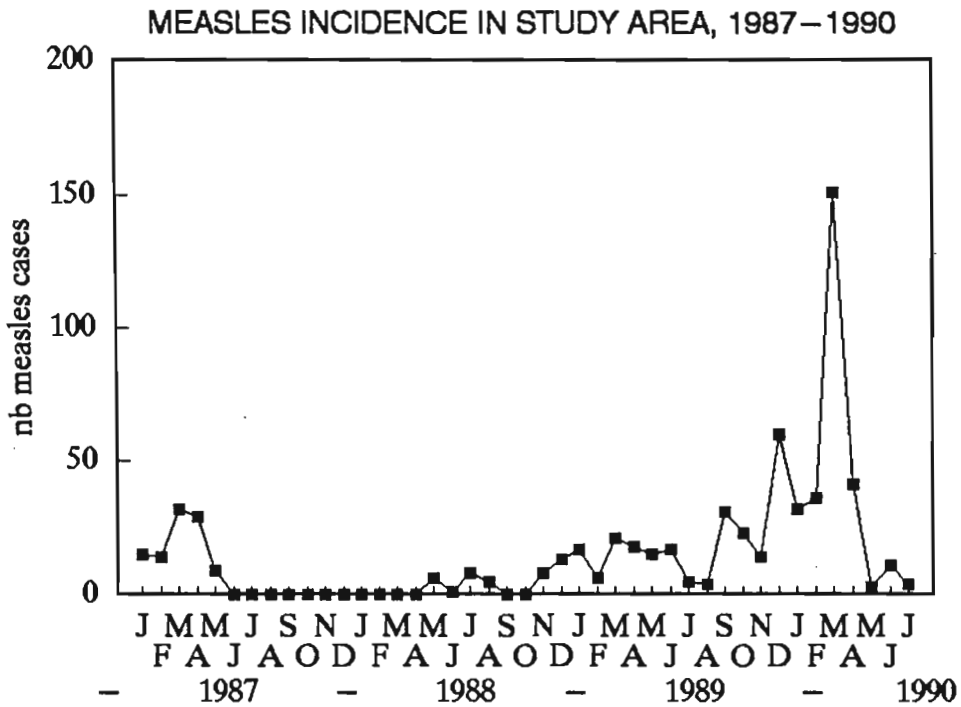
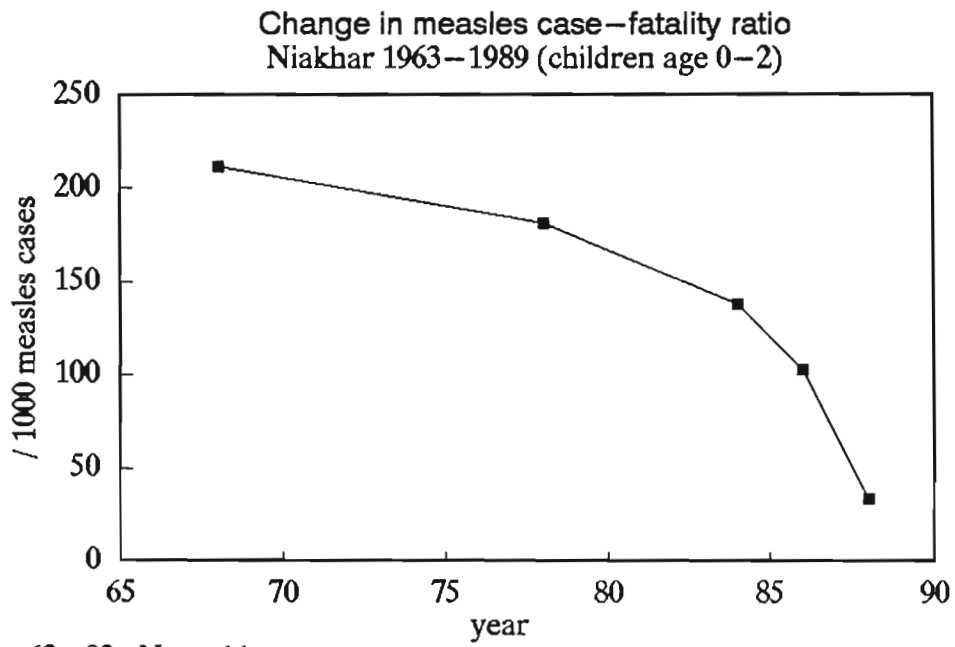


Figure 6.3



63–82 : Ngayokheme
83–89 : Niakhar

PART II : CLINICAL CONFIRMATION

6.5 CLINICAL SIGNS AND SCORES

Once a case was reported or at least suspected by the family or detected directly during home visits, it was considered "compatible" and was clinically examined once a week, more if treatment was needed, and at least 5 times if still present in the study area. Clinical aspects of measles have been described for centuries (Krugman et al. 1977). The field physician was asked to fill-out a form with all clinical signs of measles as well as other relevant signs. Most of the signs were observed by the field physician. However, a mother's declaration was also considered valid for cough and diarrhea, even if the physician did not have the opportunity to observe these symptoms directly. Signs and symptoms systematically recorded were:

1) Typical rash and desquamation: the exanthem begins as an erythematous macopapular eruption. The rash appears on the average on day 2, first behind the ears, then it spreads to the face on day 3, on the neck, thorax and arms on day 4 and on the trunk and legs on day 5; the rash stays visible until day 7 to 8. When the rash begins to fade, the skin takes on a marble appearance (staining). The desquamation then follows, in the same order as the rash.

2) Untypical rash: sometimes the rash is less typical, especially among vaccinated children. It can be similar to a rash associated with common miliaria (see chapter 4).

3) Koplik spots: they are pathognomonic of measles. They appear during the rash and last for 2 to 3 days.

4) Conjunctivitis: appears during the prodromic phase. Eyes are red and tearful, sometimes mucous is present; the child is often photophobic.

5) Stomatitis: follows the same pattern as conjunctivitis. It is often due to Herpes virus.

6) Cough: occurs during the prodromic period, becomes milder later but usually continues for all of the rash and desquamation period.

7) Fever: fever increases dramatically during the prodromic phase and can peak above 40°C on day 3 or 4. It usually diminishes gradually later on, except in the case of severe complications.

8) Pulmonary complications: all pulmonary complications were recorded, whatever their origin: pneumonia, bronchitis, bronchopneumonia, lung abscess, pleurisy, pneumothorax.

9) Diarrhea: all episodes of diarrhea were noted, usually from mother's declaration, whatever the number of stools per day, the aspect of the stools and the duration.

10) Other symptoms: were noted as well on the form, but not coded. Among them were cases of keratitis, otitis, laryngitis and neurological complications and one case of hemorrhagic measles.

Figure 6.4

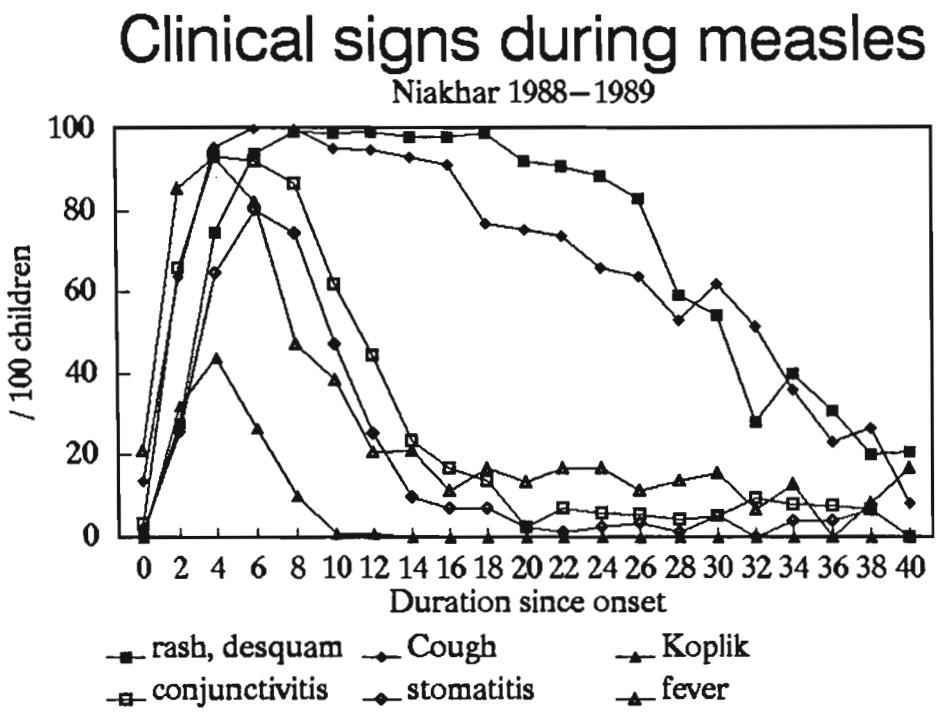
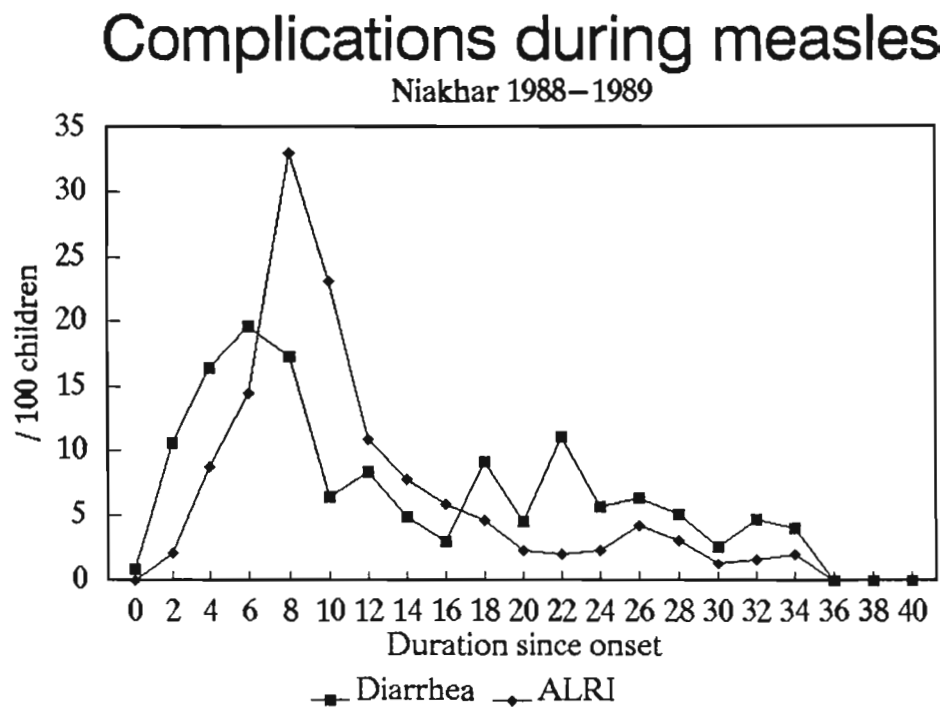


Figure 6.5



6.6 OBSERVED CLINICAL SIGNS

Results of the clinical investigation are displayed in tables 6.8 and 6.9 and in figures 6.4 and 6.5. The rash was present in virtually all cases from day 5 to 10 and staining or desquamation was visible for at least one more week until day 18. In a small number of cases the rash either started late (day 4 or 5) or ended early (day 8 or 9) which explains that the total percentage of children with rash does not add up exactly to 100%. However, all children counted as measles cases had a rash, either typical or untypical. All of them also had a cough at one point in time, and usually the cough lasted as long as the desquamation was visible.

Koplik signs were seen in 26.5 to 44.0 % of cases when the child was seen from day 1 to 6.

Conjunctivitis was present along with fever and stomatitis: these three conditions were present in 80.3 to 92.3% of cases at day 5-6 and tended to disappear around day 15, except in severe cases.

6.7 COMPLICATIONS: ALRI AND DIARRHEA

Complications of measles, namely Acute Lower Respiratory tract Infection (ALRI) and diarrhea were frequent. ALRI peaked at day 7-8 in 33.1% of cases. Diarrhea had two local peaks: one around day 5-6 (19.7 % of cases) and a second peak around day 17-22 (11.1 % of cases). Fever had a first local peak around day 3-4 (93.3% of cases) and a second local peak around day 17-22 when diarrhea complications seem to be relatively more prevalent.

These observations on dates of complications matched observations made earlier about dates of measles deaths: most deaths occurred either during the second week after onset of symptoms, and were usually associated with ALRI, or during the third week, and were usually associated with diarrhea. Complications virtually disappeared after day 35. This underlines the necessity to count as measles deaths all deaths occurring during the 6 weeks after the first symptom occurred: the 2, 3 or 4 weeks duration some researchers use does not seem to be long enough to capture all deaths due to direct complications of measles.

6.8 CLINICAL SCORE AND SEVERITY

A clinical score and a severity index were developed from those signs and symptoms. The clinical score was a weighted average of the score for each symptom. Weights were the following;

(6) typical rash/desquamation	(1) cough
(5) Koplik spot	(1) fever (>=38°C)
(2) untypical rash	(0) ALRI
(2) conjunctivitis	(0) Diarrhea
(2) stomatitis	

The maximum score was 17 (every symptom except the atypical rash). All signs were directly examined by the project physician; however cough was not always heard by the physician but mother's declaration was considered acceptable.

For all symptoms a severity index was defined, with a value assigned to each:

Figure 6.6

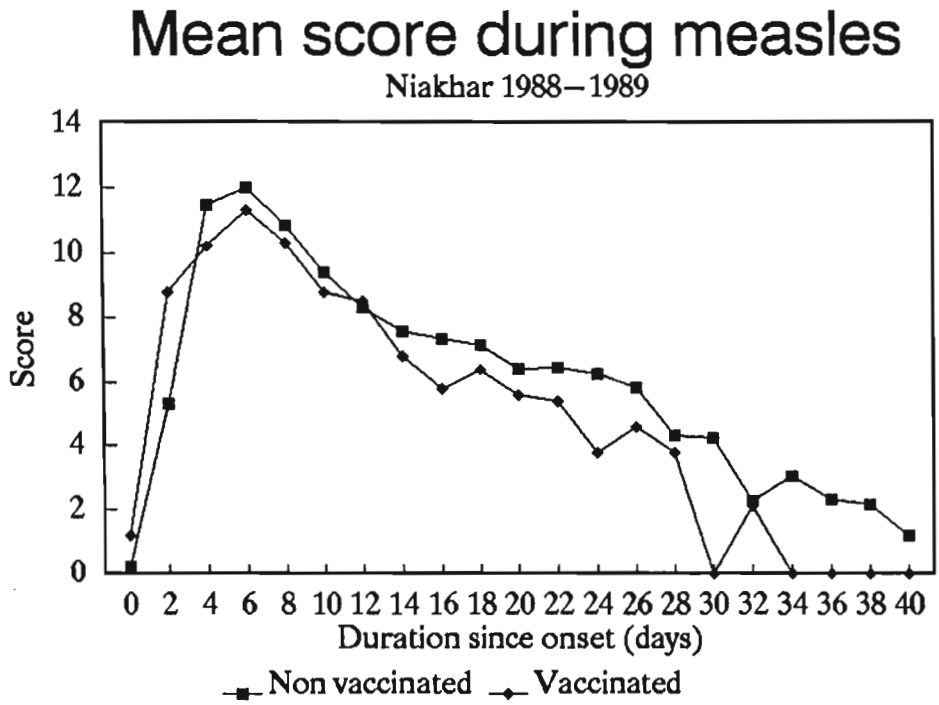
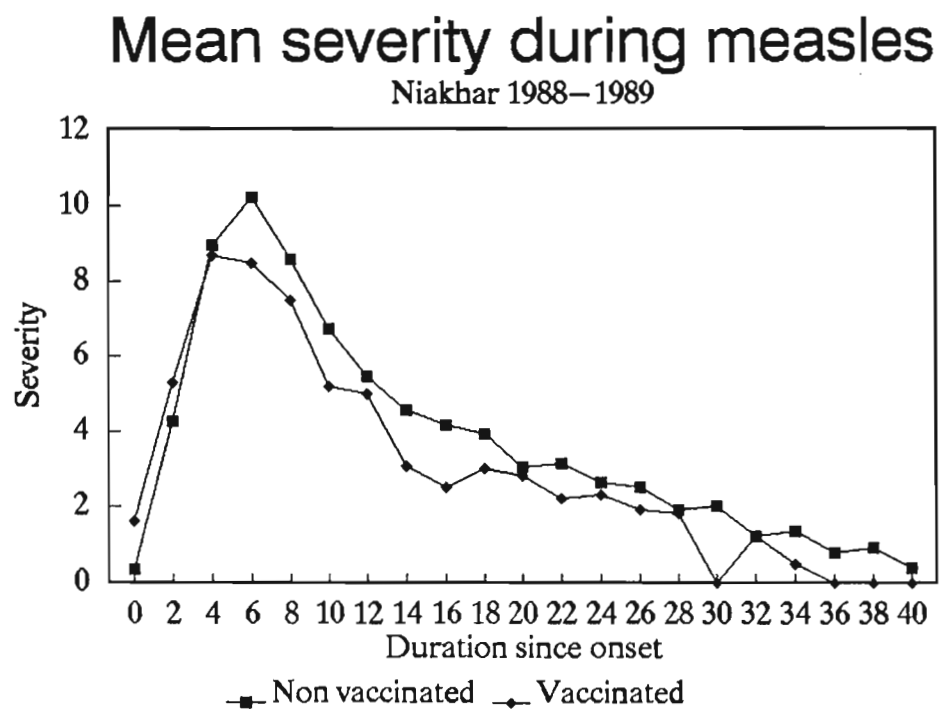


Figure 6.7



(1) mild, when the symptom was barely detectable,
(2) medium, when the symptom was as normally expected,
(3) severe, when the symptom was particularly severe.

The severity index was the sum of the severity for all 9 symptoms in the above list. Its maximum value was 24 (all severe symptoms except the atypical rash).

Clinical score and severity differed for vaccinated and unvaccinated children (table 6.10 and figures 6.6 and 6.7). Clinical score and severity peaked around days 5-6 and then declined gradually to become virtually nil around day 42. For vaccine failures, the score and the severity were virtually the same during the first week but were significantly lower afterwards. The score among vaccinated children was about half that of unvaccinated children at day 29-35. The severity was already much lower after the first week.

The frequency of complications was also much lower among vaccinated children (table 6.11). On the average there were 46% less diarrhea cases ($P<.0213$) and 78% less ALRI ($P<.0011$) among vaccinated children. This suggests that even when the vaccine does not have a protective effect against the infection, it makes the infection milder and may well protect against mortality. In the study area, never a case of measles death was recorded among a vaccinated child.

6.9 CLINICAL VALIDATION

The protocol made provision to validate clinical measles when the score was at least equal to 8 (firm clinical evidence) and to consider a possible case when clinical score was 7 or less . A score of 8 or more implies a rash in all cases, a cough plus some additional symptom (table 6.12). A score of 6-7 almost always implies a rash (98.8%).

Since children with measles were seen several times during the acute phase, the physician had several opportunities to observe a high score. Measles cases were characterized by their maximum score during the course of the disease (table 6.13). Among both the vaccinated and unvaccinated children, a large majority of those who were examined during the day 1-42 period had a score greater than or equal to 8 (89.6% and 83.3%). In comparison, no contact, that is children present in the compound who did not develop measles, had a score greater than 7. One fifth (20.0 %) of all measles case were not examined during the acute phase (day 1-42): most of these were cases which occurred outside the study area or isolated cases which were reported too late.

In a few cases which were examined at least once between day 1 and day 42, a typical rash with cough could was not observed. Among the 24 vaccinated children, all had a typical rash with cough but among the unvaccinated children, 5 out of 219 had only a typical rash, with no cough when examined (table 6.14).

To the clinically confirmed cases (at least a score higher than- or equal to 8) one could add those who were in contact with a directly confirmed case in the same compound (table 6.15). Among the 306 measles cases recorded during the period from August 15, 1987 to December 31, 1989, 71.6 % were directly confirmed and an additional 10.8% were indirectly confirmed. The proportion of confirmed cases was 98.1% for secondary cases, 89.8% for index cases and only 24.1% for cases outside of the study area. This could be regarded as a high confirmation rate, given the numerous difficulties of communication in this environment.

PART III : SEROLOGICAL CONFIRMATION

6.10 SEROLOGICAL DATA

Serological confirmation of clinical measles cases was sought for all cases every time this was physically possible. Instructions were given to get a micro blood sample before onset of the disease and four weeks after the onset. This was possible for most secondary cases in the household; for index cases, the first blood sample was taken at the time of the first visit. This could occur within the first few days after the onset of the rash, but sometimes would occur much later. When the first blood sample was taken late in the acute phase (at week 2 or 3), an effort was made to take the second blood sample to document the decrease of HI antibodies after the acute phase. For isolated cases, especially cases outside of the study area, only one blood sample could usually be taken. In this case, a high titer was not considered to be a confirmation of measles infection but was considered a useful piece of information.

Blood samples were taken in the compound, by the field physician, during the visits for clinical examination. The handling of the blood samples was identical to that of those taken after vaccination: samples were taken in cold box to the field station where they were centrifuged at night and frozen. They were taken to Dakar every Friday night and then to Fajarah regularly. The tittering of HI antibodies was done exactly the same way as for post vaccination samples.

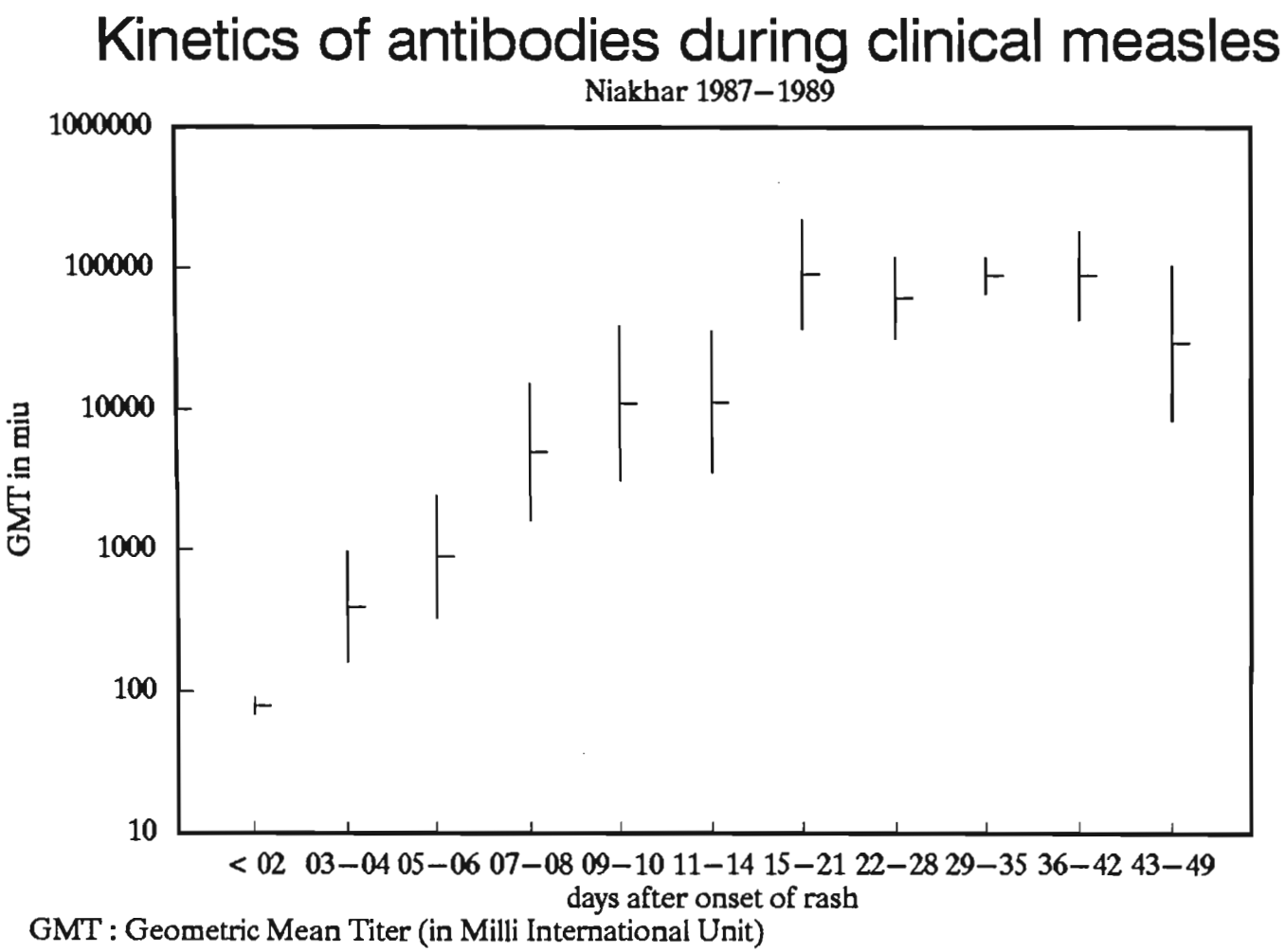
6.11 KINETICS OF HI ANTIBODIES DURING THE COURSE OF INFECTION

Because blood samples were not all taken at the same time after onset of infection, data permitted a crossectional analysis of the kinetics of HI antibodies. The GMT of HI measles antibodies were lowest during the incubation period and the first two days of clinical manifestation. It started rising at day 3, approximately the day of onset of the rash and reached a maximum after 4 weeks of clinical manifestations. The GMT stayed at high levels for about two weeks, after which it started to decay gradually (table 6.16, figure 6.8).

Distribution of HI antibodies was somewhat different for cases among vaccinated (table 6.17). Among children who later developed measles, sampled at most 42 days prior to infection and before day 3, there was a higher GMT among vaccinated children; among cases sampled from day 28 to day 42 the GMT was higher among unvaccinated children; among contacts who were susceptible but not infected the GMT was higher among vaccinated children.

Change in HI antibody titer during the course of infection was also different between vaccinated and unvaccinated children (table 6.18). For children sampled before day 3, the rise of HI antibodies was 11.1 times higher among unvaccinated children (842/76); for children sampled between day 3 and day 14, the rise of HI antibodies was 5.7 times higher among unvaccinated children (223/39). In the first group all children had at least a 16-fold increase in titer; in the second group this proportion was 83.1% in the unvaccinated group and 72.2% in the vaccinated group.

Figure 6.8



GMT : Geometric Mean Titer (in Milli International Unit)

6.12 SUBCLINICAL MEASLES AND BOOSTER EFFECT

There was no systematic attempt to study subclinical measles or booster effects after exposure to measles in a compound. However, in several instances blood samples with either a significant rise in antibody titers or with high antibody titers were available for children who did not have any clinical manifestation but were exposed in a compound. These 17 cases are displayed in detail in annex A-1:

5 children had a significant rise in antibodies after exposure to measles:
- 3 children were vaccinated with the EZ-HT vaccine
- 1 child was vaccinated earlier with a standard vaccine
- 1 child was 3 months old and had no detectable antibodies at time of exposure. He was vaccinated later at 5 months but failed to seroconvert.

12 children had very high titers (>=2^12) after exposure to measles:
- 5 children were vaccinated earlier with a standard vaccine
- 1 child had measles earlier
- 6 children had an unknown vaccination and measles status.

There was no evidence that any of these children had transmitted the virus to another child. In one of the compounds (01-002) there was a missing link between two generations: we did not find evidence of an increase in antibodies titer among the only susceptible child who could have been responsible for transmission and who did not develop measles (the child was vaccinated).

6.13 SEROLOGICAL CONFIRMATION

Serological confirmation was defined as follows:
- at least a 4-fold increase in HI antibodies during the acute phase (that is during the first 42 days of clinical signs); 157 cases met this definition (51.3%)
- or at least a 2-fold decrease in HI antibodies after the acute phase (that is after the first 42 days of clinical signs); only 2 cases met this definition (0.6%)

As in the case of indirect clinical confirmation, indirect serological confirmation was defined as a contact with a serologically confirmed case in the same compound (table 6.19): 36 children met this definition (11.8%). Altogether, 63.8% of cases were serologically confirmed.

The proportion of cases serologically confirmed depended upon the time at which the first blood sample was taken and whether a blood sample had been taken. There were only a few cases of systematic refusal of blood sampling: four entire compounds, among them was the one with the largest number of cases. In addition, in a number of cases the second blood sample could not be taken, due to refusal by mother or temporary absence of the child.

As was the case for clinical confirmation, the proportion of cases that were serologically confirmed strongly varied between cases outside of the study area (5.6 %), index cases (66.3 %) and secondary cases (82.5 %). Altogether 52.0% of cases were directly confirmed and an additional 11.8% were indirectly confirmed by contact within the same compound. These proportions were slightly lower for vaccinated children, among whom only 46.7% were directly confirmed and 13.3 % indirectly confirmed.

PART IV : CASE DEFINITION

6.14 SENSITIVITY AND SPECIFICITY OF VARIOUS CRITERIA

Table 6.20 displays the sensitivity and specificity of various criteria used for characterizing measles cases. Sensitivity was computed as the proportion of measles cases fitting the criteria. Specificity was computed as 1 minus the the proportion fitting the criteria among contacts who did not develop measles. Values of sensitivity were relative to the case detection strategy and to the time at which the child was examined or had a blood sample taken. Therefore, values of sensitivity and specificity were given for: 1) the population as a whole 2) children who were examined or sampled at the optimal time; that is day 1-42 for rash and desquamation, day 1-8 for Koplik spots, day 3-10 for maximum clinical score. Values of specificity were relative to the definition of measles. In this study, emphasis was on clinical measles: therefore 100% specificity for major clinical signs was expected.

In optimal conditions, high values of sensitivity were obtained for typical rash (99.2%), clinical score >= 8 (92.4%), 4 fold and 16 fold increase in HI antibodies (100%). Low values of sensitivity were obtained for Koplik spots (38.8%) and for titers at least equal to 16,000 miu (82.3%). High values of specificity were obtained for all signs taken in optimal conditions.

In the population as a whole, values of sensitivity were lower because many cases were not examined or sampled at the optimal time. Values were low for rash (78.8%), maximum score (71.7%), 16 fold increase in HI antibodies (51.8%), 4 fold increase in HI antibodies (60.9%), titers at least equal to 16,000 miu (57.6%) and very low for Koplik spots (25.4%).

6.15 CASE DEFINITION

Due to the high values of sensibility and specificity found among children who were examined and had blood taken at the appropriate time and to the lack of evidence for subclinical measles among contacts, we considered two case definitions:

Definition 1 : all cases, that is all cases reported by the family, that were considered as being real measles after all possible investigations were made, even if they were not clinically or serologically confirmed.

Definition 2 : confirmed cases, that is all cases meeting definition 1 that were clinically and serologically confirmed, either directly or indirectly.

Definition 1 does not include all cases that were suspected by the families, but all those that were later recognized as measles by the family and accepted as such by the investigators. In fact, it happened that in the middle of an outbreak in a village, a mother would say that she feared that her child was developing measles, because the child had, for instance, fever and cough. These cases were investigated by the physician and found to be of another etiology. Later, in May 1990, the physician went back to the family to ask the mother if she felt that the child had in fact had measles at that time; in all cases, the mother answered no. This matches previous observations in the study area, where it was found that it was easier to determine measles retrospectively, say after a few months, than it was for a physician who was examining a child in a clinic at the time of an outbreak.

Definition 2 is obviously quite restrictive in this context, since it eliminates about one third of cases that were most likely real measles cases. The proportion of confirmed cases among vaccinated children (53.3%) was slightly lower than that of cases among unvaccinated children (67.4%). Therefore, estimates of vaccine efficacy using definition 1 or definition 2 might be slightly different. A simple computation showed that if the proportion of confirmed cases was lower for vaccine failures (cv) than for unvaccinated cases (cn), then the estimate of vaccine efficacy was overestimated with definition 2:

$$e_1 = 1 - (iv)/(in)$$
$$e_2 = 1 - (cv*iv)/(cn*in)$$

$$(1-e_2)/(1-e_1) = cv/cn$$
$$e_2 = (cv/cn)*e_1 + (1-cv/cn)$$

$$\text{if } cv/cn < 1 \text{ then } e_2 > e_1$$

where e is the vaccine efficacy, iv is the incidence among the vaccinated group and in the incidence among the unvaccinated group. For instance, if cv/cn = .790 and e_1 = .850, then e_2 = .882 which will overestimate the true vaccine failure by 21%.

6.16 SUMMARY OF MAIN POINTS

- There were three outbreaks of measles between August 1987 and August 1990, with a total of 548 cases; 60% of cases were secondary in the compound. In addition 53 children developed measles outside of the study area.

- Incidence in the general population was lower than during previous years. Due to the high level of care provided, measles mortality was 73% lower than during previous years.

- Among cases of vaccine failure, clinical signs were milder, severity was lower and rates of complications were also lower.

- 80.1% of all cases that occurred in 1987-1989 were confirmed by the observation of clinical signs by the field physician. The proportion of children with a score at least equal to 8 was 92.4% when the child was examined during the acute phase (3 to 10 days after onset).

- 60.0% of all cases that occurred in 1987-1989 were serologically confirmed. The proportion of cases with at least a 4 fold increase in antibodies was 100% when the first sample was taken prior to 2 days after the onset of the rash and when the second sample was taken at least 28 days after the onset of the rash.

- 46.1% of all cases that occurred in 1987-1989 were directly confirmed (clinically and serologically) and 15.0% were indirectly confirmed. Proportion of confirmed cases was lower among cases of vaccine failure.

CHAPTER 7

VACCINE EFFICACY

Two studies of vaccine efficacy were conducted among project children: a study of cohort efficacy among the 24 birth cohorts vaccinated, and a study of case-contact efficacy among cases that occurred among the children present in the study area during measles outbreaks. In addition, and for comparison, vaccine efficacy of standard vaccines was also studied among older children who did not participate in the study but who were vaccinated during earlier vaccination campaigns. All measles cases that occurred between August 15, 1987 and August 14, 1990 were included for these studies of vaccine efficacy.

7.1 DEFINITIONS

Measles cases

The case definition for measles cases was discussed at length in the previous chapter. Two definitions were used in this chapter:

a) confirmed cases (N=211)

They include: all cases that were clinically confirmed and serologically confirmed (directly or indirectly). Indirect confirmation here means in contact with a confirmed case in the same compound.

b) all cases (N=589)

They include all confirmed cases plus:
- clinically confirmed cases which were not serologically confirmed (N=316); most of these were cases from the spring of 1990 for which blood samples were not available when this report was written;
- cases reported by family for which no confirmation could be made by the team (N=78): most of them were cases outside of the study area or isolated cases that were detected too late;
- there was no serologically confirmed case that was not clinically confirmed.

Outbreak in a compound

An outbreak in a compound is a series of measles cases linked together, ie for which there is evidence of transmission. Two outbreaks were considered different when there was a discontinuity in the transmission within the compound and when other cases developed later from another source. This occurred in a case in September 1989, where a first case did not infect anybody because he was away during the infective period, but the susceptible children were infected 17 days later by another child from a neighboring compound.

Susceptibles

For the case-contact study, susceptibles were all children present at the time of the measles outbreak in the compound, who never had measles, whatever their vaccination status. The susceptible population was broken down according to vaccination status and type of vaccine received.

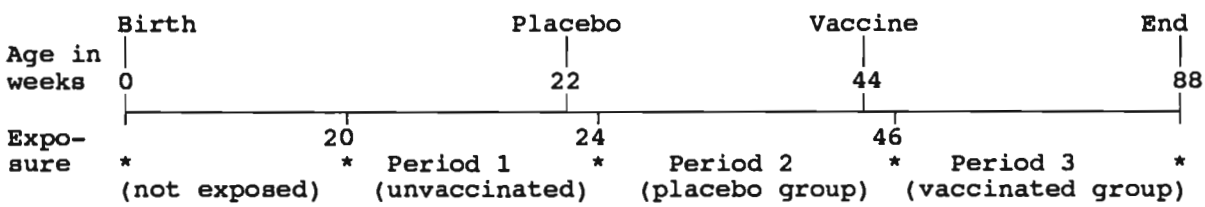
Contacts

Contacts were all susceptibles who did not develop measles during the current outbreak plus all secondary cases in the compound. In certain compounds there were two outbreaks at two different times during the study period. Some of the children could be non infected contacts for one outbreak and cases for the next outbreak. In a special case, a child was a secondary case in his own compound, therefore a contact, and index case in another compound where he was sent during the incubation period, therefore not counted as a contact in the second compound.

Exposure to measles

Exposure to measles begins at age 140 days (20 weeks), since virtually no case was ever recorded prior to this age in the study area. The exposure period ends either at onset of measles rash, if the child develops measles, or at the end of the study, or at time of death or at time of outmigration, which ever comes first. Exposure started on August 15, 1987 and lasted until August 14, 1990.

For the cohort studies, exact periods of exposure were computed in each case for each child. Exposure in a vaccinated group, including the placebo group, starts 14 days after the injection; before that date, the child is considered to belong to the unvaccinated group. For instance a child can start his exposed life in the unvaccinated group, from age 20 to age 21 weeks, then receive the placebo at age 22 weeks and later the Standard measles vaccine at age 44 weeks (see diagram below). He will have a first exposure period in the unvaccinated group from age 20 to 23 weeks, then a second exposure period in the placebo group from age 24 to 45 weeks, then a third exposure in the vaccinated group from age 46 weeks until the age at the end of the study.



For the case-contact study, the residence and susceptible situations of the children were assessed separately for each outbreak. In the case of two successive but different outbreaks in a compound, a child was considered a contact not infected during the first outbreak and a case during the second outbreak.

Incidence

Incidence was computed by dividing the number of measles cases by the person-years at risk lived by the susceptible population during the period of exposure. This could be done between two points in time or between two ages.

$$i = \text{nb cases} / \text{PYS spent between time } t_1 \text{ and time } t_2 \text{ (or between age } a_1 \text{ and age } a_2\text{) in the susceptible population}$$

Case/contact ratio

In the case contact study, the case/contact ratio (secondary attack rate) was defined as the ratio of cases over the contacts during the outbreak.

p = nb cases / nb contacts

Vaccine protection

Protection after vaccination was assumed to be effective 14 days after the injection; therefore a case whose rash developed more than 14 days after vaccination was considered a vaccine failure. In the sample, there was 1 case of a child vaccinated the day before the onset of rash: he was counted as an unvaccinated child. All the other cases among vaccinated children occurred at least 87 days after the injection (1 case at 87 days and all the others at least 1 year after vaccination).

Cohort efficacy

Vaccine efficacy in cohorts was computed using the standard formula:

$e = 1 - (i_1 / i_0)$

where i_0 = incidence in unvaccinated group
i_1 = incidence in vaccinated group

Case-contact vaccine efficacy

Vaccine efficacy was estimated in case-contact situations using the standard formula:

$f = 1 - (p_1 / p_0)$

where p_0 = case-contact ratio in unvaccinated group
p_1 = case-contact ratio in vaccinated group

7.2 VACCINE EFFICACY IN COHORTS

The cohort efficacy study was based on the 2470 children belonging to the 24 birth cohorts. 3 children were not considered because they received accidentally a vaccine that was not scheduled. Children were considered exposed to measles from the age of 20 weeks until either the end of the study, onset of measles, death or outmigration. Among the 2470 children, 2224 were still resident at age 20 weeks and 2044 were still resident at the end of the study. By August 15, 1990, the oldest cohort, born in February 1987, was exposed on the average for 25.3 months to measles and the youngest cohort, born in January 1989 was exposed only for 6.9 months.

Among the study children there were 68 cases of measles recorded prior to August 15, 1990, of which 26 were confirmed cases (table 7.1). For all groups combined, incidence was 14.0/1000 person-years, whatever the vaccination status and 40.6/1000 person-years among the unvaccinated children.

Four vaccine groups were considered for analyzing the exposure according to vaccination status:
- EZ-HT, who received the Edmonston-Zagreb vaccine age at 5 months,
- SW-HT, who received the Schwarz high titer vaccine at age 5 months,
- Placebo, who received the placebo at age 5 months (only between 5 and 10 months)
- Standard, who received the standard measles vaccine at 10 months or more.
- Not vaccinated, the unvaccinated group.

Results of the detailed computations of cohort efficacy are displayed in tables 7.2a to 7.2c. Before the 5 months vaccination session there were 3 measles cases: they all appear in the unvaccinated group. Between 5 and 10 months there were 18 cases, 1 in the EZ-HT group, none in the SW-5 group, 5 in the placebo group and 12 in the unvaccinated group. Between 10 months and the deadline, there were 47 cases, 4 in the EZ-HT group, 5 in the SW-HT group, none in the Standard group and 37 in the unvaccinated group. The remaining 3 cases were among non-residents.

Contacts with measles within the compound were similar in all groups, which gives a high value to the cohort studies (table 7.3). Computed as the number of project children exposed within a compound of the study area divided by the number of person-years at risk, the exposure rate was for the first 16 cohorts: 45/1000 in the EZ-HT group, 32/1000 in the SW-HT group, 39/1000 in the Standard group and 27/1000 in the unvaccinated group; for the last 8 cohorts, the exposure rate was 41/1000 in the EZ-HT group, 54/1000 in the Standard group and 51/1000 in the unvaccinated group.

Incidence was much lower in the vaccinated groups, as expected: between 5 and 10 months, measles incidence was 4.0/1000 in the EZ-HT group, 0 in the SW-HT group, 19.4/1000 in the placebo group and 28.6/1000 in the unvaccinated group. None of these differences was significant (table 7.2a).

After age 10 months, measles incidence was 4.2/1000 in the EZ-HT group, 8.0/1000 in the SW-HT group, 0.8/1000 in the Standard group and 56.8/1000 in the unvaccinated group (table 7.2b). Each of the three vaccines was protective against measles after 10 months, when compared to the unvaccinated group.

For all ages grouped together, final values of vaccine efficacy could be derived (table 7.2c). For all cohorts, vaccine efficacy was 98.0% for the Standard vaccine, [95% confidence interval CI=85.8-99.7, p=1.0E-4], 89.9% for the EZ-HT vaccine [CI=74.7-95.9, p=1.1E-6], and 83.6% for the SW-HT vaccine [CI=58.9-93.4, p=1.2E-4]. There were 5.2 times more vaccine failures after the EZ-HT vaccine and 8.3 times more vaccine failures after the SW-HT vaccine than after the Standard vaccine (figure 7.1). These results could be correlated with the low values of geometric mean titers of measles antibodies 5 months after the vaccination (see chapter 5).

When restricted to confirmed cases, vaccine efficacy was: 100% for the Standard vaccine, 84.4% for the EZ-HT vaccine [CI=47.6-95.3, p=0.0026], and 83.1% for the SW-HT vaccine [CI=28.0-96.0, p=0.0164].

Figure 7.1

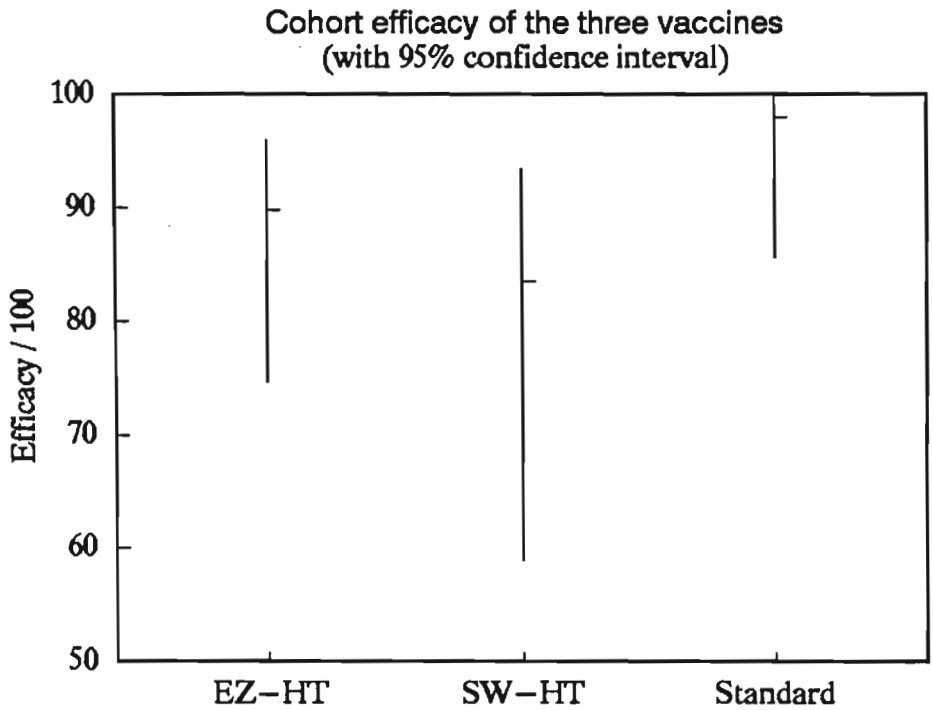
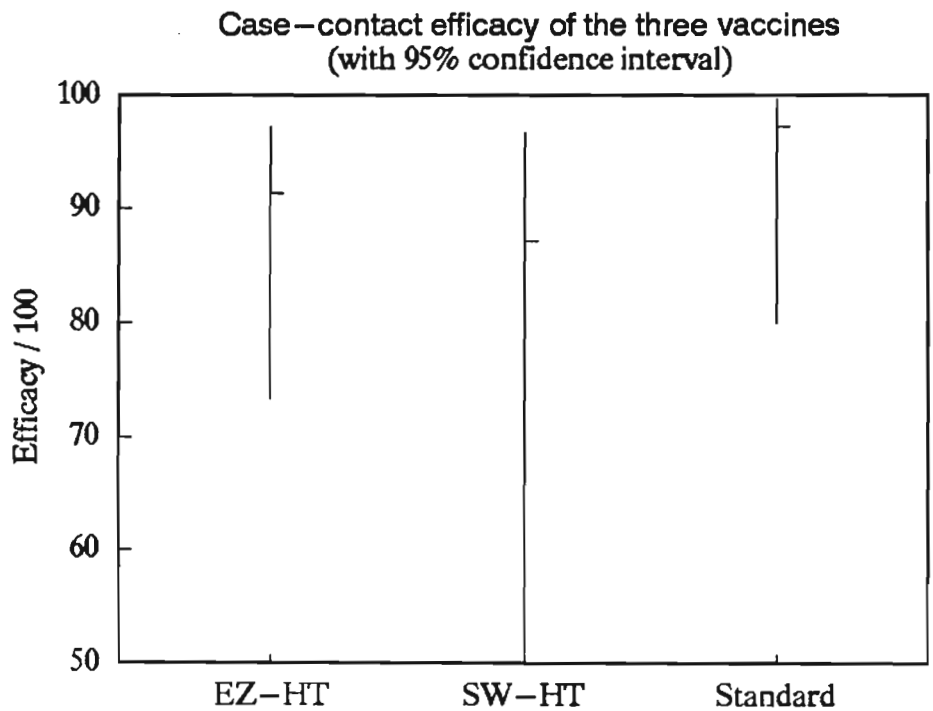


Figure 7.2



7.3 CASE-CONTACT EFFICACY

Results of the cohort study were confirmed by the case-contact study, which controls for exposure. Therefore, all ages were combined (table 7.3). For all cohorts, estimates of vaccine efficacy fell close to those of the cohort study: 97.4% for the Standard vaccine [CI=81.4-99.6, p=0.0008], 91.7% for the EZ-HT vaccine [CI=74.4-97.3, p=0.0001], 86.4% for the SW-HT vaccine [CI=47.7-96.5, p=0.0072]. Relative risks of vaccine failure were also high for the two high titer vaccines: 3.2 for the EZ-HT and 5.2 for the SW-HT (figure 7.2).

When restricted to confirmed cases, estimates of vaccine efficacy were somewhat higher: 100% for the Standard vaccine, 94.2% for the EZ-HT vaccine [CI=77.1-98.5, p=0.0001], 93.6% for the SW-HT vaccine [CI=56.0-99.1, p=0.0086].

7.4 MULTIVARIATE ANALYSIS

Since the number of cases was small, it was not possible to conduct an in-depth multivariate analysis that included prevaccination antibody titers and seroconversion. Only three variables were introduced in the multivariate analysis: sex, age which is also a measure of the duration since vaccination for those vaccinated and a proxy for maternal antibody titers for unvaccinated children, and intensity of exposure based on a scale from 1 to 4 which measured the social proximity between index and secondary cases. Results (table 7.4) show that age and sex were not significant; intensity of exposure was a significant factor (odds ratio RR=2.3, P=0.0272); vaccine efficacy was found to be highly significant: P=5.6E-6 for the Standard vaccine, P=3.2E-7 for the EZ-HT vaccine, 2.0E-4 for the SW-HT vaccine. Higher values of the odds ratio were found in the multivariate analysis because intensity of exposure was controlled for, but the relative risks of vaccine failure in the two high titer vaccine groups were of the same order of magnitude when compared to the univariate analysis: 2.7 for the relative failure rate of the EZ-HT vaccine and 6.8 for the relative failure rate of the SW-HT vaccine.

7.5 EFFICACY OF STANDARD VACCINES AMONG OTHER CHILDREN

The measles and vaccination status of other children living in the community was also known for most children born since 1978 and for most children of the phase II area. Incidence of measles for children born between January 1, 1978 and December 31, 1986 was also investigated during the period from August 15, 1987 to August 14, 1990. Although these children were not randomized, it was still possible to control for exposure to measles in the study area and therefore to compute valuable estimates of cohort and case-contact efficacy.

There were two vaccination campaigns that could have affected those children: a campaign organized by the director of this study in the spring of 1981, 1982 and 1983 in the 8 villages of the phase II area (1089 children vaccinated), for which the quality of the vaccine and the safety of the cold chain were high; the national vaccination campaign which was monitored by the team between October 1986 and April 1987 but for which there was no control on the cold chain (1397 children vaccinated). Some of the children were also vaccinated during the project (1987-1989). Other information on vaccination came from vaccination cards which were systematically asked for every year during the demographic census and every time a new immigrant arrived in the study area. Children whose vaccination status and measles status were unknown as well as children who had a record of two measles vaccinations were counted with the "other and unknown". There were 28 cases of vaccine failure among other children, 451 cases among unvaccinated children and 41 cases among children of unknown vaccine status (table 7.5).

Results of the cohort efficacy study appear in table 7.6. The 81-83 campaign had a 96.4% efficacy [CI=74.2-99.5, p=0.0010]; the 86-87 campaign had a 86.4% efficacy [CI=77.2-91.9, p=1.0E-13].

Results of the case-contact efficacy study appear in table 7.7. The 81-83 campaign had a 100% efficacy and the 86-87 campaign had a 92.5% efficacy [CI=84.5-96.4, p=3.2E-11]. When restricted to confirmed cases, the efficacy of the 86-87 campaign was 94.6% [CI=87.3-97.7, p=1.9E-10].

7.6 PROTECTIVE VALUES OF ANTIBODIES

Since in many cases antibody levels were measured at time of exposure, it was possible to evaluate the protective levels of measles antibodies. The analysis was done separately for vaccinated and unvaccinated children (table 7.8). Among unvaccinated children, 42.9 % having a titer from 250-499, 40.0% having a titer from 500-999, and 9.1% having a titer from 1000-1999 contracted measles. A titer above 125 miu was fully protective among vaccinated children. A titer below 125 miu was 26.1% protective among unvaccinated children and 66.7% protective among vaccinated children. This indicates that our definition of "sero-positivity" (at least 125 miu) might be the closest to vaccine protection within two to three years after vaccination, despite the fact that it includes a small proportion of children who are protected despite having no detectable levels of antibodies.

7.7 DISCUSSION

The principal objective of the study was to assess whether high titer measles vaccines were effective in protecting against clinical measles between the ages of 5 and 10 months. Due to the low incidence of measles during the first 18 months, the study failed to provide a definitive answer to this question. However, efficacy of the high titer vaccines was demonstrated both in cohort and in case-contact studies after 10 months: this demonstrates a posteriori the efficacy of the vaccines between the ages of 5 and 10 months.

The standard vaccine had a failure rate comparable to what was found in the United States where the vaccine is administered in the second year of life (chart 7.1). The fact that high relative vaccine failure rates were found among the recipients of the high titer vaccines indicates that the strategy of vaccinating early in life with high titer vaccines is not an optimal approach.

Chart 7.1 Estimates of measles vaccine efficacy in the USA.

Location	Author	Year	Study	Efficacy [95% CI]	(N)	Age (mostly)
Texarcana	Landrigan	1971	P-B	95.9	(606)	1-9
Connecticut	DeWayne	1972	C/C	95.9	(134)	3-14
N+S Dakota	McCormick	1974	C/C	97.3 [80.1-99.9]	(9)	0-9
New Jersey	Ziskin	1974	C/C	a 94.3 b 87.2	(172) (75)	13-18
Chicago	Bennish	1983	Hos	?[1]	(85)	all (0-10)
Waltham, MA	Nkowane	1984	C/C	94.4 [90.6-97.0]	(27)	school (14-18)
Montana	Davis	1985	R-C	96.9 [89.5-98.2]	(137)	all (0-14)
Wisconsin	Mast	1986	C/C	93.2 [81-98]	(10)	school (1-24)
Colorado	Hersh	1991	R-C	a 94. b 80.[2]	[86-98] (84)	college

Method: C/C= case-contact, R-C= retrospective cohort, P-B= population based, Hos=hospital based

[1] 92.5% of cases were vaccinated; assuming 98% coverage, this would lead to an estimate of 74.5%.

[2] if child vaccinated before 15 months.

7.8 SUMMARY OF MAIN FINDINGS

- Both EZ-HT and SW-HT were protecting against clinical measles. This was demonstrated in a cohort study as well as in a case-contact study. In the cohort study, the EZ-HT vaccine had a 89.9% efficacy, the SW-HT vaccine a 83.6% efficacy and the Standard vaccine a 98.0% efficacy.

- The Standard vaccine had an efficacy comparable to values found in the USA.

- Within 2 to 3 years after vaccination, the failure rate of the EZ-HT vaccine was 5 times higher than the failure rate of the Standard vaccine; the failure rate of the SW-HT vaccine was 8 times higher than the failure rate of the Standard vaccine.

- These results were stable in a multivariate analysis which controlled for intensity of exposure.

- The efficacy of the Standard vaccine among older children vaccinated in 1981-1983 was also high (96.4%): this value was consistent with the efficacy of the Standard vaccine given during the project, despite the fact that these children were vaccinated 5-9 years before.

DISCUSSION

8.1 ETHICAL ISSUES

An increase of mortality after high titer measles vaccine was obviously not expected by the investigators. When preparing the research protocol for this trial from March to November 1986, extensive consultations were held with experts on measles vaccines worldwide, in West Africa, Europe and the United States. The question of potential impact on mortality was raised at that time, but no empirical evidence was found to support this hypothesis. In fact, the alternate hypothesis was thought to be likely, and this was the aim of the project: that is, that live vaccines given early in life would reduce mortality rates of infants and children, by protecting them against measles. The EZ vaccine has been used in Yugoslavia for about 22 years without any evidence of causing harm to children. It is likely that the excess mortality effect the only relative to the combination of high titer, early age at vaccination and poor health conditions of the children.

Mortality data were carefully monitored month by month from 1987 to 1989, using a computer program (SAFEMONE): mortality was similar in all groups during the first two years of the trial. The differences in mortality by group were presented at two of the Data Monitoring and Safety Committees, in October 1988 and in June 1989. There was no significant difference in mortality between the groups. The statistical evidence of excess mortality became clear in April 1990, when the data from the 1989 rainy season became available and definite after the 1990 rainy season. The use of the EZ-HT vaccine was stopped in November of 1990. The use of the SW-HT vaccine was stopped in October 1988, when it became clear that it produced a lower serologic response.

Children who participated in the trial and received the high titer measles vaccines had at most the mortality rate of the cohorts preceding them. Children who participated in the study but did not receive the high titer vaccines had better chances of survival than previous cohorts. In addition, the population benefitted from the project in terms of survival: there was a marked reduction in age specific mortality rates at all ages. However, if the vaccine can account for 5% of excess deaths among vaccinated children, then the potential harm is greater than the potential benefit of an early vaccination at 5 months, which would save only 0.4% lives.

The local population received information about the study, its aim and methodology through three main channels. In February and March 1987, four months before the trial started, village gatherings were organized: the field physician explained the aims and the methodology of the project as well as the right of the women to refuse to participate and the right to withdraw. Field workers who had weekly contacts with the mothers were informed and were asked to provide any further information to mothers and fathers at their request. The physicians who were organizing the vaccination sessions were available to provide any further information. Informed consent was simultaneously collective and individual. Some families and even whole hamlets refused to participate in the trial. Some changed their minds during the course of the study. Some mothers individually refused to participate in the trial. Of course those who refused to participate were offered the standard routine vaccines and received the same care as the others.

Children who were at higher risk of dying after high titer measles vaccines, seemed to have died from common childhood diseases. They should receive more intensive care to compensate for their increased risk. A design for appropriate care specially targeted to children who received a high titer measles vaccine was presented to the health authorities.

8.2 THE CONTROL OF EARLY MEASLES MORTALITY

The issue of the control of early measles mortality remains open. A major lesson of this study was that measles mortality could well be controlled in local conditions when appropriate, timely care was provided to children. A combination of early and appropriate medical care together with high vaccination coverage, using standard vaccines at 9 months is one of the currently available strategy to control measles in developing countries.

Alternatively, two or three doses strategies may be studied. Since a proportion of children have already lost most of their maternal antibodies at age 3 and a higher proportion at 6 and 9 months, it might be desirable to investigate the impact of administering low titer measles vaccines systematically two or three times before age 12 months. Furthermore, it is possible that early vaccination prevents against the risk of death, if not against clinical infection.

The development of new vaccines that would be efficient, safe and immunogenic, even at very low titers and even when given early in life, could be a third valuable strategy. The ideal situation would be to be able to combine these new vaccines with other EPI vaccines.

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TABLES

Table 0.1 Measles vaccines reported among the resident of the 8 villages of phase II area, Ngayokheme, 1963-1989.

	Year											
Month	66	69	79	81	82	83	85	86	87	88	89	Total
Jan	0	425	0	0	0	0	0	0	41	14	15	495
Feb	0	0	0	0	122	0	0	0	218	6	9	355
Mar	156	0	0	312	50	600	0	0	90	14	14	1237
Apr	382	0	0	0	0	0	0	0	0	11	15	408
May	0	0	0	0	0	0	0	0	1	17	21	39
Jun	0	0	0	0	0	0	0	0	0	15	24	39
Jul	0	0	0	0	0	0	0	0	1	13	23	37
Aug	0	0	0	0	0	0	0	0	27	22	23	71
Sep	0	0	0	0	0	0	2	0	12	11	23	48
Oct	0	0	0	0	0	0	0	0	11	9	8	28
Nov	0	0	0	0	0	0	1	2	5	10	6	24
Dec	0	0	130	0	0	63	4	15	13	8	16	249
Total	538	425	130	312	172	663	7	19	419	149	197	3031

Table 0.2 Measles cases among the resident of the 8 villages of phase II area, by month and year, Ngayokheme, 1963-1989.

	Month												
Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total
1963	14	14	30	22	18	19	32	19	15	16	15	12	226
1964	6	5	17	35	10	4	7	20	11	6	3	8	132
1965	2	5	140	20	4	13	4	4	4	1	4	1	202
1966	1	73	86	18	4	2	1	2	1	1	1	2	192
1967	0	1	5	3	4	0	0	1	0	2	0	0	16
1968	1	2	2	2	0	1	1	0	0	0	0	0	9
1969	1	3	2	2	2	4	0	1	0	1	0	0	16
1970	0	0	0	0	0	2	0	0	1	0	0	0	3
1971	8	1	3	32	9	2	0	2	1	1	1	1	61
1972	2	1	0	11	36	3	1	9	1	0	3	2	69
1973	0	3	19	12	30	9	12	3	4	4	4	20	120
1974	42	2	2	1	4	3	3	1	6	5	2	2	73
1975	3	5	5	8	5	3	5	0	3	5	1	2	45
1976	2	1	7	2	6	5	4	0	5	3	8	0	43
1977	6	4	17	9	7	20	9	5	9	10	6	8	110
1978	14	21	18	28	39	7	6	16	8	9	9	18	193
1979	1	25	20	18	15	6	3	4	0	3	1	5	101
1980	1	1	9	9	15	0	0	2	5	0	3	1	46
1981	8	10	3	1	9	0	0	2	1	0	1	0	35
1982	1	5	9	2	2	0	0	0	0	1	4	14	38
1983	69	55	45	45	13	0	0	2	0	0	1	0	230
1984	3	4	2	9	5	0	3	4	1	8	2	1	42
1985	6	5	2	8	12	4	3	2	6	9	4	28	89
1986	6	10	19	2	6	0	0	0	0	0	0	0	43
1987	0	1	14	13	3	0	0	2	0	0	0	0	33
1988	0	0	0	0	1	0	0	0	0	0	1	0	2
1989	4	2	9	3	11	11	4	0	0	0	0	0	44
Total	201	259	485	315	270	118	98	101	82	85	74	125	2213

Table 2.1 : Basic demographic rates and events by calendar year, Niakhar 1983-1989 (updated in April 1990).

Year	1983*	1984	1985	1986	1987	1988	1989	total
EVENTS								
Resident 1/1	22830*	23137	23459	23569	24202	24865	25247	26356**
Births	773	1236	1096	1277	1247	1214	1252	8095
Deaths	276	555	706	432	567	410	314	3260
Nat. Increase	497	681	390	845	680	804	938	4835
Inmigration	609	778	646	1041	1087	995	874	6030
Outmigration	799	1137	926	1253	1104	1417	703	7339
Net migration	-190	-359	-280	-212	-17	-422	171	-1309
Pop. growth	307	322	110	633	663	382	1109	3526
Move within	346	488	443	644	632	752	612	3917
Migrat. flow	2100	2891	2458	3582	3455	3916	2801	21203
Mean Popul.	23177	23421	23459	23816	24560	25060	25722	24229
Duration	0.630	1.000	1.000	1.000	1.000	1.000	1.000	6.630
Person-years	14604	23420	23459	23816	24560	25060	25722	160643
RATES /1000								
Birth	52.9	52.8	46.7	53.6	50.8	48.4	48.7	50.4
Death	18.9	23.7	30.1	18.1	23.1	16.4	12.2	20.3
Nat.increase	34.0	29.1	16.6	35.5	27.7	32.1	36.5	30.1
Inmigration	41.7	33.2	27.5	43.7	44.3	39.7	34.0	37.5
Outmigration	54.7	48.5	39.5	52.6	45.0	56.5	27.3	45.7
Net migration	-13.0	-15.3	-11.9	-8.9	-0.7	-16.8	6.6	-8.1
Pop Growth	21.0	13.7	4.7	26.6	27.0	15.2	43.1	21.9
Moves within	23.7	20.8	18.9	27.0	25.7	30.0	23.8	24.4
Migrat. flow	143.8	123.4	104.8	150.4	140.7	156.3	108.9	132.0

* Year 1983 was incomplete. First Census was on average on 16 May 1983.

** Population on January 1, 1990.

Table 2.2 : Demographic events by month and year, Niakhar 1987-1989, (updated in April 1990).

Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total
Births													
1987	104	106	111	102	101	90	88	110	123	104	98	110	1247
1988	82	99	88	83	97	71	77	112	142	154	99	110	1214
1989	113	98	111	106	94	76	75	125	137	125	101	91	1252
Total	299	303	310	291	292	237	240	347	402	383	298	311	3713
Deaths													
1987	44	30	27	26	62	56	52	52	49	63	69	37	567
1988	33	29	26	23	21	24	38	38	43	74	41	20	410
1989	26	29	21	28	25	14	20	31	47	36	21	16	314
Total	103	88	74	77	108	94	110	121	139	173	131	73	1291
Inmigration													
1987	70	74	102	152	120	202	102	75	21	83	34	52	1087
1988	79	84	78	98	129	156	100	39	27	84	52	69	995
1989	84	57	106	61	121	120	80	41	34	106	34	30	874
Total	233	215	286	311	370	478	282	155	82	273	120	151	2956
Outmigration													
1987	50	68	82	164	170	204	65	66	54	88	40	53	1104
1988	68	96	119	174	218	220	142	85	71	99	47	78	1417
1989	80	75	99	115	121	116	23	11	14	22	19	8	703
Total	198	239	300	453	509	540	230	162	139	209	106	139	3224

Table 2.3 : Changes in age specific fertility rates by sex and period, Niakhar 1984-1989 (updated in April 1990).

Age	Baseline		Project					
	84-86		1987		1988		1989	
	ASFR	(N)	ASFR	(N)	ASFR	(N)	ASFR	(N)
Female fertility								
13-14	11.5	16	5.3	3	8.4	5	8.0	5
15-19	177.8	491	178.7	162	136.2	133	160.2	160
20-24	318.4	903	347.2	325	331.6	305	307.9	284
25-29	338.4	948	322.2	302	339.4	301	361.8	314
30-34	317.8	599	302.6	218	321.0	252	302.4	247
35-39	259.8	404	270.8	143	248.5	135	252.8	143
40-44	134.5	203	153.1	77	135.0	65	177.3	86
45-49	29.6	45	34.1	17	34.8	18	26.3	13
TFR	7.90	3609	8.05	1247	7.75	1214	7.96	1252
Index/ baseline	100.0		101.9		98.0		100.7	
Male fertility								
15-19	2.7	7	8.8	8	5.2	5	3.9	4
20-24	79.9	173	71.9	49	46.3	33	64.9	48
25-29	244.4	523	254.2	167	225.5	148	251.0	164
30-34	357.8	594	389.4	242	373.3	242	365.4	236
35-39	399.5	470	426.6	176	422.1	186	439.7	207
40-44	440.9	457	413.1	139	382.8	131	398.8	143
45-49	355.4	382	343.9	120	420.0	148	382.5	130
50-54	272.3	255	278.9	88	254.4	85	314.6	106
55-59	180.3	144	188.0	52	183.5	53	127.3	37
60-64	84.8	56	125.8	28	101.1	23	80.9	19
65-69	83.1	42	54.7	10	45.0	9	69.8	14
70-74	49.5	23	49.2	7	92.1	12	47.0	6
75+	30.1	16	34.2	6	37.7	7	16.0	3
Unknown*		467		155		132		135
TFR	13.20	3609	13.53	1247	13.32	1214	12.97	1252
Index/ baseline	100.0		102.5		100.9		98.3	

* Age of father was unknown when father was not resident in study area Births to non resident fathers were allocated proportionally to ages of resident fathers.

Table 2.4 : Multiplicity, sex ratio and life status of deliveries, Niakhar 1983-1989 (updated in April 1990).

I Sex ratio of live births according to multiplicity

Multiplicity	F	M	total	sex ratio	confidence interval	
Simple	3838	4030	7868	105.0	100.4	109.6
Twins	115	107	222	93.0	68.6	117.5
Triplets	3	2	5	66.7	0.0	183.5
Total	3956	4139	8095	104.6	100.1	109.2

II : Sex ratio of still births according to duration of pregnancy

duration	F	M	unknwon	total	sex ratio	% unknown
< 7 mo	25	23	284	332	92.0	85.5
7-10 mo	141	159	17	317	112.8	5.4
Unknown	17	25	32	74	147.0	43.2
Total	183	207	333	723	113.1	46.1

III Life status of deliveries according to multiplicity

multi-plicity	born alive	still birth	total	number deliv.	propo still birth /1000
Simple	7868	688	8556	8556	80.4
Twins*	222	34	256	128	132.8
Triplets	5	1	6	2	166.7
Total	8095	723	8818	8686	82.0

* 106 pairs 2 born alive, 12*2 still born, 10* one alive+one dead.

IV Multiplicity of deliveries according to life status

	born alive	still birth	total	number deliveries	% deliv.	ratio of multiple per deliv.	per live birth
Simple	7868	688	8556	8556	98.5		
Twins	222	34	256	128	1.5	67.9	36.5
Triplets	5	1	6	2	0.0	4343	1619
Total	8095	723	8818	8686	100.0		

Table 2.5 : Life table of the population over the course of the project, Niakhar 1987-1989 (updated in April 1990).

	Observed			Life table estimates					
Age x	P.Years PYS	Deaths D(x)	Rate nMx	Probab. nQx	Survivors l(x)	Deaths nDx	P.years nLx	Cumul. T(x)	Life ex. e(x)
Male									
0	1698.7	178	104.8	97.7	100000	9768	93219	5187305	51.9
1	5763.0	173	30.0	135.0	90232	12180	405760	5094085	56.5
5	5899.9	17	2.9	14.3	78052	1114	386703	4688325	60.1
10	4841.7	5	1.0	5.1	76938	396	383532	4301622	55.9
15	3265.5	3	0.9	4.6	76542	350	381852	3918089	51.2
20	2407.1	14	5.8	28.7	76192	2186	375932	3536237	46.4
25	2219.2	13	5.9	28.9	74006	2137	364794	3160305	42.7
30	2160.9	8	3.7	18.3	71869	1318	356050	2795510	38.9
35	1493.2	9	6.0	29.7	70551	2095	347622	2439460	34.6
40	1170.1	6	5.1	25.3	68456	1733	338086	2091838	30.6
45	1174.8	13	11.1	53.9	66723	3596	325020	1753752	26.3
50	1112.8	15	13.5	65.3	63127	4123	305946	1428731	22.6
55	965.7	22	22.8	108.0	59004	6374	279786	1122786	19.0
60	772.7	15	19.4	92.7	52630	4879	251342	842999	16.0
65	658.2	28	42.5	192.6	47751	9198	216219	591657	12.4
70	451.7	28	62.0	268.5	38553	10351	166991	375437	9.7
75	324.9	24	73.9	311.6	28202	8787	118954	208446	7.4
80	181.1	23	127.0	480.6	19415	9331	73467	89491	4.6
85	112.5	30	266.6	1000.0	10084	10084	16023	16023	1.6
Female									
0	1758.3	206	117.2	108.3	100000	10834	92479	5247643	52.5
1	5607.1	177	31.6	141.2	89166	12592	398894	5155164	57.8
5	5790.6	25	4.3	21.3	76574	1630	377665	4756269	62.1
10	4449.4	8	1.8	8.9	74944	670	372761	4378604	58.4
15	2881.8	7	2.4	12.1	74274	896	369174	4005842	53.9
20	2778.4	6	2.2	10.7	73378	788	365077	3636667	49.6
25	2692.2	15	5.6	27.5	72590	1994	358064	3271590	45.1
30	2322.4	13	5.6	27.6	70596	1948	348110	2913525	41.3
35	1637.9	9	5.5	27.1	68648	1861	338680	2565415	37.4
40	1469.4	8	5.4	26.9	66787	1794	329593	2226734	33.3
45	1510.9	9	6.0	29.4	64993	1908	320404	1897141	29.2
50	1396.6	14	10.0	49.0	63085	3089	308165	1576736	25.0
55	1185.7	23	19.4	92.7	59996	5561	286689	1268570	21.1
60	1016.6	8	7.9	38.6	54435	2101	267090	981881	18.0
65	745.8	28	37.5	171.9	52334	8996	239629	714790	13.7
70	548.7	25	45.6	204.6	43338	8867	194611	475161	11.0
75	394.8	31	78.5	327.9	34471	11304	143982	280549	8.1
80	280.0	27	96.4	387.6	23167	8978	93120	136567	5.9
85	202.5	28	138.3	1000.0	14189	14189	43446	43447	3.1

Table 2.6 : Changes in age specific death rates during the project, Niakhar 1984-1989, (updated in April 1990).

Age at death	Baseline (mean) 84-86	Project 1987	Project 1988	Project 1989	% reduction in death rate by age 89/84-86
0	129.1	127.3	135.2	73.1	-43.4
1-4	58.1	43.8	28.3	20.8	-64.3
5-9	5.0	3.7	1.9	2.3	-53.5
15-24	2.7	2.7	3.7	1.5	-43.2
25-34	5.3	9.6	2.9	3.2	-40.0
35-44	6.8	6.4	5.8	4.5	-33.0
45-54	12.9	13.4	9.7	6.4	-50.5
55-64	24.8	23.9	12.9	15.1	-39.0
65-74	54.5	76.2	34.0	25.9	-52.4
75-84	96.8	98.0	82.8	86.5	-10.6
85+	212.9	245.3	143.3	166.0	-22.0
all	23.9	23.1	16.4	12.2	-49.0

NB : for details of interventions, see text.

Table 2.7 : Changes in cause-specific probabilities of dying (/1000) during the project, children age 0-14 years, Niakhar 1987-1989, (updated in April 1990).

Cause of death	Baseline (mean) 84-86	Project 1987	Project 1988	Project 1989	% reduction in proba. of dying by cause 89/84-86
Neonatal					
Tetanus	15.8*	32.1	25.5	14.4	-9.1*
Hypotrophy	15.5	8.0	22.3	8.8	-43.4
Other,unknown	19.4	16.0	23.9	14.4	-25.9
Total	50.7	56.1	71.7	37.5	-26.0
Post-neonatal					
Measles	3.0	0.0	0.0	0.0	-100.0
Pertussis	6.5	3.2	0.0	0.0	-100.0
Diarrhea	19.8	23.1	13.3	6.6	-66.5
ARI	15.1	8.8	9.5	3.3	-78.0
Other,unknown	27.0	29.5	33.2	23.2	-13.8
Total	71.4	64.5	55.9	33.2	-53.5
Children age 1-4					
Measles	25.4	3.5	0.0	3.6	-85.8
Pertussis	15.1	3.5	0.0	0.0	-100.0
Diarrhea	76.2	52.3	28.4	24.1	-68.4
ARI	19.8	8.1	16.6	3.6	-81.8
Other,unknown	102.4	120.8	83.0	65.1	-36.4
Total	238.9	188.2	128.0	96.4	-59.6
Children age 5-14					
Measles	3.0	0.0	0.0	2.6	-11.4
Pertussis	1.0	1.3	0.0	0.0	-100.0
Diarrhea	9.5	10.7	1.4	2.6	-72.0
ARI	1.0	1.3	1.4	1.3	+32.9
Other,unknown	31.9	20.1	15.1	15.9	-50.2
Total	46.3	33.5	17.9	22.5	-51.4

* see text for comments

Table 2.8 : Residence status of the 24 monthly birth cohorts on 01/01/1990 (project children), Niakhar 1987-1989.

	Birth cohort	Size at birth	Status on 01/01/90			% Dead	% Outmig.	Age on 01/01/90
			Dead	Outmig.	Resident			
01	Feb 87	106	20	11	75	18.9	10.4	34
02	Mar 87	111	17	10	84	15.3	9.0	33
03	Apr 87	102	16	14	72	15.7	13.7	32
04	May 87	101	14	12	75	13.9	11.9	31
05	Jun 87	90	16	9	65	17.8	10.0	30
06	Jul 87	88	15	6	67	17.0	6.8	29
07	Aug 87	110	23	5	82	20.9	4.5	28
08	Sep 87	123	21	7	96	17.1	5.7	27
09	Oct 87	104	14	8	80	13.5	7.7	26
10	Nov 87	98	12	13	73	12.2	13.3	25
11	Dec 87	110	14	9	87	12.7	8.2	24
12	Jan 88	82	13	8	61	15.9	9.8	23
13	Feb 88	99	15	7	77	15.2	7.1	22
14	Mar 88	88	11	9	68	12.5	10.2	21
15	Apr 88	83	17	3	63	20.5	3.6	20
16	May 88	97	13	9	75	13.4	9.3	19
17	Jun 88	71	8	6	57	11.3	8.5	18
18	Jul 88	77	9	9	59	11.7	11.7	17
19	Aug 88	112	15	6	91	13.4	5.4	16
20	Sep 88	142	17	9	115	12.4	6.3	15
21	Oct 88	154	21	8	125	13.6	5.2	14
22	Nov 88	99	13	0	86	13.1	0.0	13
23	Dec 88	110	12	4	94	10.9	3.6	12
24	Jan 89	113	4	3	106	3.5	2.7	11
Total		2470	350	185	1933	14.2	7.5	

Table 2.9 : Survival of birth cohorts before and during project, Niakhar 1983-1989, from age 0 to 36 months.

Age in months x	Baseline Cohorts Feb 83-Jan 84 (N = 2073)			Project Cohorts Feb 87-Jan 89 (N = 2470)			% reduction in death rate
	Deaths	nQx	S(x)	Deaths	nQx	S(x)	
0	109	52.6	100000	157	63.6	100000	20.9
1	76	39.5	94742	47	20.8	93644	-47.2
6	75	41.1	90999	68	31.6	91692	-23.2
12	97	57.5	87257	37	22.6	88797	-60.6
18	73	46.3	82239	18	16.2	86787	-65.1
24	58	39.3	78431	15	23.4	85384	-40.4
30	25	18.1	75348	2	12.0	83382	-33.6
36	-	-	73983	-	-	82379	-

NB : Cohorts are truncated for project children.
Age 0 is < 28 days (neonatal period)

Table 3.1 : Attendance to vaccination sessions 01 through 29, Niakhar 1987-1989.

Vaccination session		Among project children convoked					Other		% refusal	% not conv
No	Week	Present (1)	Absent (2)	Refusal (3)	Emig (4)	Death (5)	P.C. (6)	else (7)	3/ 1+3	6+7/ 1+6+7
01	10/08/87	178	4	3	2	10	0	7	1.7	3.8
02	17/08/87	165	13	7	8	13	1	14	4.1	8.3
03	07/09/87	138	17	11	6	13	6	31	7.4	21.1
04	26/10/87	183	25	43	10	25	1	24	19.0	12.0
05	23/11/87	210	24	30	7	33	8	26	12.5	13.9
06	07/12/87	197	22	50	10	33	8	13	20.2	9.6
07	18/01/88	174	51	51	9	32	4	8	22.7	6.5
08	15/02/88	169	33	81	9	28	8	3	32.4	6.1
09	14/03/88	183	32	54	9	20	16	16	22.8	14.9
10	11/04/88	142	42	48	13	23	20	6	25.3	15.5
11	23/05/88	182	24	55	8	24	22	7	23.2	13.7
12	13/06/88	168	26	46	12	27	20	10	21.5	15.2
13	18/07/88	195	10	55	6	31	14	9	22.0	10.6
14	15/08/88	171	17	57	14	19	11	2	25.0	7.1
15	05/09/88	146	18	42	17	22	17	6	22.3	13.6
16	17/10/88	170	16	54	12	27	17	6	24.1	11.9
17	21/11/88	171	19	43	8	22	15	6	20.1	10.9
18	12/12/88	196	28	53	6	32	19	97	21.3	37.2
19	23/01/89	219	46	44	9	32	20	9	16.7	11.7
20	13/02/89	194	34	48	5	37	23	6	19.8	13.0
21	20/03/89	216	38	56	14	33	17	13	20.6	12.2
22	17/04/89	225	29	47	6	21	17	6	17.3	9.3
23	15/05/89	275	56	64	21	50	16	7	18.9	7.7
24	19/06/89	288	33	74	8	27	24	13	20.4	11.4
25	24/07/89	279	25	78	18	28	22	2	21.8	7.9
26	07/08/89	280	36	73	12	29	9	6	20.7	5.1
27	25/09/89	165	16	45	1	20	19	6	21.4	13.2
28	23/10/89	177	19	43	6	28	21	6	19.5	13.2
29	13/11/89	218	18	55	3	13	7	4	20.1	4.8
	Total	5674	771	1410	269	752	402	369	19.9	12.0
	%	63.9	8.7	15.9	3.0	8.5	6.2	5.7		

NB : vaccination sessions were conducted from Tuesday to Thrusday.

Table 3.2 : Attendance to vaccination sessions at age 5 months, according to birth cohort, Niakhar 1987-1989.

Cohort	Month of birth	Date of 5 months session	Attendance at 5 months session						% attend.
			Present (1)	Absent (2)	Refus. (3)	Emig (4)	Death (5)	Total (6)	1/1+2+3
01	02/87	17/08/87	78	12	2	6	8	106	97.5
02	03/87	10/08/87	99	6	1	0	5	111	99.0
03	04/87	07/09/87	71	11	11	3	6	102	86.6
04	05/87	26/10/87	65	10	16	3	7	101	80.2
05	06/87	23/11/87	58	9	12	3	8	90	82.9
06	07/87	07/12/87	53	8	16	1	10	88	76.8
07	08/87	18/01/88	66	15	9	3	17	110	88.0
08	09/87	15/02/88	66	12	32	1	12	123	67.3
09	10/87	14/03/88	65	12	16	4	7	104	80.2
10	11/87	11/04/88	50	14	20	6	8	98	71.4
11	12/87	23/05/88	69	12	18	4	7	110	79.3
12	01/88	13/06/88	46	12	14	4	6	82	76.7
13	02/88	18/07/88	69	6	15	2	7	99	82.1
14	03/88	15/08/88	59	5	15	5	4	88	79.7
15	04/88	05/09/88	48	7	13	2	13	83	78.7
16	05/88	17/10/88	60	6	15	5	11	97	80.0
17	06/88	21/11/88	48	4	11	4	4	71	81.4
18	07/88	12/12/88	52	5	11	2	7	77	82.5
19	08/88	23/01/89	77	17	8	1	9	112	90.6
20	09/88	13/02/89	92	16	20	2	12	142	82.1
21	10/88	20/03/89	96	12	26	5	15	154	78.7
22	11/88	17/04/89	57	10	20	0	12	99	74.0
23	12/88	15/05/89	82	8	10	2	8	110	89.1
24	01/89	19/06/89	80	6	21	3	3	113	79.2
All cohorts 01-24			1606	235	352	71	206	2470	82.0
	%		65.0	9.5	14.2	2.9	8.3	100.0	

(2) Absent = not present in the village on vaccination day,
(3) Refusal = did not come to vaccination, although present in the village on vaccination day, whatever the reason.

Table 3.3 : Status of birth cohorts at the 5 months vaccination session, according to vaccination group, Niakhar 1987-1989.

	Vaccination group	Cohorts 01-16		Cohorts 17-24	
		N	%	N	%
(1)	EZ-HT	336	21.1	292	33.3
(2)	SW-HT	323	20.3	0	0.0
(3)	Placebo	357	22.4	281	32.0
(4)	Participant to trial	1016	63.8	573	65.3
(5)	Not participant	391	24.6	217	24.7
(6)	Dead or outmigrated at 5 mo	185	11.6	88	10.0
(7)	Total	1592	100.0	878	100.0
(4/4+5) % participant if resident			72.3		72.5

Table 3.4 : Status at the 5 months and the 10 months vaccination sessions, according to groups of cohorts, Niakhar 1987-1989.

Presence at 10 months	Presence at 5 months				Total
	Present	Absence +refusal	Outmigrant +death	Other	
I Cohorts 01-16					
Present	689	137	2	3	831
Absent+refusal	275	216	0	4	495
Outmig+dead	45	23	186	0	254
Other	7	5	0	0	12
Total	1016	381	185	7	1592
II Cohorts 17-24					
Present	447	83	2	8	540
Absent+refusal	93	107	0	0	200
Outmig+dead	16	10	86	1	113
Other	17	6	0	2	25
Total	573	206	88	11	878

Nb : other included children who were sick, who came at the vaccination session but were not vaccinated because of contra-indication, as well as children who did not receive the expected vaccine.

Table 3.5 : Measles vaccine coverage in December 1989, project children still resident, Niakhar 1987-1989.

Measles vaccine given	Cohort 01-16	Cohort 17-24	Total	%
EZ-HT at 5 months	275	277	552	29.1
SW-HT at 5 months	274	0	274	14.5
Placebo at 5 + Standard at 10 mo	272	218	490	25.9
Other resident vaccinated with standard vaccine	146	84	230	12.4
Resident not vaccinated	200	148	348	18.4
Total	1167	727	1894	100.0
% vaccinated against measles	82.9	79.6	81.6	

Table 3.6 : Age at vaccination in weeks for the three scheduled sessions, project children, Niakhar 1987-1989.

Age in weeks	3 months session			5 months session		10 months session
	Cohorts			Cohorts		Cohorts
	01-02	03	04-24	01	02-24	01-24
9			3			
10			57			
11			212			
12			270			
13			334			
14			284			
15			181			
16		13	73			
17		24	4			
18		18			8	
19		19			104	
20		5			260	
21					331	
22					347	
23					290	
24				10	132	
25				22	44	
26				17		
27				15		
28				14		
29						
30						
31						
32						
33						
34	28					
35	35					
36	26					
37	28					
38	20					
39						
40						26
41						112
42						236
43						320
44						310
45						247
46						109
47						10
Total	137	79	1418	78	1516	1370
Mean (months)	8.26	4.09	3.00	6.00	5.00	10.01
St.dev (months)	0.31	0.27	0.36	0.30	0.35	0.35

Table 3.7 : Distribution of difference in weeks between the vaccination sessions at 5 and 10 months, according to vaccination group, Niakhar 1987-1989.

Difference in number of weeks	Vaccine received at 5 months			
	EZ-HT	SW-HT	Placebo	Total
I Cohort 01				
16	16	14	19	49
II Cohorts 02-16				
20	26	22	30	78
21	50	59	64	173
22	46	45	59	150
23	57	70	71	198
24	13	11	17	41
III Cohorts 17-24				
20	41	0	37	78
21	84	0	81	165
22	15	0	19	34
23	81	0	89	170
Total	221	0	226	447
Mean	21.53	21.57	21.59	
St.dev	1.58	1.81	1.60	

Table 4.1: Age specific probabilities of dying from birth until time of 5 months vaccination, according to vaccination group assigned at birth, project children, Niakhar 1987-1989, (/1000 children at risk).

Vaccination group assigned at birth	0 - 27 days		28 days - 5 months		0 - 5 months	
	q	D/N	q	D/N	q	D/N
Cohorts 01-16						
EZ-HT	62.7	(33/526)	28.4	(14/493)	89.4	(47/526)
SW-HT	58.8	(31/527)	22.2	(11/496)	79.7	(42/527)
Standard	63.1	(34/539)	15.8	(8/505)	77.9	(42/539)
Total	61.6	(98/1592)	22.1	(33/1494)	82.3	(131/1592)
Cohorts 17-24						
EZ-HT	67.9	(30/442)	9.7	(4/412)	76.9	(34/442)
Standard	71.1	(31/436)	12.3	(5/405)	82.6	(36/436)
Total	69.5	(61/878)	11.0	(9/817)	79.7	(70/878)
Cohorts 01-24						
EZ-HT	65.1	(63/968)	19.9	(18/905)	83.7	(81/968)
SW-HT	58.8	(31/527)	22.2	(11/496)	79.7	(42/527)
Standard	66.7	(65/975)	14.3	(13/910)	80.0	(78/975)
Total	64.4	(159/2470)	18.2	(42/2311)	81.4	(201/2470)

NB : 5 months = date of the scheduled 5 months vaccination session.

Table 4.2: Age specific probabilities of dying between the 5 months and the 10 months vaccination, according to vaccination group, project children, Niakhar 1987-1989, (/1000 children at risk).

Vaccination group	5 mo - 5+42 days		5+42 days - 10 mo		5 - 10 months	
	q	D/N	q	D/N	q	D/N
Cohorts 01-16						
EZ-HT	6.0	(2/336)	18.0	(6/334)	23.8	(8/336)
SW-HT	6.2	(2/323)	40.5	(12/319)	46.4	(15/323)
Placebo	5.6	(2/357)	25.4	(9/355)	30.8	(11/357)
Other	2.6	(1/391)	15.4	(7/390)	17.9	(8/391)
Total	5.0	(7/1407)	24.3	(34/1400)	29.2	(41/1407)
Cohorts 17-24						
EZ-HT	3.4	(1/292)	3.4	(1/291)	6.8	(2/292)
Placebo	0.0	(0/281)	17.8	(5/281)	17.8	(5/281)
Other	9.2	(2/217)	18.6	(4/215)	27.6	(6/217)
All	3.8	(3/790)	12.7	(10/787)	16.5	(13/790)
Cohorts 01-24						
EZ-HT	4.8	(3/628)	11.2	(7/625)	15.9	(10/628)
SW-HT	6.2	(2/323)	40.5	(13/319)	46.4	(15/323)
Placebo	3.1	(2/638)	22.0	(14/636)	25.0	(16/638)
Other	4.9	(3/608)	16.5	(10/605)	21.4	(13/608)
All	4.6	(10/2197)	20.1	(44/2186)	24.6	(54/2197)

NB : 5 months = date of the scheduled 5 months vaccination session.
10 months = date of the scheduled 10 months vaccination session.

Table 4.3a: Survival after the 10 months vaccination, by vaccination group, 2 sexes combined, project children, Niakhar, 1987-1990, cohorts 01-16, updated in October, 1990.

Age in month	Survival per 1000 at 10 months				Standard deviations			
	EZ-HT at 5	SW-HT at 5	Standard at 10	Other	EZ-HT at 5	SW-HT at 5	Standard at 10	Other
10	1000.0	1000.0	1000.0	1000.0	0.0	0.0	0.0	0.0
11	993.8	990.2	992.3	1000.0	4.4	5.7	4.4	0.0
12	990.7	986.9	984.7	990.4	5.4	6.5	6.2	5.5
13	990.7	983.6	979.5	977.6	5.4	7.3	7.2	8.4
14	984.4	980.3	979.5	977.6	6.9	8.0	7.2	8.4
15	981.3	980.3	979.5	971.1	7.6	8.0	7.2	9.5
16	974.9	973.6	974.3	964.6	8.8	9.2	8.0	10.5
17	955.8	970.3	971.7	964.6	11.6	9.8	8.4	10.5
18	949.4	970.3	971.7	964.6	12.3	9.8	8.4	10.5
19	943.0	960.2	971.7	957.9	13.1	11.3	8.4	11.4
20	933.4	956.8	971.7	957.9	14.0	11.7	8.4	11.4
21	930.2	953.5	966.4	954.6	14.4	12.1	9.2	11.9
22	930.2	943.3	966.4	954.6	14.4	13.4	9.2	11.9
23	927.0	943.3	966.4	954.6	14.7	13.4	9.2	11.9
24	917.3	939.9	966.4	951.2	15.5	13.7	9.2	12.3
25	917.3	939.9	958.5	951.2	15.5	13.7	10.2	12.3
26	914.1	936.5	955.8	944.3	15.8	14.1	10.5	13.1
27	914.1	929.7	955.8	934.1	15.8	14.8	10.5	14.3
28	901.1	929.7	955.8	923.7	16.9	14.8	10.5	15.3
29	897.8	929.7	955.8	923.7	17.1	14.8	10.5	15.3
30	888.0	926.3	947.8	920.3	17.8	15.1	11.4	15.6
31	881.0	919.0	944.9	920.3	18.4	15.9	11.7	15.6
32	881.0	915.1	944.9	920.3	18.4	16.3	11.7	15.6
33	881.0	915.1	944.9	920.3	18.4	16.3	11.7	15.6
34	881.0	915.1	944.9	920.3	18.4	16.3	11.7	15.6
35	881.0	910.3	944.9	910.4	18.4	16.9	11.7	16.9
36	870.8	904.9	941.0	910.4	19.5	17.6	12.3	16.9
37	870.8	904.9	941.0	910.4	19.5	17.6	12.3	16.9
38	858.9	904.9	941.0	910.4	21.0	17.6	12.3	16.9
39	852.3	897.9	941.0	910.4	21.9	18.8	12.3	16.9
40	852.3	897.9	941.0	910.4	21.9	18.8	12.3	16.9
41	852.3	897.9	941.0	910.4	21.9	18.8	12.3	16.9

Table 4.3b: Survival after the 10 months vaccination, by vaccination group, 2 sexes combined, project children, Niakhar, 1987-1990, cohorts 01-24, updated in October, 1990.

Age in month	Survival per 1000 at 10 months				Standard deviations			
	EZ-HT at 5	SW-HT at 5	Standard at 10	Other	EZ-HT at 5	SW-HT at 5	Standard at 10	Other
10	1000.0	1000.0	1000.0	1000.0	0.0	0.0	0.0	0.0
11	993.4	990.2	994.2	995.9	3.3	5.7	2.9	2.9
12	991.7	986.9	985.6	987.7	3.7	6.5	4.5	5.0
13	990.1	983.6	981.3	979.4	4.0	7.3	5.2	6.4
14	985.1	980.3	979.8	979.4	4.9	8.0	5.3	6.4
15	981.8	980.3	975.4	973.1	5.4	8.0	5.9	7.3
16	978.4	973.6	972.5	964.8	5.9	9.2	6.2	8.4
17	968.3	970.3	971.1	964.8	7.1	9.8	6.4	8.4
18	965.0	970.3	971.1	962.6	7.5	9.8	6.4	8.6
19	961.6	960.2	971.1	958.4	7.8	11.3	6.4	9.1
20	954.9	956.8	968.1	958.4	8.5	11.7	6.7	9.1
21	953.2	953.5	962.2	956.3	8.6	12.1	7.3	9.3
22	949.8	943.3	959.3	956.3	8.9	13.4	7.5	9.3
23	946.1	943.3	959.3	954.0	9.3	13.4	7.5	9.6
24	938.2	939.9	956.0	949.2	10.0	13.7	7.9	10.1
25	938.2	939.9	950.8	946.7	10.0	13.7	8.4	10.4
26	933.5	936.5	948.9	941.2	10.5	14.1	8.6	11.0
27	933.5	929.7	948.9	932.2	10.5	14.8	8.6	12.1
28	921.9	929.7	948.9	922.7	11.8	14.8	8.6	13.2
29	918.8	929.7	948.9	922.7	12.2	14.8	8.6	13.2
30	908.8	926.3	940.9	919.3	13.4	15.1	9.7	13.6
31	901.6	919.0	938.1	919.3	14.2	15.9	10.0	13.6
32	901.6	915.1	938.1	919.3	14.2	16.3	10.0	13.6
33	901.6	915.1	938.1	919.3	14.2	16.3	10.0	13.6
34	901.6	915.1	938.1	919.3	14.2	16.3	10.0	13.6
35	901.6	910.3	938.1	909.4	14.2	16.9	10.0	15.1
36	891.2	904.9	934.2	909.4	15.8	17.6	10.7	15.1
37	891.2	904.9	934.2	909.4	15.8	17.6	10.7	15.1
38	879.0	904.9	934.2	909.4	17.8	17.6	10.7	15.1
39	872.2	897.9	934.2	909.4	18.9	18.8	10.7	15.1
40	872.2	897.9	934.2	909.4	18.9	18.8	10.7	15.1
41	872.2	897.9	934.2	909.4	18.9	18.8	10.7	15.1

Table 4.4a: Survival after the 5 months vaccination, by vaccination group, 2 sexes combined, project children, Niakhar, 1987-1990, Cohorts 01-16, updated in October, 1990.

Age in month	Survival per 1000 at 5 months				Standard deviations			
	EZ-HT	SW-HT	Standard	Other	EZ-HT	SW-HT	Standard	Other
5	1000.0	1000.0	1000.0	1000.0	0.0	0.0	0.0	0.0
6	1000.0	996.9	994.4	997.4	0.0	3.1	4.0	2.6
7	991.0	987.6	986.0	997.4	5.1	6.2	6.2	2.6
8	985.1	975.1	977.5	994.8	6.6	8.7	7.8	3.7
9	979.0	962.6	977.5	986.8	7.8	10.6	7.8	5.9
10	976.0	950.1	969.1	981.5	8.4	12.2	9.2	6.9
11	969.9	943.9	963.4	978.8	9.4	12.9	10.0	7.4
12	966.9	940.7	957.7	968.0	9.8	13.2	10.7	9.1
13	966.9	937.6	957.7	951.8	9.8	13.5	10.7	11.1
14	960.8	934.5	957.7	951.8	10.7	13.8	10.7	11.1
15	957.7	934.5	954.8	949.0	11.1	13.8	11.0	11.4
16	951.5	928.1	946.1	946.2	11.8	14.4	12.0	11.7
17	932.8	924.9	943.2	946.2	13.8	14.7	12.3	11.7
18	926.6	924.9	943.2	946.2	14.4	14.7	12.3	11.7
19	920.4	915.3	943.2	940.6	15.0	15.6	12.3	12.3
20	911.0	912.1	943.2	940.6	15.8	15.9	12.3	12.3
21	907.9	908.9	937.3	937.8	16.0	16.1	12.9	12.6
22	907.9	899.2	937.3	937.8	16.0	16.9	12.9	12.6
23	904.7	899.2	937.3	937.8	16.3	16.9	12.9	12.6
24	895.3	896.0	937.3	935.0	17.0	17.1	12.9	12.8
25	895.3	896.0	928.5	935.0	17.0	17.1	13.8	12.8
26	892.2	892.7	925.5	929.2	17.2	17.4	14.1	13.4
27	892.2	886.3	925.5	920.7	17.2	17.9	14.1	14.2
28	879.5	886.3	922.5	914.9	18.1	17.9	14.3	14.6
29	876.3	886.3	922.5	914.9	18.3	17.9	14.3	14.6
30	866.7	883.0	913.5	912.0	18.9	18.1	15.1	14.9
31	859.8	876.0	910.4	912.0	19.4	18.6	15.4	14.9
32	859.8	872.4	910.4	912.0	19.4	18.9	15.4	14.9
33	859.8	872.4	910.4	912.0	19.4	18.9	15.4	14.9
34	859.8	872.4	910.4	912.0	19.4	18.9	15.4	14.9
35	859.8	867.7	910.4	903.8	19.4	19.4	15.4	15.8
36	849.9	862.6	906.0	903.8	20.4	19.9	15.9	15.8
37	849.9	862.6	906.0	903.8	20.4	19.9	15.9	15.8
38	838.3	862.6	906.0	903.8	21.7	19.9	15.9	15.8
39	831.8	856.0	906.0	903.8	22.5	20.8	15.9	15.8
40	831.8	856.0	906.0	903.8	22.5	20.8	15.9	15.8
41	831.8	856.0	906.0	903.8	22.5	20.8	15.9	15.8

Table 4.4b: Survival after the 5 months vaccination, by vaccination group, 2 sexes combined, project children, Niakhar, 1987-1990, cohorts 01-24, updated in October, 1990.

Age in month	Survival per 1000 at 5 months				Standard deviations			
	EZ-HT	SW-HT	Standard	Other	EZ-HT	SW-HT	Standard	Other
5	1000.0	1000.0	1000.0	1000.0	0.0	0.0	0.0	0.0
6	998.4	996.9	996.9	995.0	1.6	3.1	2.2	2.9
7	993.6	987.6	992.2	995.0	3.2	6.2	3.5	2.9
8	990.4	975.1	985.9	989.9	3.9	8.7	4.7	4.1
9	987.2	962.6	982.7	984.8	4.5	10.6	5.2	5.0
10	982.3	950.1	974.8	979.7	5.3	12.2	6.2	5.8
11	977.5	943.9	968.4	974.5	6.0	12.9	6.9	6.5
12	975.8	940.7	960.5	965.9	6.2	13.2	7.7	7.5
13	974.2	937.6	958.9	955.5	6.4	13.5	7.9	8.5
14	969.3	934.5	957.3	955.5	6.9	13.8	8.0	8.5
15	966.0	934.5	950.9	952.0	7.3	13.8	8.6	8.8
16	962.7	928.1	944.4	948.5	7.6	14.4	9.1	9.2
17	952.8	924.9	942.8	948.5	8.6	14.7	9.3	9.2
18	949.5	924.9	941.2	948.5	8.8	14.7	9.4	9.2
19	946.2	915.3	941.2	945.0	9.1	15.6	9.4	9.5
20	939.6	912.1	937.9	945.0	9.6	15.9	9.6	9.5
21	937.9	908.9	931.4	943.2	9.8	16.1	10.1	9.6
22	934.6	899.2	928.2	943.2	10.0	16.9	10.3	9.6
23	930.9	899.2	928.2	941.3	10.3	16.9	10.3	9.8
24	923.1	896.0	926.3	935.4	10.9	17.1	10.5	10.3
25	923.1	896.0	920.5	933.3	10.9	17.1	10.9	10.5
26	918.5	892.7	918.4	928.8	11.3	17.4	11.1	10.9
27	918.5	886.3	918.4	921.3	11.3	17.9	11.1	11.6
28	907.1	886.3	915.8	916.1	12.5	17.9	11.4	12.1
29	904.1	886.3	915.8	916.1	12.9	17.9	11.4	12.1
30	894.2	883.0	906.9	913.2	13.9	18.1	12.4	12.5
31	887.1	876.0	903.8	913.2	14.7	18.6	12.7	12.5
32	887.1	872.4	903.8	913.2	14.7	18.9	12.7	12.5
33	887.1	872.4	903.8	913.2	14.7	18.9	12.7	12.5
34	887.1	872.4	903.8	913.2	14.7	18.9	12.7	12.5
35	887.1	867.7	903.8	905.0	14.7	19.4	12.7	13.6
36	876.9	862.6	899.5	905.0	16.2	19.9	13.4	13.6
37	876.9	862.6	899.5	905.0	16.2	19.9	13.4	13.6
38	864.9	862.6	899.5	905.0	18.1	19.9	13.4	13.6
39	858.2	856.0	899.5	905.0	19.1	20.8	13.4	13.6
40	858.2	856.0	899.5	905.0	19.1	20.8	13.4	13.6
41	858.2	856.0	899.5	905.0	19.1	20.8	13.4	13.6

Table 4.5 : Comparison of the vaccination groups according to family characteristics, cohorts 01-16, Niakhar 1987-1990.

Variable	EZ-HT	SW-HT	Standard	Not participant
Mean age of mother	27.7	28.1	28.0	28.6
% mother literate	3.7	3.8	3.2	3.6
Size of compound	22.8	22.8	23.0	23.4
Distance to dispensary (km)	3.8	3.9	3.9	4.1
Mortality of older siblings of same mother	0.313	0.309	0.313	0.297
% outmigrant	6.5	4.7	6.1	11.1
Death rate in compound of residence (/1000)	17.6	17.9	17.3	20.0

Table 4.6 : Comparison of the groups according to characteristics of children at 5 months, cohorts 01-16, Niakhar 1987-1990.

Variable	EZ-HT	SW-HT	Standard
Mean age at vaccination (weeks)	21.6	21.6	21.5
Mean weight (kg)	6.45	6.46	6.40
Mean height (cm)	63.0	63.3	63.2
Mean arm circumference (mm)	132	132	132
Mortality 0-4 months (/1000)	89	80	78

Table 4.7 : Clusters of deaths by month, village and vaccine group, Cohorts 01-16, Niakhar 1987-1990, updated in October, 1990.

Date in month	Vaccine group					Village number	Vaccine group				
	EZ	SW	St	NP	Total		EZ	SW	St	NP	Total
08/87	1	0	0	0	1	1	0	0	0	0	0
09/87	0	1	1	0	2	2	0	3	0	3	6
10/87	1	0	2	2	5	3	1	2	1	0	4
11/87	2	2	3	0	7	4	1	0	0	2	3
12/87	0	0	0	0	0	5	1	1	0	0	2
01/88	0	0	0	0	0	6	1	4	3	4	12
02/88	0	2	0	0	2	7	0	1	1	1	3
03/88	0	1	0	1	2	8	2	0	1	2	5
04/88	0	0	0	0	0						
05/88	0	1	1	1	3	10	0	1	0	0	1
06/88	3	0	2	0	5	11	2	0	0	5	7
07/88	3	3	1	0	7	12	2	1	1	0	4
08/88	4	0	2	2	8	13	2	1	0	0	3
09/88	1	3	2	0	6	14	0	1	1	0	2
10/88	7	8	2	9	26	15	0	0	0	0	0
11/88	0	3	2	3	8	16	0	1	2	2	5
12/88	0	0	0	0	0	17	1	3	2	2	8
01/89	0	0	0	1	1	18	2	1	0	2	5
02/89	0	1	0	2	3	19	4	3	5	4	16
03/89	0	1	0	1	2	20	0	0	1	1	2
04/89	1	0	0	0	1	21	5	5	2	0	12
05/89	1	0	0	0	1	22	6	2	2	1	11
06/89	0	0	2	1	3	23	3	2	3	0	8
07/89	2	2	1	0	5	24	3	4	1	1	9
08/89	3	2	5	2	12	25	2	3	2	1	8
09/89	8	4	2	1	15	26	0	0	0	0	0
10/89	4	1	0	2	7	27	6	1	1	1	9
11/89	1	0	1	1	3	28	0	0	0	0	0
12/89	1	0	0	1	2	29	2	1	2	2	7
01/90	0	1	0	0	1	30	0	1	0	0	1
02/90	0	0	0	0	0	31	4	1	1	0	6
03/90	0	0	0	0	0						
04/90	0	1	1	1	3						
05/90	0	0	0	0	0						
06/90	0	0	0	0	0						
07/90	0	0	0	0	0						
08/90	2	1	1	2	6						
09/90	4	2	0	0	6						
10/90	1	3	1	1	6						

Table 4.8 : Distribution of probable causes of death (from verbal autopsies), after the 5 months vaccination, by various characteristics, Niakhar, 1987-1990, updated in October, 1990.

Probable cause of death	EZ-HT a+b	SW-HT a	Standard a+b	Not participant a+b
	< Principal Cause >			
Acute diarrhea	4+1	2	3+1	1+2
Chronic Diarrhea	19+6	13	13+4	19+5
Dysentery	1	5	0+2	0
Meningitis	1	1	1	2
Septicemia	0	0	0	1+1
Chicken pox	3	0	0	0
Measles	0	0	0	1
Hepatitis	1+1	0	0	0
Malaria	8+2	6	7+3	2
Kwashiorkor	8+1	2	2+2	1+1
Other malnutrition	2	2	3+1	3+1
Acute Respiratory Inf	0+1	8	0+4	2+2
Accident	0	0	0	1
Other and Unknown	3+1	4	3+7	2+2
Total	50+13	43	32+24	35+14
	< Immediate Cause >			
Acute diarrhea	2+1	4	2+1	3+1
Chronic diarrhea	9+1	7	0+2	2+3
Dysentery	1	0	0	0
Septicemia	0	0	1	0
Malaria	0+1	0	1	0
Acute Respiratory Inf	1	1	1+1	1
Other and Unknown	4	0	4	4+2
	< Associated cause >			
Chronic diarrhea	0	2	0+1	1
Whooping cough	1	0	0	0
Chichen pox	1	1	0+1	0+1
Kwashiorkor	0	1	0	0
Other malnutrition	1	2	1	1
Other and Unknown	4	0	3	6+2

NB : a = cohorts 01-16
b = cohorts 17-24

Table 4.9 : Distribution of deaths after the 5 months vaccination by vaccination group, according to various characteristics, cohorts 01-16, Niakhar 1987-1990, updated in October 1990.

	EZ-HT	SW-HT	Standard	Not participant	Total	CHI2	(df)	P	
Period of death									
Jul 87-Oct 87	2	1	3	2	8				
Nov 87-Jun 88	5	6	6	2	19				
Jul 88-Oct 88	15	14	7	11	47				
Nov 88-Jun 89	2	5	5	8	20				
Jul 89-Oct 89	17	9	7	5	38				
Nov 89-Jun 90	2	2	2	4	10				
Jul 90-Oct 90	7	6	2	3	18	19.0	(18)	0.3908	
Age at death (in months)									
V5-16 mo	22	24	20	20	86				
17-28 mo	18	12	7	12	49				
29-40 mo	10	7	5	3	25	4.7	(6)	0.5807	
% >= 17 mo	56.0	44.2	37.5	42.9	46.9				
Season of death									
Dry (Nov-Jun)	9	13	13	14	49				
Rainy (Jul-Oct)	41	30	19	21	111	6.7	(3)	0.0818	
% rainy season	82.0	69.8	59.4	60.0	69.4				
Sex									
Male	21	18	20	16	75				
Female	29	25	12	19	85	4.0	(3)	0.2543	
% female	58.0	58.1	37.5	54.3	53.1				
Season of vaccination									
Dry (Nov-Jun)	19	26	13	23	81				
Rainy (Jul-Oct)	31	17	19	12	79	9.3	(3)	0.0253	*
% rainy season	62.0	39.5	59.4	34.3	49.4				
Mean age at vaccination									
Age in weeks	22.4	22.3	22.0	22.2	22.2				
Total	50	43	32	35	160				

* P<.05

NB : There was no death after 40 months by October, 1990.
One death by accident among non-participants not included.

Table 4.10 : Results of the multivariate survival analysis after the 5 months vaccination, Cox model, cohorts 01-16, Niakhar 1987-1990, updated in October, 1990.

Covariate	Estimate	St. Dev.	T	P (2 T)
Vaccine (ref=placebo)				
EZ-HT	0.531	0.227	2.341	.0196 *
SW-HT	0.414	0.234	1.769	.0774 *
Sex (ref=male)	0.014	0.179	0.077	.9386
Season of vaccination	0.034	0.180	0.186	.8526
Age at vaccination	-0.051	0.043	-1.201	.2300

Score test : $X^2(5) = 6.686$, P= 0.245 (NS)

Table 4.11 : Results of the multivariate Logit analyses of age specific death rates after the 5 months vaccination, by age and season, cohorts 01-16, Niakhar 1987-1990, updated in October, 1990.

Covariate	Estimate	Standard Error	T-test	P (2 T)	
I General Model: $X^2(7)=94.1$, P=E-13					
Vaccine (ref=placebo)					
EZ-HT	0.5340	0.2295	2.3264	0.0204	*
SW-HT	0.4179	0.2365	1.7671	0.0778	
Season (ref=dry)	1.5858	0.2015	7.8636	2E-13	*
Age (in months)	-0.0313	0.0088	-3.5452	0.0004	*
Age at vaccination	-0.0387	0.0478	-0.8084	0.4192	
Season of vaccination	-0.1311	0.1837	-0.7137	0.4756	
Sex (ref=male)	0.0128	0.1818	0.0704	0.9438	
Constant	-3.9502	1.0685	-3.6967	0.0002	*
II Models by vaccine					
Coefficient of age					
EZ-HT	-0.0111	0.0132	-0.8451	0.3984	
SW-HT	-0.0456	0.0160	-2.8448	0.0046	*
Placebo	-0.0459	0.0183	-2.5015	0.0126	*
Coefficient of titer at 5 months					
EZ-HT	-0.0108	0.1094	-0.0988	.9214	
SW-HT	0.0118	0.1054	0.1125	.9106	
Placebo	0.0955	0.1230	0.7761	.4382	
Coefficient of seroconversion					
EZ-HT	-0.6146	0.6924	-0.8876	.3760	
SW-HT	0.0081	0.6651	0.1218	.9032	

Table 4.12a: Results of simulations of mortality experience,
(1000 samples in each vaccination group)
cohorts 01-16, Niakhar 1987-1990, updated in October, 1990.

Hypotheses :
- mean monthly probability of dying = .00172
- same mortality for males and females
- linear decline of mortality with age
- relative risk of death in rainy season = 3.1

Expected	EZ-HT	SW-HT	Standard	Not participant
Number of deaths				
mean	30.839	29.625	33.052	34.871
st. deviation	5.782	5.638	5.920	6.130
Proportion of deaths in rainy season				
mean	0.6322	0.6367	0.6371	0.6376
st. deviation	0.0908	0.0886	0.0814	0.0830
Proportion of female deaths				
mean	0.5362	0.5339	0.4809	0.5121
st. deviation	0.0843	0.0852	0.0819	0.0806
Proportion of deaths after age 17 months				
mean	0.5351	0.5345	0.5346	0.5286
st. deviation	0.0857	0.0878	0.0828	0.0818
Relative risk (observed/expected)				
mean	1.680	1.506	1.000	1.005
st. deviation	0.0325	0.0296	0.0182	0.0178
Log Relative risk = log(observed/expected)				
mean	0.501	0.391	-0.017	0.010
st. deviation	0.188	0.191	0.179	0.174

Table 4.12b : Empirical probabilities in 1000 simulations for each group.

Event	Empirical probability in 1000 samples	Computed probability from mean+ st. deviat.
EZ-HT group		
- at least 50 deaths	.004 *	.0005 *
- at least 82.0% of deaths in rainy season	.012 *	.0193 *
- at least 58.0% of female deaths	.296	.3019
- at least 56.0% of deaths after 17 months	.400	.3855
SW-HT group		
- at least 43 deaths	.025 *	.0088 *
- at least 69.7% of deaths in rainy season	.249	.2481
- at least 58.1% of female deaths	.302	.2901
- at least 44.2% of deaths after 17 months	.859	.9376
Standard group		
- at most 37.5% of female deaths	.110	.0982

* $P < 0.05$ (1 tail)

Table 4.13a : Comparison of testing procedures, cohorts 01-16, Niakhar 1987-1990.

A) Mortality after 5 months

Vaccin	RR	95% CI	Test	P(2 T)
1) Life table : Kaplan-Meier, (T test, STD= KM)				
EZ-HT	1.80	1.18 - 2.74	T = 2.706	0.0070 *
SW-HT	1.53	0.99 - 2.37	T = 1.911	0.0564
2) Death rates : D/PYS (T test, STD= m/PYS)				
EZ-HT	1.71	1.10 - 2.66	T = 2.368	0.0182 *
SW-HT	1.52	0.96 - 2.40	T = 1.784	0.0750
3) Direct : D/N (Binomial)				
EZ-HT	1.66	1.10 - 2.53	T = 2.258	0.0242 *
SW-HT	1.49	0.96 - 2.29	T = 1.689	0.0918
4) Age Standardized death rates : (Mantel-Haenzel, in EPIINFO)				
EZ-HT	1.70	1.09 - 2.59	X^2= 5.15	0.0232 *
SW-HT	1.50	0.96 - 2.33	X^2= 2.73	0.0938
5) Linear Logistic Model				
(Odds Ratio)				
EZ-HT (1.71)	1.53	1.08 - 2.64	T = 2.326	0.0204 *
SW-HT (1.52)	1.49	0.96 - 2.43	T = 1.767	0.0778
6) Proportional Hazards				
EZ-HT	1.70	1.09 - 2.65	T = 2.326	0.0204 *
SW-HT	1.51	0.96 - 2.39	T = 1.767	0.0778
7) Log Rank Test				
EZ-HT			X^2= 5.628	0.0180 *
SW-HT			X^2= 3.184	0.0740
8) Simulations (testing log(RR) directly)				
EZ-HT	1.65	1.14 - 2.39	T = 2.665	.0080 *
SW-HT	1.48	1.02 - 2.15	T = 2.047	.0414 *

* P< 0.05

Table 4.13b : Comparison of testing procedures, cohorts 01-16, Niakhar 1987-1990.

B) Mortality after 10 months

Vaccin	RR	95% CI	Test	P(2 T)
1) Life table : Kaplan-Meier, (T test, STD= KM)				
EZ-HT	2.50	1.52 - 4.13	T = 3.537	.0004
SW-HT	1.73	1.00 - 2.98	T = 1.925	.0560
2) Death rates : D/PYS (T test, STD= m/PYS)				
EZ-HT	2.37	1.41 - 3.97	T = 3.233	.0012
SW-HT	1.63	0.93 - 2.85	T = 1.677	.0940
3) Direct : D/N (Binomial)				
EZ-HT	2.32	1.42 - 3.81	T = 3.174	.0016
SW-HT	1.64	0.96 - 2.80	T = 1.693	.0910
4) Age Standardized death rates : (Mantel-Haenzel, in EPIINFO)				
EZ-HT	2.37	1.43 - 3.93	X^2=11.070	.0009
SW-HT	1.66	0.96 - 2.87	X^2= 2.810	.0936
5) Linear Logistic Model				
(Odds Ratio)				
EZ-HT (2.52)	2.06	1.39 - 3.97	T = 3.459	.0006
SW-HT (1.75)	1.62	0.99 - 3.08	T = 1.930	.0540
6) Proportional Hazards				
EZ-HT	2.39	1.42 - 4.01	T = 3.299	.0010
SW-HT	1.65	0.94 - 2.88	T = 1.754	.0798
7) Log Rank Test				
EZ-HT			X^2=11.702	.0006
SW-HT			X^2= 3.154	.0757

Table 4.14: Survival of preceding birth cohorts between 5 and 41 months by sex, Niakhar, 1983-1989, Cohort 1 born from 2/83 to 1/85, and cohort 2 born from 2/85 to 1/87

Age in months	Survival per 1000 at 5 months				Standard deviations			
	Cohort 1		Cohort 2		Cohort 1		Cohort 2	
	M	F	M	F	M	F	M	F
5	1000.0	1000.0	1000.0	1000.0	0.0	0.0	0.0	0.0
6	993.8	989.8	989.3	996.3	2.5	3.4	3.1	1.9
7	992.8	984.2	983.1	989.7	2.7	4.2	3.8	3.1
8	987.6	979.7	975.0	985.0	3.6	4.7	4.7	3.7
9	980.3	974.0	968.7	978.4	4.5	5.4	5.2	4.5
10	969.9	968.2	966.0	973.6	5.5	5.9	5.4	4.9
11	963.6	953.2	958.8	966.9	6.0	7.1	6.0	5.5
12	955.2	945.1	954.2	959.2	6.7	7.7	6.3	6.1
13	941.4	938.1	949.7	956.3	7.6	8.2	6.6	6.3
14	934.0	928.6	946.1	950.6	8.0	8.7	6.8	6.7
15	927.7	914.4	941.5	944.8	8.4	9.5	7.0	7.1
16	916.0	906.1	937.8	939.9	9.0	9.9	7.3	7.3
17	906.4	902.6	933.2	936.0	9.4	10.1	7.5	7.6
18	900.0	893.0	924.8	932.1	9.7	10.5	7.9	7.8
19	895.7	889.4	922.0	927.2	9.9	10.7	8.1	8.0
20	890.3	883.4	916.4	922.2	10.2	11.0	8.4	8.3
21	877.3	881.0	911.6	918.3	10.7	11.1	8.6	8.5
22	868.7	872.5	902.2	913.3	11.0	11.4	9.0	8.7
23	863.2	866.4	892.7	908.3	11.2	11.7	9.4	9.0
24	860.0	849.4	885.0	904.3	11.3	12.3	9.7	9.2
25	856.7	842.0	878.3	902.3	11.4	12.5	9.9	9.2
26	849.1	835.9	875.5	898.2	11.7	12.7	10.0	9.4
27	844.7	831.0	869.7	890.0	11.8	12.9	10.2	9.8
28	836.0	823.6	867.8	890.0	12.1	13.1	10.3	9.8
29	831.6	821.1	861.9	886.9	12.2	13.2	10.5	9.9
30	824.9	817.4	860.0	883.7	12.4	13.3	10.6	10.0
31	819.4	816.1	858.0	881.7	12.6	13.4	10.6	10.1
32	818.3	812.4	852.2	878.5	12.6	13.5	10.8	10.2
33	816.0	811.1	852.2	874.3	12.7	13.5	10.8	10.4
34	813.8	809.9	851.2	873.3	12.8	13.6	10.9	10.4
35	813.8	806.1	850.2	871.2	12.8	13.7	10.9	10.5
36	810.4	802.2	846.3	870.1	12.8	13.8	11.0	10.6
37	808.2	798.4	844.2	865.6	12.9	13.9	11.1	10.7
38	807.1	794.5	844.2	864.5	12.9	14.0	11.1	10.8
39	804.8	790.6	844.2	862.0	13.0	14.1	11.1	10.9
40	801.4	789.3	841.8	862.0	13.1	14.2	11.2	10.9
41	801.4	788.0	841.8	859.1	13.1	14.2	11.2	11.1

Table 4.15: Follow-up of morbidity after vaccination sessions, details of person-months and absences, project children, cohorts 01-24, Niakhar 1987-1989.

Category and age	Vaccine group		
I From 3 months to 5 months			
Group :	(A)	(B)	(C)
No children	403	413	416
No absences	46	57	64
Mean duration absence	13.1	9.4	11.2
Person-years lived	63.57	65.60	67.03
Person-years lost	1.65	1.46	1.97
Person-years at risk	61.92	64.13	65.06
II From 5 months to 10 months			
Group :	EZ-HT	SW-HT	Placebo
No children	336	322	358
No absences	189	158	179
Mean duration absence	15.2	16.1	13.2
Person-years lived	134.9	129.1	144.4
Person-years lost	7.88	6.97	6.48
Person-years at risk	127.0	122.1	137.9
III From 10 months to 12 months			
Group :	EZ-HT	SW-HT	Standard
No children	322	306	425
No absences	99	87	99
Mean duration absence	12.3	16.9	12.7
Person-years lived	50.8	48.4	66.6
Person-years lost	3.35	4.03	3.45
Person-years at risk	47.5	44.4	63.2

NB : A, B, C : groups assigned at birth.

Table 4.16 : Number of morbid episods registered by the field workers according to disease and field worker, project children, cohorts 01-24, Niakhar 1987-1989.

Field worker #	No of children	No of episodes recorded					
		Fever	Diarrhea	ARI	Rash	Other	Total
1	227	507	392	122	82	389	1492
2	210	621	286	106	33	405	1451
3	285	656	289	69	42	342	1398
4	215	525	280	105	50	324	1284
5	258	593	300	76	43	256	1268
6	193	524	180	199	50	285	1238
7	251	480	293	57	77	292	1199
8	154	369	229	128	82	264	1072
9	260	437	171	67	52	311	1038
10	178	313	144	76	33	199	765
11	235	208	98	39	48	79	472
12	*	314	290	95	50	318	1067
Total	2470	5547	2952	1139	642	3464	13744

NB : field worker # 12 includes all supervisors or enumerators who replaced field workers who were either sick or in vacation

Table 4.17 : Incidence of morbid episods after vaccination sessions, (/ 100 person-months), according to age and vaccine group cohorts 01-16, Niakhar 1987-1989, (N=number of episods terminated).

Disease	Incidence	(N)	Incidence	(N)	Incidence	(N)
I From 3 months to 5 months						
Group:	- A	-	- B	-	- C	-
Fever	49.0	364	48.2	371	47.3	369
Diarrhea	15.7	117	12.6	97	15.2	119
ARI	8.9	66	7.5	58	7.4	58
Rash	6.6	49	4.2	32	3.3	26
Other	20.7	154	21.7	167	18.7	146
All	100.9	750	94.2	725	92.0	718
II From 5 months to 10 months						
Group	- EZ-HT	-	- SW-HT	-	- Placebo	-
Fever	41.2	628	41.8	612	38.9	643
Diarrhea	20.5	313	23.7	347	20.5	340
ARI	9.1	139	8.1	118	8.9	148
Rash	5.2	80	5.0	74	5.4	90
Other	25.5	388	25.5	374	26.2	434
All	101.6	1548	104.1	1525	100.0	1655
III From 10 months to 12 months						
Group	- EZ-HT	-	- SW-HT	-	- Standard	-
Fever	37.2	212	37.2	198	42.6	323
Diarrhea	22.6	129	20.1	107	23.5	178
ARI	5.4	31	6.0	32	4.1	31
Rash	2.3	13	3.2	17	3.8	29
Other	24.4	139	19.1	102	16.2	123
All	92.0	524	85.6	456	90.2	684

Table 4.18 : Incidence of persistent diarrhea between age 5 and 12 months, by vaccine group, cohorts 01-16, Niakhar 1987-1989.

	EZ-HT	SW-HT	Placebo
No of children	336	321	358
No of episodes	98	86	119
Incidence / 100	29.2	26.8	33.2
Mean duration (days)	24.2	22.3	24.9
S.dev duration (days)	12.2	9.7	12.7

Table 4.19 : Sex specific morbidity between vaccinations at 5 and 10 months, according to vaccination group, cohorts 01-16, Niakhar 1987-1989.

	EZ-HT		SW-HT		Placebo	
Disease	Incidence	(N)	Incidence	(N)	Incidence	(N)
I Males						
Fever	42.9	293	43.3	298	43.6	368
Diarrhea	23.4	160	27.0	186	23.1	195
ARI	8.4	57	8.0	55	9.8	83
Rash	5.0	34	5.2	36	5.1	43
Other	25.6	175	25.8	178	26.0	220
All	105.4	719	109.3	753	107.6	909
II Females						
Fever	39.8	335	40.4	314	34.0	275
Diarrhea	18.2	153	20.7	161	17.9	145
ARI	9.7	82	8.1	63	8.0	65
Rash	5.5	46	4.9	38	5.8	47
Other	25.3	213	25.2	196	26.4	214
All	98.5	829	99.4	772	92.1	746
III Sex ratio of incidences						
Fever	107.9		106.9		128.3	
Diarrhea	129.0		130.2		128.9	
ARI	85.7		98.4		122.4	
Rash	91.1		106.8		87.7	
Other	101.3		102.3		98.5	
All	107.0		109.9		116.8	

Table 4.20: Mother's history of convulsions, according to dates of vaccination (or scheduled vaccination) and vaccine received cohorts 01-16, Niakhar 1987-1989.

Vaccine received	(N)	< 28 days after	>= 28 days after
I Between 3 and 5 months			
BCG + DPTP	(1055)	0	2
Not vaccinated	(365)	0	1
II Between 5 and 10 months			
DPTP + EZ-HT	(336)	1 (D-18)	7
DPTP + SW-HT	(322)	0	2
DPTP + Placebo	(357)	0	6
Not vaccinated	(387)	0	2
III After 10 months			
DPTP + YF	(428)	1 (D-2)	2
DPTP + YF + Standard	(392)	1 (D-20)	2
Not vaccinated	(511)	1 (D-5)	0

D-n = n days after vaccination or date of scheduled vaccination.

Table 4.21 : Anthropometry of children at time of vaccination, project children, cohorts 01-24, and comparison with those who died after high titer vaccines. Niakhar 1987-1989.

Anthropometric measurement	3 months		5 months		10 months	
	mean	(std)	mean	(std)	mean	(std)
All children	(N=1886)		(N=1872)		(N=1419)	
Age in weeks	13.1	(1.57)	21.7	(1.56)	43.5	(1.50)
Weight (kg)	5.64	(.828)	6.56	(.957)	7.56	(1.091)
Height (mm)	595	(25.3)	635	(26.0)	693	(28.9)
Arm circumference (mm)	128	(12.0)	133	(12.6)	134	(13.2)
Z-score weight/age	0.340	(1.023)	-0.162	(1.042)	-1.542	(1.093)
Z-score height/age	0.130	(0.977)	-0.217	(0.965)	-1.032	(1.056)
Z-score weight/height	0.310	(0.833)	-0.017	(0.902)	-0.853	(0.910)
Children who died after EZ-HT vaccine	(N= 54)		(N= 62)		(N= 32)	
Weight (kg)	5.88	(0.911)	6.45	(0.857)	7.62	(1.277)
Height (mm)	603	(33.5)	631	(25.1)	691	(33.3)
Arm circumference (mm)	129	(9.5)	133	(11.2)	133	(14.1)
Z-score weight/age	0.197	(1.189)	-0.254	(1.050)	-1.440	(1.324)
Z-score height/age	-0.082	(1.021)	-0.340	(0.921)	-1.062	(1.231)
Z-score weight/height	0.342	(0.906)	-0.002	(0.933)	-0.693	(0.932)
Children who died after SW-HT vaccine	(N= 34)		(N= 42)		(N= 22)	
Weight (kg)	5.51	(1.094)	6.29	(1.191)	7.09	(1.237)
Height (mm)	591	(34.9)	630	(32.3)	677	(39.1)
Arm circumference (mm)	126	(16.1)	131	(15.9)	130	(13.6)
Z-score weight/age	-0.034	(1.280)	-0.447	(1.312)	-1.904	(1.234)
Z-score height/age	-0.256	(1.070)	-0.389	(1.167)	-1.449	(1.450)
Z-score weight/height	0.204	(1.083)	-0.232	(1.014)	-0.880	(0.871)

Table 4.22 : Adverse reactions during post-vaccination medical examination, project children vaccinated at 5 months, according to vaccination group, session 10-24, Niakhar 1988-1989.

A) Presence and point prevalence of condition

Vaccine	No children	% present (No visits)	% diarrhea (No days)	% fever (No days)	% rash (No days)
EZ-HT	87	86.6 (377)	9.4 (41)	8.7 (38)	26.2 (114)
SW-HT	35	85.7 (150)	7.3 (11)	10.6 (16)	6.0 (9)
Placebo	102	88.0 (449)	12.8 (61)	10.5 (50)	27.5 (131)
Total	224	87.1 (976)	10.0 (113)	9.2 (104)	27.6 (254)

NB : 15 children were randomly chosen after each vaccination session; each child was visited up to 5 times, randomly, within 3 weeks after the 5 months vaccination.

Diarrhea : from mother's declaration
Fever : temperature >= 37.5 °C
Rash : any kind

B) Prevalence of disease during the 5 visits (at least one episode)

Vaccine	No children	% diarrhea	% fever	% rash (any kind)	% measles like rash
EZ-HT	87	29.8 (26)	39.0 (34)	45.9 (40)	11.4 (10)
SW-HT	35	20.0 (7)	31.4 (11)	17.1 (6)	17.1 (6)
Placebo	102	35.2 (36)	37.2 (38)	41.1 (42)	5.8 (6)
Total	224	30.8 (69)	37.0 (83)	39.2 (88)	9.8 (22)

NB: Measles like rash: rash looking like a rash after natural measles, although mild: occuring 6-14 days after vaccination, starting from the face, spreading on the body symetrically and followed by some kind of desquamation.

Table 5.1 : Proportion of mothers who refused the blood sample at vaccination session, according to age of the child and birth cohort, Niakhar 1987-1989 .

Cohort	5 months	10 months	% refusal
	Refusal / # children	Refusal / # children	
01 - 04	5 / 311	2 / 200	1.4 %
05 - 08	14 / 243	13 / 227	5.7 %
09 - 12	7 / 230	28 / 209	8.0 %
13 - 16	12 / 235	17 / 195	6.7 %
17 - 20	27 / 261	20 / 245	9.3 %
21 - 24	18 / 313	23 / 295	6.7 %
Total	83 / 1593	103 / 1371	6.3 %
% refusal	5.2	7.5	

Table 5.2 : Detail of batches for the titering of measles antibodies, Niakhar 1987-1990.

batch #	date analyzed	# of samples	standard HW	samples taken at 5 months N	mean	st. deviation	
1	21/09/87	80	3.0	74	1.176	1.070	*
2	22/09/87	86	3.3	2	1.000	1.000	*
3	15/10/87	69	5.0	69	1.739	1.800	
4	17/11/87	61	5.0	61	1.590	1.210	
5	10/02/88	100	5.0	14	2.929	0.800	*
6	11/02/88	100	5.0	20	1.700	0.900	
7	16/02/88	67	5.0				
8	23/02/88	100	5.0	56	2.125	1.350	
9	24/02/88	100	5.0	68	0.971	0.940	
10	29/02/88	70	0.0	29	1.586	1.190	
11	31/03/88	108	5.0	20	1.650	1.390	
12	04/04/88	96	5.0	55	0.691	1.170	*
13	07/04/88	96	5.0	44	1.682	1.740	
14	12/04/88	5	5.0	4	1.000	0.710	
15	04/05/88	99	5.0	48	2.125	1.070	*
16	04/07/88	100	5.0	35	1.543	1.200	
17	05/07/88	113	5.0	58	1.621	1.110	
18	07/07/88	34	5.0	18	1.500	1.890	
19	28/10/88	28	5.0	9	0.000	0.000	
20	17/01/89	79	5.0	35	2.286	1.300	
21	18/01/89	70	5.3	32	3.500	1.820	*
22	19/01/89	76	5.0	45	2.244	2.320	
23	23/01/89	73	5.0	29	1.483	1.500	
24	24/01/89	77	5.3	33	1.242	1.500	
25	25/01/89	93	5.0	47	1.255	1.330	
26	26/01/89	87	5.0				
27	06/03/89	85	5.0	2	0.000	0.000	
28	07/03/89	86	5.0				
29	23/05/89	85	5.0	1	3.000	0.000	
30	25/05/89	84	5.0				
31	29/05/89	88	5.0				
32	31/05/89	61	5.0	57	2.107	1.520	
33	28/09/89	77	7.0				*
34	23/10/89	87	5.0				
35	25/10/89	54	5.0				
36	26/10/89	100	5.0				
37	02/04/90	98	5.0				
38	03/04/90	100	5.0				
39	04/04/90	100	5.0				
40	05/04/90	51	5.3				
41	10/04/90	98	5.0	42	2.952	1.630	*
42	16/04/90	18	4.7				
Not yet titered		1185					
All samples		4524					

* outstanding high or low titer

Table 5.3 : Statistics of the reciprocal of dilution for blood samples analyzed twice, Niakhar 1987-1989.

Origin	(N)	Statistic	Value 1	Value 2	r	P
R-07	(58)	batch	(08+10)	(11)		
		mean	1.914	2.655		
		standard deviation	1.546	1.935		
		percent negative	31.0	20.7		
		correlation			.809	E-04
R-01	(59)	batch	(01+06)	(32)		
		mean	1.254	2.051		
		standard deviation	1.051	1.534		
		percent negative	30.5	30.5		
		correlation			-.071	(NS)
sero-converters	(28)	batch	(varia)	(19)		
		mean	1.286	1.107		
		standard deviation	1.887	1.858		
		percent negative	53.6	32.2		
		correlation			.837	E-04
others	(20)	batch	(varia)	(41)		
		mean	2.450	5.300		
		standard deviation	2.906	3.195		
		percent negative	50.0	15.0		
		correlation			.707	E-04
Difference between sample 1 and sample 2 (N=106)*		mean	0.896			
		standard deviation	1.759			
		percent identical	34.0			

* All but R-01

Table 5.4 : Cross tabulation of the reciprocal of dilution in 106 samples analyzed twice, Niakhar 1987-1989.

Second sample	First sample										Total
	0	1	2	3	4	5	6	7	8	9	
0	26	6	1								33
1	2										2
2	5	3	6	5	1						20
3	4	1	4	3	2			1			15
4	2	1	4	6	1	1					15
5			1	3	1						5
6	2			1	2				1		6
7				2	2		2				6
9					2						2
10										1	1
13									1		1
Total	41	11	16	20	11	1	2	1	2	1	106

Table 5.5: Natural decay of antibodies according to age, cohorts 01 to 16, children not vaccinated, who never had measles, without any known exposure to measles, Niakhar 1987-1989.

Age (weeks)	Mean age (month)	GMT (miu)	(N)	% <125	(N)	GMT >=125	(N)	% >=1000	(N)
10-13	2.9	490	(33)	6.1	(2)	559	(31)	30.3	(10)
14-17	3.5	366	(82)	13.4	(11)	481	(71)	22.0	(18)
18-25	5.0	207	(871)	31.1	(271)	355	(600)	11.4	(99)
26-33	6.5	112	(19)	57.9	(11)	250	(8)	5.3	(1)
34-41	8.8	133	(82)	69.5	(57)	737	(25)	14.6	(12)
42-49	10.0	121	(334)	67.1	(224)	442	(113)	10.2	(34)
50+	16.0	102	(27)	77.8	(21)	561	(6)	7.4	(2)

NB : batches 01 and 02 eliminated.

Table 5.6: Response to high titer measles vaccines according to various definitions, cohorts 03-16, children who never had measles, without any known exposure to measles, who came at both the 5 months and the 10 months session, Niakhar 1987-1989.

Criteria	EZ-HT (N= 163)		SW-HT (N= 168)		Placebo (N= 204)	
	mean	conf. int.	mean	conf. int.	mean	conf. int.
At 5 months (before vaccination)						
% <125 miu	32.5	[28.7-36.9]	35.1	[31.1-39.7]	30.4	[27.1-34.1]
GMT (all)	197	[167- 232]	198	[168- 235]	206	[179- 237]
GMT if>= 125	343	[301- 390]	371	[325- 424]	347	[312- 385]
At 10 months (5 months after vaccination)						
% <125 miu	3.7	[3.2- 4.3]	22.0	[19.3-25.2]	67.6	[62.6-73.1]
GMT (all)	1638	[1287-2085]	678	[509- 905]	111	[96- 127]
GMT if>=125	1856	[1482-2324]	1331	[1043-1697]	365	[316- 421]
Seropositive	96.3	[93.5-99.2]	78.0	[72.6-83.7]	32.4	[28.9-36.2]
Seroresponse	89.0	[84.5-93.6]	68.5	[62.9-74.5]	24.0	[21.3-27.1]
Seroconversion	71.2	[65.5-77.3]	50.6	[45.5-56.3]	13.2	[11.6-15.0]

Definitions : seropositive at 10 mo: >=125 miu
seroresponse at 10 mo: at least same titer if >=125
or from <125 to >=125
seroconversion 5-10 m: at least four fold increase in GMT
or from <125 to >=250

Table 5.7 : Distribution of measles antibody titers at 5 and 10 months, cohorts 03-16, children who never had measles, without any known exposure to measles, who came at both the 5 months and the 10 months session.

Titer in miu	At 5 months (before vaccination)	At 10 months (after vaccination at 5 months)					
		EZ-HT		SW-HT		Placebo	
		N	%	N	%	N	%
< 125	174	6	3.7	37	22.0	138	67.6
125	57	0	0.0	7	4.2	15	7.4
250	167	15	9.2	19	11.3	26	12.7
500	79	26	16.0	30	17.9	12	5.9
1000	31	35	21.5	22	13.1	8	3.9
2000	15	33	20.2	18	10.7	1	0.5
4000	10	19	11.7	13	7.7	1	0.5
8000	2	16	9.8	6	3.6	2	1.0
16000	0	4	2.5	7	4.2	1	0.5
32000	0	1	0.6	5	3.0	0	0.0
64000	0	2	1.2	1	0.6	0	0.0
128000	0	5	3.1	2	1.2	0	0.0
256000	0	0	0.0	1	0.6	0	0.0
512000	0	1	0.6	0	0.0	0	0.0
Total	535	163	100	168	100	204	100

Table 5.8: Analysis of response to measles vaccines, according to the level of antibody at time of vaccination (5 months), cohorts 03-16, children who never had measles, without any known exposure to measles, who came at both the 5 months and the 10 months session, Niakhar 1987-1989.

Measles antibody titer at 5 months in miu	EZ-HT (N= 169) mean	conf. int.	SW-HT (N= 168) mean	conf. int.	Placebo (N=204) mean	conf. int.
GMT at 10 months, for those with at least 125 miu						
< 250	3044	[2037- 4549]	1621	[1062-2475]	136	[105- 176]
250-999	1175	[909- 1520]	393	[272- 569]	94	[81- 108]
1000+	579	[292- 1145]	177	[95- 328]	108	[63- 184]
% sero-positive						
< 250	98.6	[95.9- 99.9]	92.1	[86.5-98.1]	40.5	[34.3-47.7]
250-999	97.3	[93.6- 99.9]	72.2	[63.9-81.6]	26.7	[22.6-31.6]
1000+	84.2	[70.4- 99.9]	45.0	[32.5-62.3]	26.3	[17.9-38.7]
% sero-response						
< 250	98.6	[95.9- 99.9]	92.1	[86.5-98.1]	40.5	[34.3-47.7]
250-999	94.5	[89.6- 99.7]	59.7	[51.6-69.2]	13.9	[11.6-16.6]
1000+	31.6	[21.8- 45.8]	10.0	[6.6-15.2]	5.3	[3.4- 8.2]
% sero-conversion						
< 250	98.6	[95.9- 99.9]	85.5	[78.5-93.2]	28.6	[23.8-34.2]
250-999	61.6	[53.5- 71.1]	26.4	[21.6-32.2]	2.0	[1.6- 2.4]
1000+	5.3	[3.4- 8.2]	5.0	[3.3- 7.7]	5.3	[3.4- 8.2]

Table 5.9 : Multinomial Logit analysis of the factors of sero-conversion, sero-positivity and sero-response, children of cohorts 03-16, who never had measles, without any known exposure to measles, who came at both the 5 months and the 10 months session, Niakhar 1987-1990.

Variable or interactions	Coef-ficient	Standard Deviation	T	P (2 tail)	
Dependent variable : Sero-conversion					
Constant	-2.494	2.439	-1.022	0.307	
Vaccine (EZ/SW)	1.574	0.341	4.608	5.8E-06	*
Titer at 5 months	-1.527	0.173	-8.805	1.0E-13	*
Age at vacc (weeks)	0.204	0.104	1.965	0.050	*
Cohort	0.097	0.044	1.204	0.229	
Season (dry/rainy)	-0.296	0.341	-0.866	0.387	
CHI (5) : 198.40 P = 1.0E-13					
Dependent variable : sero-positivity					
Constant	-4.139	2.738	-1.511	0.132	
Vaccine (EZ/SW)	2.289	0.505	4.526	6.4E-06	*
Titer at 5 months	-0.640	0.119	-5.363	1.5E-07	*
Age at vacc (weeks)	0.274	0.125	2.183	0.030	*
Cohort	0.080	0.048	1.679	0.094	
Season (dry/rainy)	0.064	0.388	0.166	0.868	
CHI (5) = 71.99 P = 1.0E-13					
Dependent variable : sero-response					
Constant	-1.612	2.772	-0.581	0.561	
Vaccine (EZ/SW)	2.117	0.433	4.885	1.6E-06	*
Titer at 5 months	-1.307	0.170	-7.664	3.6E-13	*
Age at vacc (weeks)	0.165	0.120	1.365	0.172	
Cohort	0.096	0.048	1.975	0.049	*
Season (dry/rainy)	0.335	0.379	0.883	0.377	
CHI (5) : 152.50 P = 1.0E-13					

For definitions see table 5.6

Table 5.10 : Multinomial Logit analysis of sero-positivity at 10 months (probability of having a seropositive at 10 month), Niakhar 1987-1989.

Variable	Estimate	Standard error	T	P (2 tail)
Vaccine = EZ-HT				
Constant	3.5672	6.6058	0.540	0.590
Titer at 5 months	-0.8754	0.2755	-3.177	0.001 *
Age at vaccination (weeks)	0.0682	0.2823	0.241	0.809
Cohort	0.0573	0.1140	0.502	0.616
Season (dry/rainy)	0.0779	0.9379	0.083	0.934
Chi (4) = 13.99 P = 0.0073				
Vaccine = SW-HT				
Constant	-5.1306	3.0288	-1.694	0.092
Titer at 5 months	-0.5823	0.1338	-4.349	2.4E-05 *
Age at vaccination (weeks)	0.3169	0.1409	2.248	0.026 *
Cohort	0.0804	0.0529	1.520	0.130
Season (dry/rainy)	0.0343	0.4266	0.080	0.936
Chi (4) = 32.37 P = 1.6E-06				

Table 5.11 : Multinomial regression analysis of the log(GMT) at 10 months, for seropositive cases at 10 months, Niakhar 1987-1990

Variable	Coefficient	Standard error	Standard coefficient	T	P (2 tail)	
Vaccine = EZ-HT						
Constant	2.383	2.405	0.000	0.991	0.323	
Log(GMT) at 5 mo	-0.493	0.111	-0.330	-4.439	0.000	*
Age at vacc (week)	0.056	0.102	0.041	0.550	0.583	
Cohort	0.108	0.040	0.209	2.674	0.008	*
Season (dry)	0.673	0.332	0.158	2.025	0.045	*
R = 0.159	F(4,152) = 7.163		P = 2.6E-05			
Vaccine = SW-HT						
Constant	2.845	2.894	0.000	0.983	0.327	
Log(GMT) at 5 mo	-0.562	0.139	-0.340	-4.053	0.000	*
Age at vacc (week)	0.091	0.124	0.063	0.736	0.463	
Cohort	0.057	0.052	0.101	1.110	0.269	
Season (dry)	-0.138	0.423	-0.030	-0.327	0.744	
R = 0.130	F(4,126) = 4.711		P = 0.001			

Table 5.12: Change in antibody titers after vaccination, according to age, cohorts 01 to 16, children who never had measles and without any known exposure to measles, for whom an extra bood sample was taken after 10 months, Niakhar 1987-1989, (revaccinated children are excluded).

Age at sample	EZ-HT at 5 months (N= 41)			SW-HT at 5 months (N= 32)			Standard at 10 months (N= 31)		
	mean	conf.	int.	mean	conf.	int.	mean	conf.	int.
5 months	139	[96 - 202]		209	[144- 303]		-		
10 months		-			-		90	[62-131]	
11-24 mo	1402	[762-2580]		859	[375-1967]		4090	[1598-10470]	
(mean age at third sample)		(16.5)			(16.2)			(17.4)	
% < 125 miu		19.5			34.4			22.6	

Table 5.13 : Mortality after 10 months according to immunigenicity criteria, cohorts 03-16, children who never had measles, without any known exposure to measles, who came at both the 5 months and the 10 months session (/1000 children), Niakhar 1987-1990.

Criteria	EZ-HT (N= 163)	SW-HT (N= 168)	RR	P (2 tail)
Seroconversion				
Yes	112 (13)	82 (7)	0.77	0.5483
No	128 (6)	120 (10)		
Seroresponse				
Yes	117 (17)	104 (12)	1.13	0.9862
No	111 (2)	94 (5)		
Seropositivity				
Yes	121 (19)	104 (12)	0.93	0.9749
No	0 (0)	94 (5)		
All categories	117 (19)	101 (17)		
RR (/ placebo)	1.59	1.38		
P (/ placebo)	0.158	0.344		

Table 5.14 : Expected percentage of children who would respond to high titer vaccines, according to various criteria of antibody response, Niakhar 1987-1990.

Age at vaccination (in weeks)	% expected sero-conversion		% expected sero-response		% expected sero-positivity	
	EZ-HT	SW-HT	EZ-HT	SW-HT	EZ-HT	SW-HT
10-13	46.8	23.5	75.7	46.6	93.4	65.2
14-17	54.2	29.6	81.2	53.1	94.6	68.9
18-25	66.7	42.4	88.6	64.1	96.2	75.3
26-33	80.1	59.5	93.6	75.8	97.4	82.3
34-41	79.1	64.4	88.1	74.9	96.3	82.1
42-49	80.7	63.9	90.8	76.4	96.8	82.8
50+	86.2	70.8	93.0	81.2	97.3	85.7

NB : computed from tables 5.5 and 5.6; see text for details.

Table 6.1 : Incidence of measles by month and year (date at onset of measles rash), and according to residence status, Niakhar 1987-1989.

Month	1987	1988	1989	Total
	RA + RP + VP	RA + RP + VP	RA + RP + VP	
January	0 + 15 + 0	0 + 0 + 0	4 + 17 + 0	36
February	3 + 14 + 0	0 + 0 + 0	4 + 6 + 0	27
March	0 + 32 + 0	0 + 0 + 0	8 + 21 + 0	61
April	0 + 29 + 0	0 + 0 + 0	6 + 16 + 2	53
May	2 + 9 + 0	3 + 6 + 0	3 + 15 + 0	38
June	0 + 0 + 0	2 + 0 + 0	4 + 16 + 1	23
July	0 + 0 + 0	0 + 8 + 0	0 + 5 + 0	13
August	2 + 0 + 0	2 + 5 + 0	3 + 3 + 1	16
September	0 + 0 + 0	1 + 0 + 0	0 + 30 + 1	32
October	0 + 0 + 0	2 + 0 + 0	0 + 23 + 0	25
November	1 + 0 + 0	2 + 7 + 1	0 + 14 + 0	27
December	2 + 0 + 0	4 + 12 + 1	2 + 57 + 3	81
Total	10 + 99 + 0	16 + 37 + 2	34 +225 + 8	431
Resident (RA+RP)	109	53	259	421
Present (RP+VP)	99	40	231	370

Nb : RP : resident, present (within study area)
RA : resident, absent (outside study area)
VP : visitor, present (within study area)

Table 6.2 : Three outbreaks of measles after the start of the study, according to residence status (date of first case in compound), Niakhar 1987-1990.

Period	Cases within the study area				No cases outside study area (RA)	Total No of cases studied RP+VP+RA
	# Villages attacked (VL)	# compound infected (CC)	# cases resident (RP)	# cases visitor (VP)		
1) Before trial started 01 Jan 87 - 14 Aug 87	15	28	103	0	8	111
2) After trial started 15 Aug 87 - 30 Apr 88	0	0	0	0	3	3
3) First outbreak 01 May 88 - 30 Sep 88	2	5	19	0	8	27
4) Second outbreak 01 Oct 88 - 14 Aug 89	20	48	117	5	39	161
5) Third outbreak 15 Aug 89 - 14 Aug 90	11	119	396	11	6	413
Total	26	200	635	16	64	715

NB : There are 30 villages in the study area

During vaccine trial : first case - last case in study area:

First outbreak : 02 May 88 - 03 Aug 88
Second outbreak : 06 Nov 88 - 18 Jul 89
Third outbreak : 17 Aug 89 - 14 Jul 90

Table 6.3 : Pattern of contamination of index cases in compounds, Niakhar, 1987-1989.

Source of contamination of index case in compound	No of compounds	%
Village life (games, ceremonies etc.)	44	48.9 %
Travel outside study area	18	20.0 %
School	11	12.2 %
Visitor from outside study area	8	8.9 %
Dispensary	5	5.6 %
Unknown	4	4.4 %
Total	90	100.0 %

Nb : Unknown : most likely infected in village, but clear evidence of the index case was not found (several were possible).
Travel outside of study area includes 3 cases of children infected in a dispensary or medical center while outside of study area.

Table 6.4 : Definition of generations within a compound: intervals between cases of the same and of successive generations, Niakhar, 1987-1989.

	In same generation		Wrt previous generation		
Nb of days since :	First case	Previous case	First case	Source case	Last case
0	22	14			
1-2	37	19			
3-4	16	5			
5-6	9				2
7-8	1		12	13	15
9-10			28	30	36
11-12			41	39	41
13-14			40	39	35
15-16			23	24	21
17-18			9	9	4
19-20			0		
21-22			1		
Total	85	38	154	154	154
Mean	1.88	1.13	12.36	12.24	11.72
St. dev	1.74	1.20	2.72	2.68	2.56

Table 6.5 : Distribution of cases and compounds according to the generation, measles cases in the study area, Niakhar, 1987-1989.

Generation k (1)	No generations (2)	No measles cases (3)	Mean No cases per generation (3/2)	Among unvaccinated children: No measles cases (5)	Among unvaccinated children: No susceptibles (6)	Among unvaccinated children: Secondary attack rate /100 (5/6)
1	89	98	1.10	-	-	-
2	52	108	2.08	98	248	39.6
3	20	38	1.90	31	103	30.1
4	3	4	1.33	4	35	11.4
5+	2	2	1.00	2	11	18.2
all	166	250	1.50	135	248	54.8

Note : mean length between 2 generations : 12.2 days
G1->G2 = 11.9 days; G2->G3 = 12.1 days; G3+->G4+ = 14.6 days

Table 6.6 : Incidence of measles according to age, sex and survival, resident population, 1987-1989.

Age group	Measles cases			Person -years lived	Incidence /1000 PYS	Measles deaths	CFR /1000
	male	female	all				
0-3 months	0	0	0	924.2	0.0	0	0.0
4-5 months	2	3	5	448.3	11.2	0	0.0
6-7 months	5	2	7	453.0	15.5	0	0.0
8-9 months	5	5	10	442.5	22.6	0	0.0
10-11 months	2	2	4	446.3	11.2	0	0.0
1-2 years	25	29	54	4842.8	11.4	3	54.5
3-4 years	5	16	21	4253.2	4.9	0	0.0
5-9 years	62	70	132	9361.3	14.1	2	15.2
10-14 years	38	30	68	7499.0	8.8	0	0.0
15-29 years	7	8	15	12939.0	1.2	0	0.0
Total	151	165	316	41609.6	7.6	5	15.8

NB : measles death = death within 42 days after onset of measles rash.

Table 6.7 : Measles case fatality ratios, with and without medical intervention Niakhar 1983-1989, (CFR /1000 measles cases).

Age at measles onset	March 83 - July 87		August 87- Dec 89		% decrease in CFR
	Without medical interv.		With medical interv.		
	CFR	(D/cases)	CFR	(D/cases)	
< 1 year	102.0	(20/196)	0.0	(0/26)	100.0 %
1-4 years	86.0	(76/884)	40.0	(3/75)	53.5 %
5-9 years	10.4	(5/480)	15.2	(2/132)	-
10+ years	0.0	(0/157)	0.0	(0/83)	-
Total	58.8	(101/1717)	15.8	(5/316)	73.1 %

Table 6.8 : Clinical features of measles, according to duration since onset, (% children with clinical sign among children who had measles), Niakhar 1987-1989.

Duration	Rash/desquam typical	Rash/desquam untyp	Koplik sign	Conjunctivitis	Stomatitis	Cough	Pulmo. sign	Diar-rhea	Fever >38°C	(N)
0	0.0	0.8	0.0	3.3	1.6	13.8	0.0	0.8	20.9	123
1-2	25.5	2.1	31.9	66.0	25.5	63.8	2.1	10.6	85.4	47
3-4	74.7	0.0	44.0	93.4	64.8	95.6	8.8	16.5	93.3	91
5-6	92.3	1.7	26.5	92.3	80.3	100.0	14.5	19.7	82.2	117
7-8	99.2	0.0	9.9	86.8	74.4	100.0	33.1	17.4	47.4	121
9-10	98.1	0.9	0.9	62.0	47.2	95.4	23.1	6.5	38.5	108
11-12	97.5	1.7	0.8	44.5	25.2	95.0	10.9	8.4	20.7	119
13-14	97.1	1.0	0.0	23.5	9.8	93.1	7.8	4.9	21.0	102
15-16	98.0	0.0	0.0	16.7	6.9	91.2	5.9	2.9	11.1	102
17-18	97.7	1.1	0.0	13.8	6.9	77.0	4.6	9.2	16.7	87
19-20	92.1	0.0	0.0	2.2	2.2	75.3	2.2	4.5	13.3	89
21-22	90.9	0.0	0.0	7.1	1.0	73.7	2.0	11.1	16.7	99
23-24	88.6	0.0	0.0	5.7	2.3	65.9	2.3	5.7	16.7	88
25-26	81.9	1.1	0.0	5.3	3.2	63.8	4.3	6.4	11.2	94
27-28	58.2	1.0	0.0	4.1	1.0	53.1	3.1	5.1	13.7	98
29-30	53.2	1.3	0.0	5.1	5.1	62.0	1.3	2.5	15.6	79
31-32	28.1	0.0	0.0	9.4	0.0	51.6	1.6	4.7	6.7	64
33-34	40.0	0.0	0.0	8.0	4.0	36.0	2.0	4.0	12.8	50
35-36	26.9	3.8	0.0	7.7	3.8	23.1	0.0	0.0	0.0	26
37-42	20.0	0.0	0.0	6.7	6.7	26.7	0.0	0.0	8.3	15
43 +	20.8	0.0	0.0	0.0	0.0	8.3	0.0	0.0	16.7	24
Total	74.2	0.7	5.7	114.5	21.7	72.6	7.9	7.8	29.6	1743

Nb : duration 0 = before onset of first symptom.
1 = first day of first symptom.

Table 6.9 : Mean score and mean severity according to duration since onset and to vaccination status, Niakhar 1987-1989.

Duration	Unvaccinated children			Vaccine failure			Ratio vac/unvac	
	(N)	Score	Severity	(N)	Score	Severity	Score	Severity
0	101	0.2	0.4	10	1.2	1.6	-	-
1-2	39	5.3	4.3	4	8.8	5.3	1.64	1.23
3-4	73	11.5	9.0	11	10.2	8.7	0.89	0.97
5-6	99	12.0	10.2	13	11.3	8.5	0.94	0.83
7-8	98	10.8	8.6	11	10.3	7.5	0.95	0.87
9-10	90	9.4	6.7	13	8.8	5.2	0.94	0.78
11-12	104	8.3	5.5	8	8.5	5.0	1.02	0.91
13-14	82	7.6	4.6	15	6.8	3.1	0.90	0.67
15-16	91	7.4	4.2	4	5.8	2.5	0.78	0.60
17-18	76	7.2	3.9	9	6.4	3.0	0.90	0.76
19-20	72	6.4	3.0	10	5.6	2.8	0.87	0.92
21-22	86	6.5	3.1	9	5.4	2.2	0.84	0.71
23-24	76	6.3	2.6	8	3.8	2.3	0.60	0.86
25-26	82	5.8	2.5	8	4.6	1.9	0.79	0.74
27-28	81	4.3	1.9	10	3.8	1.8	0.88	0.94
29-30	72	4.3	2.0	2	0.0	0.0	0.00	0.00
31-32	51	2.3	1.2	10	2.1	1.2	0.91	0.97
33-34	47	3.1	1.4	2	0.0	0.5	0.00	0.37
35-36	23	2.3	0.8	1	0.0	0.0	0.00	0.00
37-38	12	2.2	0.9	1	0.0	0.0	0.00	0.00
39-40	5	1.2	0.4	0	0.0	0.0	0.00	0.00
41-42	2	3.0	0.5	0	0.0	0.0	0.00	0.00
Total	1361	7.2	4.6	149	6.7	4.1	0.93	0.89

Nb : duration 0 = before onset of first symptom.
1 = first day of first symptom.

Table 6.10 : Comparison of score and severity among vaccinated and unvaccinated children, Niakhar 1987-1989.

Duration since onset	Unvaccinated children			Vaccine failure			Comparison vac/unvac		
	(N)	mean	st.dev.	(N)	mean	st.dev.	ratio	T-test	P (2T)
Score									
1-7	250	10.7	4.37	37	10.5	3.32	0.98	-0.35	.7266
8-14	335	8.8	2.12	38	8.0	2.22	0.91	-2.14	.0130 *
15-21	273	6.9	1.50	29	5.8	2.70	0.83	-2.31	.0216 *
22-28	291	5.7	2.67	29	4.3	3.02	0.76	-2.36	.0190 *
29-35	185	3.2	3.17	14	1.4	2.19	0.44	-2.96	.0034 *
36-42	27	2.4	2.86	1	0.0	0.00	0.00	-4.44	.0001 *
Severity									
1-7	250	8.7	3.75	36	8.0	3.23	0.92	-1.17	.2430
8-14	335	6.1	2.88	37	4.4	2.20	0.72	-4.45	1.2E-5 *
15-21	273	3.7	1.82	29	2.8	1.43	0.75	-3.14	.0018 *
22-28	291	2.5	1.92	28	1.9	1.66	0.77	-1.74	.0828
29-35	185	1.5	1.51	14	0.9	0.88	0.57	-2.57	.0110 *
36-42	27	0.8	0.90	1	0.0	0.00	0.00	-4.68	.0007 *

* P< 0.05

Table 6.11 : Frequence of diarrhea and ALRI among vaccinated and unvaccinated children, Niakhar 1987-1989.

Duration since onset	Unvaccinated children			Vaccine failure			Comparison vac/unvac		
	(N)	% diarrhea	mean sever.	(N)	% diarrhea	mean sever	ratio	T-test	P (2T)
Diarrhea									
1-7	250	17.6	1.91	42	13.5	1.80	0.77	-0.70	.4844
8-14	335	9.9	1.70	58	0.0	0.00	0.00	-6.05	3.4E-09 *
15-21	273	7.3	1.70	12	0.0	0.00	0.00	-4.65	9.3E-06 *
22-28	291	6.5	1.95	11	10.3	2.00	1.58	0.41	.1152
29-35	185	3.2	1.67	3	0.0	0.00	0.00	-2.49	.0136 *
36-42	27	0.0	0.00	0	0.0	0.00	-	-	-
Total	1361	9.0	1.81	126	5.4	1.88	0.54	-1.67	.0952
ALRI									
1-7	250	16.8	1.81	42	0.0	0.00	0.00	-7.10	9.6E-12
8-14	335	17.3	1.84	58	7.9	1.67	0.46	-2.30	.0220 *
15-21	273	4.4	1.67	12	0.0	0.00	0.00	-3.54	.0004 *
22-28	291	3.8	2.00	11	0.0	0.00	0.00	-3.38	.0008 *
29-35	185	1.6	2.00	3	0.0	0.00	0.00	-1.75	.0818
36-42	27	0.0	0.00	0	0.0	0.00	-	-	-
Total	1361	9.3	1.83	126	2.0	1.67	0.22	-4.90	1.1E-6 *

* P< 0.05

Table 6.12 : Analysis of score among cases according to major symptoms associated and to date of examination (all cases examined), Niakhar 1987-1989.

Clinical score	Measles cases examined day 1-42		Measles cases examined day 3-10	
	N	major symptoms	N	major symptoms and analysis
0	164	none (after end)	1	after rash (day 9)
1	96	cough (94)	2	before rash (day 3)
2	16	various	2	before rash (n=9)
3	23	combination	5	after rash (n=1)
4	10	without rash	2	rash not seen that day
5	7		3	but seen before or after (n=2)
6	186	rash only (180)	6	rash only (3) rash not seen (3)
7	705	rash+cough (700)	56	idem
8	40	rash+cough+	9	
9	201	stomatitis or	77	idem
10	25	conjunctivitis	20	
11	175	or combination	141	
12	94		90	
13	0	(impossible)	0	(impossible)
14	6	rash+koplik+	4	
15	20	other signs	19	idem
16	18		18	
17	49	all possible	44	
Total	1835		499	

Table 6.13 : Maximum score obtained according to when examinations occurred and to vaccination status, Niakhar 1987-1989.

Maximum score	Unvaccinated children		Vaccinated children		Susceptible contacts not infected
	day 1-42	day 3-10	day 1-42	day 3-10	
0-1	4 *	1 *	0	0	232
2-5	1 *	2 *	0	2 *	20
6-7	18	8	4	3	1
8-12	145	129	16	14	0
13-17	54	48	5	5	0
No exam	54	88	5	6	76
Total	276	276	30	30	329
% 8+	89.6	94.1	84.0	79.2	0.0
% no exam	19.6	31.9	16.7	20.0	23.1

* See text for comments

Table 6.14 : Clusters of clinical symptoms among cases and contacts and according to vaccination status (maximum signs in at least one of the examinations), Niakhar 1987-1989.

Cluster of clinical signs	cases among unvaccinated children	cases among vaccinated children	susceptible contacts not infected
Typical rash with cough	212	25	0
Typical rash without cough	5	0	0
Untypical rash	0	0	6
No rash, score>=6	0	0	0
None of above	7 *	0	323
No examination day 1-42	52	5	0
Total	276	30	329

* Children examined late without any symptom.

Table 6.15 : Clinical confirmation of measles cases during repeated home visits, Niakhar 1987-1989.

Nature of case	Not confirmed	Directly confirmed	Indirectly confirmed	Total	% confirmed
All measles cases					
Outside study area	46	5	3	54	14.8
Index case	10	79	9	98	90.0
Secondary case	5	136	13	154	96.8
Total	61	220	25	306	80.1
%	19.9	71.9	8.2	100.0	
Cases among vaccinated children	8	21	1	30	73.3

Directly confirmed : score >= 8 during at least one examination

Indirectly confirmed : in contact with a confirmed case in same compound.

Table 6.16 : Geometric mean levels of measles antibodies during the course of clinical measles, Niakhar 1987-1989.

Day after onset of illness	N	GMT in miu	95 % confidence interval min	max
< 02	152	79	68	90
03-04	26	393	161	963
05-06	27	903	330	2467
07-08	22	4986	1627	15279
09-10	15	11058	3175	38508
11-14	16	11314	3576	35793
15-21	6	90510	37120	220689
22-28	35	61521	31988	118319
29-35	148	89140	67035	118534
36-42	23	89140	43262	183670
43-49	9	29630	8463	103736

NB : day 1 = day of onset of illness

Table 6.17 : distribution of antibody titers according to exposure status, vaccine status and infection, Niakhar 1987-1989.

Class	Antibody levels in miu	Measles cases sampled prior to onset (D-42 to D2)		Measles cases sampled after infection (D28 to D42)		Contacts not infected +/- 42 days around exposure	
		Not vacc.	Vacci-nated	Not vacc.	Vacci-nated	Not vacc.	Vacci-nated
0	< 125	107	8	1 *	1 *	38	14
1	125	3	0	0	0	3	0
2	250	2	0	0	0	5	2
3	500	3	1	0	1	6	6
4	1000	1	0	0	1	12	22
5	2000	0	0	5	0	13	22
6	4000	0	0	10	1	13	21
7	8000	0	0	15	0	7	23
8	16000	0	1	12	0	4	17
9	32000	0	0	8	2	8	13
10	64000	0	0	15	4	2	8
11	128000	0	0	35	6	3	3
12	256000	0	0	1	1	0	0
13	>=512000	0	0	61	2	3	6
	Total	116	10	163	19	117	157
	GMT (miu)	75	250	50224	14341	948	3165

* Both cases <125 were clinically confirmed; one was serologically confirmed by another sample.

Table 6.18: Rise in measles HI antibodies titers during the course of infection, (second sample taken from day 15 to 42), children for whom two samples were available, Niakhar 1987-1989.

Increase in HI titers from first to second sample	First sample taken before day 3		First sample taken from day 3 to day 14	
	no vacc	vacc	no vacc	vacc
no increase	0	0	13	3
2 fold	0	0	4	2
4 fold	0	0	6	0
8 fold	0	0	3	0
16 fold	0	0	7	1
32 fold	4	0	7	0
64 fold	8	0	13	0
128 fold	8	0	9	0
256 fold	6	0	7	1
512 fold	5	0	8	1
1024 fold	9	5	10	5
2048 fold	20	2	23	4
4096 fold	1	0	1	0
8192 fold	38	1	43	1
Total	99	8	154	18
Geometric mean	842	76	223	39
% 16+ fold	100	100	83.1	72.2

Day 1 = onset of illness

Table 6.19 : Serological confirmation and validation of measles cases, Niakhar 1987-1989.

Nature of case	Not confirmed	Directly confirmed	Indirectly confirmed	Total	% confirmed
All measles cases : serological confirmation					
Outside study area	51	2	1	54	5.6
Index case	33	48	17	98	66.3
Secondary case	27	109	18	154	82.5
Total	111	159	36	306	63.7
%	36.3	52.0	11.8	100.0	
Cases among vaccinated children	12	14	4	30	60.0
All measles cases : serological and clinical confirmation					
Outside study area	52	1	1	54	3.7
Index case	35	45	18	98	64.3
Secondary case	32	95	27	154	79.2
Total	119	141	46	306	61.1
%	38.9	46.1	15.0	100.0	
Cases among vaccinated children	13	12	5	30	56.7

NB:

Directly confirmed : 4+ fold increase in antibody titers during acute phase, or -2 fold decrease after acute phase (2cases)

Indirectly confirmed : in contact with a confirmed case in same compound.

(for definitions of clinical signs, see table 6.15)

Table 6.20 : Sensitivity and specificity of various criteria for diagnosis, Niakhar 1987-1990.

Criteria	(N)	Sensitivity	Specificity
1) Typical rash (all cases)	(307)	78.8	100.0
Typical rash (examined day 1-42)	(242)	99.2	100.0
2) Koplik spots (all cases)	(307)	25.4	100.0
Koplik spots (examined day 1-8)	(196)	38.8	100.0
3) Score >= 8 (all cases)	(307)	71.7	100.0
Score >=8 (examined day 3-10)	(212)	92.4	100.0
4) 16 fold increase in AB (all cases)	(307)	51.8	99.4
16 fold increase in AB (first<D2, second >=D28)	(112)	100.0	99.1
5) 4 fold increase in AB (all cases)	(307)	60.9	99.5
4 fold increase in AB (first<D2, second >=D28)	(112)	100.0	95.7
6) Titer >= 16000 miu (all cases)	(307)	57.6	67.5
Titer >= 16000 miu (after D28)	(175)	82.3	96.6

Table 7.1 : Measles cases among project children according to vaccination status and various characteristics, Niakhar 1987-1990.

	Vaccine failures			Not vaccinated	Total
	EZ-HT (5 mo)	SW-HT (5 mo)	Standard (10 mo)		
Total	5	5	1	57	68
Confirmation					
Direct	1	2	0	16	19
Indirect	2	0	0	5	7
Not confirmed	2	3	1	36	42
Residence status					
Resident	5	5	1	54	65
Not resident	0	0	0	3	3
Exposure status in compound					
Single, index	2	2	0	11	15
Secondary	3	2	1	30	36
Outside study area	0	1	0	16	17
Age					
< 10 months	1	0	0	18	19
>= 10 months	4	5	1	39	49
Sex					
Male	4	3	0	29	36
Female	1	2	1	28	32
Cohort					
01-16	2	5	1	34	42
17-24	3	-	0	23	26
Seroconversion after vaccination					
Yes	0	0	-	-	0
No	0	4	-	-	4
Unknown	5	1	1	57	64

Table 7.2a: Cohort efficacy of three measles vaccines among project children, between age 5 and 10 months, Niakhar 1987-1990, (confirmed cases in parentheses).

	Vaccine group			Not participant	Total
	EZ-HT (5 mo)	SW-HT (5 mo)	Placebo (5 mo)		
I Cohorts 01-16					
No children	336	323	357	397	1413
Measles cases	0	0	2 (0)	2 (1)	4 (1)
Person-years	134.3	128.3	143.4	271.9	677.9
Incidence /1000	0.00	0.00	13.95	7.36	5.90
Cohort efficacy %	100.0	100.0			
II Cohorts 17-24					
No children	291	-	281	224	796
Measles cases	1 (0)	-	3 (0)	10 (7)	14 (7)
Person-years	118.7	-	114.3	148.2	381.3
Incidence /1000	8.42	-	26.24	67.46	36.72
Cohort efficacy %	67.9	-			
Confidence interval	0-95.5	-			
T	0.984				
P	0.3256				
III Cohorts 01-24					
No children	627	321	639	621	2208
Measles cases	1 (0)	0	5 (0)	12 (8)	18 (8)
Person-years	253.1	128.3	257.7	420.0	1059.2
Incidence /1000	3.95	0.00	19.38	28.57	16.99
Cohort efficacy %	79.6	100.0	0.0	-	
Confidence interval	0-97.1	-			
T	1.451				
P	0.1470				

Table 7.2b: Cohort efficacy of three measles vaccines among project children, after 10 months, Niakhar 1987-1990, (confirmed cases in parentheses).

	Vaccine group			Not vaccinated	Total
	EZ-HT (5 mo)	SW-HT (5 mo)	Standard (10 mo)		
I Cohorts 01-16					
No children	322	304	469	233	1328
Measles cases	2 (2)	5 (2)	1	28 (11)	36 (15)
Person-years	644.2	621.7	896.1	486.0	2648.0
Incidence /1000	3.10	8.04	1.12	57.62	13.59
Cohort efficacy %	94.6	86.0	98.1	0.0	
Confidence interval	77.4-98.7	63.8-94.6	85.8-99.7		
T	3.991	4.056	3.876		
P	7.4E-5	5.8E-5	1.1E-4		
II Cohorts 17-24					
No children	281	-	317	145	743
Measles cases	2 (1)	-	0	9 (2)	11 (3)
Person-years	316.9	-	354.3	165.4	836.6
Incidence /1000	6.31	-	0.00	54.42	13.15
Cohort efficacy %	88.4	-	100.0	0.0	
Confidence interval	46.2-97.5	-	-		
T	2.756				
P	0.0062				
III Cohorts 01-24					
No children	603	304	786	378	2071
Measles cases	4 (3)	5 (2)	1 (0)	37 (13)	47 (18)
Person-years	961.1	621.7	1250.5	651.3	3484.6
Incidence /1000	4.16	8.04	0.80	56.81	13.49
Cohort efficacy %	92.7	85.8	98.6	0.0	
Confidence interval	79.4-97.4	64.0-94.4	89.7-99.8		
T	4.966	4.103	4.207		
P	8.0E-7	4.6E-5	2.8E-5		
IV Cohorts 01-24, confirmed cases only					
Efficacy / 100	84.4	83.9	100.0	0.0	
Confidence interval	45.1-95.5	28.6-96.4	-		
T	2.897	2.403	-		
P	0.0038	0.0166			

Table 7.2c: Cohort efficacy of three measles vaccines among project children, all ages, Niakhar 1987-1990, (confirmed cases in parentheses).

	Vaccine group			Not vaccinated	Total
	EZ-HT (5 mo)	SW-HT (5 mo)	Standard (10 mo)		
I Cohorts 01-16					
No children	336	323	357	397	1413
Measles cases	2 (2)	5 (2)	1 (0)	32 (12)	40 (16)
Person-years	778.6	750.0	896.1	901.2	3325.9
Incidence /1000	2.57	6.67	1.12	35.50	12.03
Cohort efficacy %	92.8	81.2	96.9	(ref)	
Confidence interval	69.8-98.3	51.8-92.7	77.0-99.6		
T	3.603	3.478	3.407		
P	0.0004	0.0006	0.0006		
II Cohortes 17-24					
No children	291	-	281	224	796
Measles cases	3 (1)	-	0	22 (9)	25 (10)
Person-years	435.6	-	354.3	427.9	1217.8
Incidence /1000	6.89	-	0.00	51.41	20.53
Cohort efficacy %	86.6	-	100.0	0.0	
Confidence interval	55.2-96.0	-	-	(ref)	
T	3.266				
P	0.0012				
III Cohortes 01-24					
No children	627	323	638	621	2209
Measles cases	5 (3)	5 (2)	1 (0)	54 (21)	65 (26)
Person-years	1214.2	750.0	1250.5	1329.4	4543.7
Incidence /1000	4.12	6.67	0.80	40.63	14.31
Cohort efficacy %	89.9	83.6	98.0	0.0	
Confidence interval	74.7-95.9	59.0-93.4	85.8-99.7		
T	4.896	3.865	3.892		
P	1.1E-6	1.2E-4	1.0E-4		
Relative risk of vaccine failure	5.15	8.34	(ref)		
IV Cohortes 01-24, confirmed cases only					
Cohort efficacy %	84.4	83.1	100.0	0.0	
Confidence interval	47.6-95.3	28.0-96.0	-		
T	3.006	2.404	-		
P	0.0026	0.0164			

Table 7.3 : Case-contact efficacy of three measles vaccines among project children, Niakhar 1987-1990, (confirmed cases in parentheses).

	Vaccine received			Not vaccinated
	EZ-HT (5 mo)	SW-HT (5 mo)	Standard (10 mo)	
I Cohorts 01-16				
No children exposed	35	24	35	24
Person-years at risk	778.6	750.0	896.1	901.2
Exposure rate / 1000	45.0	32.0	39.1	26.6
No secondary cases	1 (1)	2 (1)	1 (0)	15 (6)
Secondary attack rate/1000	28.6	83.3	28.6	625.0
Case-contact efficacy %	95.4	86.7	95.4	(ref)
Confidence interval	67.7-99.4	47.9-96.6	67.7-99.4	
T	2.987	2.677	2.987	
P	0.0042	0.0102	0.0042	
RR of vaccine failure	1.00	2.92	1.00	
II Cohorts 17-24				
No children exposed	18	-	19	22
Person-years at risk	435.6	-	354.3	427.9
Exposure rate /1000	41.3	-	53.6	51.4
No secondary cases	2 (1)	-	0	15 (7)
Sec. attack rate /1000	111.1	-	0.0	681.8
Case contact efficacy %	83.7	-	100.0	(ref)
Confidence interval	37.9-95.7	-	-	
T	2.410	-	-	
P	0.0228			
III Cohorts 01-24				
No children exposed	53	24	54	46
Person-years at risk	1214.2	750.0	1250.5	1329.2
Exposure rate /1000	43.7	32.0	43.2	34.6
No secondary cases	3 (2)	2 (1)	1 (0)	30 (13)
Sec. attack rate /1000	56.6	83.3	18.5	652.2
Case contact efficacy %	91.3	87.2	97.2	
Confidence interval	73.4-97.2	51.0-96.7	80.0-99.6	
T	4.037	2.817	3.504	
P	0.0001	0.0072	0.0008	
RR of vaccine failure	3.06	4.50	1.00	
IV Cohorts 01-24, confirmed cases only				
Case contact efficacy %	94.2	93.6	100.0	
Confidence interval	77.1-98.5	56.0-99.1	-	
T	3.902	2.706		
P	0.0001	0.0086		

Table 7.4 : Linear logistic analysis of the risk factors of vaccine failure, among project children, (case-contact efficacy), Niakhar 1987-1990.

Variable	Odds ratio	Estimate	Standard Error	T statistic	P (2 tail)	
Constant		-2.268	1.2133	-1.8700	0.0632	
Vaccine						
EZ-HT	0.0129	-4.354	0.8179	-5.3231	3.2E-7	*
SW-HT	0.0317	-3.452	0.9306	-3.7095	2.0E-4	*
Standard	0.0047	-5.367	1.1434	-4.6939	5.6E-6	*
(ref=not vaccinated)						
Age in months	1.050	0.049	0.0341	1.4372	0.1526	
Sex (ref=male)	0.493	-0.708	0.5771	-1.2273	0.2214	
Intensity of exposure	2.284	0.826	0.3708	2.2285	0.0272	*

NB: based on 34 secondary cases and 172 children exposed.
Log Likelihood: -46.455, $X^2(6) = 78.113$, P= E-13.

Table 7.5 : Measles cases among other children, according to vaccination status, and various characteristics, Niakhar 1987-1990.

	Vaccine failures after standard vaccine			Not vaccinated	Other & unknown status
	81-83	86-87	Else		
Total	2	15	10	465	44
Confirmation					
Direct	1	4	3	115	12
Indirect	0	3	0	42	4
Not confirmed	1	8	7	308	28
Residence status					
Resident	2	15	10	452	41
Not resident	0	0	0	13	3
Exposure status in compound					
Single, index	2	5	3	166	14
Secondary	0	7	5	268	27
Outside study area	0	3	2	31	3
Age					
< 1 year	0	0	0	22	0
1-4 years	0	8	1	77	10
5-9	2	7	9	366	34
Sex					
Male	1	5	4	238	17
Female	1	10	6	227	27
Duration since vaccination					
< 5 years	0	15	6	-	0
5+ years	2	0	4	-	1
Not vaccinated	-	-	0	465	43
Age at vaccination					
< 9 months	1	4	1	-	0
9+ months	1	11	9	-	1
Cohorts 1978-1986	1	15	10	332	38

81-83 : ORSTOM vaccination in 8 villages
86-87 : National EPI campaign

Table 7.6 : Cohort efficacy of standard measles vaccines, among children born from 1978 to 1986, according to vaccination campaign, Niakhar 1987-1990.

	Vaccine failures after standard vaccine			Not vaccinated	Other & unknown status
	81-83	86-87	else		
I All cases					
No children	301	1190	635	3745	3435
Measles cases	1	15	8	307	60
Person-years at risk	821.9	3289.6	1557.2	9132.7	7914.7
Incidence /1000	1.22	4.56	5.14	33.62	7.58
Cohort efficacy %	96.4	86.4	84.7	(ref)	
Confidence interval	74.2-99.5	77.2-91.9	69.2-92.4		
T	3.313	7.555	5.245		
P	0.0010	1.0E-13	1.7E-7		
II Confirmed cases					
Cohort efficacy %	92.9	87.6	88.8	(ref)	
Confidence interval	49.4-99.0	73.6-94.2	64.9-96.4		
T	3.308	7.144	4.906		
P	0.0010	1.0E-13	9.8E-7		

81-83 : ORSTOM vaccination campaigns in 8 villages
86-87 : National EPI campaign

Table 7.7 : Case-contact efficacy of standard measles vaccines among other children, according to vaccination campaign, Niakhar 1987-1990.

	Vaccine failures after standard vaccine			Not Vaccinated	Other & unknown vaccination status
	81-83	86-87	Else		
I All cases					
No children exposed	10	156	52	441	101
No secondary cases	0	7 (5)	5 (2)	264 (101)	22 (9)
Sec. attack rate /1000	0.0	44.9	96.2	598.6	21.8
Case contact efficacy %	100.0	92.5	83.9		
Confidence interval	-	84.5-96.4	62.9-93.0		
T	-	6.766	4.051		
P		3.2E-11	5.9E-5		
II Confirmed cases					
Case contact efficacy %	100.0	94.6	93.6		
Confidence interval	-	87.3-97.7	74.9-98.4		
T	-	6.485	3.867		
P		1.9E-10	1.2E-4		

81-83 : ORSTOM vaccination campaigns in 8 villages
86-87 : National EPI campaign

Table 7.8 : Protective values of various levels of antibodies at time of exposure in a compound, according to vaccination status, (cases within study area, of known vaccine status), Niakhar 1987-1989.

Class	Antibody levels at time of exposure in miu	Secondary cases sampled prior to onset		Contact not infected in compound		Protective value of antibody level	
		Not vaccin.	Vacci-nated	Not vaccin.	Vacci-nated	Not vaccin.	Vacci-nated
0	< 125	88	7	31	14	26.1	66.7
1	125	3	0	1	2	25.0	100.0
2	250	3	0	4	2	57.1	100.0
3	500	2	0	3	5	60.0	100.0
4	1000	1	0	10	24	90.9	100.0
5	2000	0	0	14	18	100.0	100.0
6	4000	0	0	12	18	100.0	100.0
7	8000	0	0	7	20	100.0	100.0
8	16000	0	0	4	16	100.0	100.0
9	32000	0	0	8	11	100.0	100.0
10	64000	0	0	2	7	100.0	100.0
11	128000	0	0	3	2	100.0	100.0
12	256000	0	0	0	0	100.0	100.0
13	>=512000	0	0	3	6	100.0	100.0
	Total	97	7	102	145		

ANNEXES

ANNEX 1

LISTS OF CASES

A-1.1 LIST OF MEASLES DEATHS FROM AUGUST 1987 TO DECEMBER 1989.

During the study period, August 1987 to December 1989, the five measles deaths were the following:

Death 1 : 06-199-58162 M 07/06/87 died on 20/02/89 (20 months) on day 11.

The child contracted measles in Dakar where he was with his mother. He died on day 11 of acute diarrhea in Dakar. He was seen by a nurse there but did not receive appropriate care. We learned about his death on June 28, 1989, about four months later. The child was eligible for vaccination during the project but his mother refused to bring him at 5 and 10 months when called.

Death 2 : 11-002-51266 F 30/01/84 died on 21/04/89 (5 years) at day 22.

She developed measles on 25 March 89; she was the index case in the compound, infected in the village. She was seen by the physician on April 18 only for the first time (day 19): she had high fever (39.5 °C), pneumonia and laryngitis and a poor nutritional status; she was first treated at home with antibiotics (Ceporexin) and aspirin and fever was down to 36.8°C the following day. However her health worsened three days later and she was referred to the Fatick hospital where she died during the night.

Death 3 : 11-002-20563 F 24/01/83 died on 25/04/89 (6 years) at day 10.

Same compound as death 2. She was a secondary case, infected by a boy sleeping in the same hut. She was also seen on April 18 for the first time, at day 3 of her measles. She was a deaf and dumb child with a poor nutritional status (14 kg). On day 10 she developed acute diarrhea, laryngitis and pneumonia and had epistaxis and cardiac arrythmia. She was treated with corticoid and antibiotics (ampicillin) and was transferred to Dakar Fann hospital, where she died during the night.

As for the previous case, this child was too young to have been vaccinated in March 1983, the last major vaccination campaign in the study area prior to 1986, and too old to be in the target group for the 1986 National Vaccination campaign. Both could have been vaccinated during the project if they had come spontaneously.

Death 4 : 16-031-60856 F 01/11/87 died on 03/09/89 (22 months) at day 14.

The child was infected in Dakar, she was sleeping in the same bed as another girl, and developed measles on August 21. She came back to the study area on the same day and was seen for the first time on August 30 by the physician. She was severely malnourished and with severe anemia, she had an acute pneumonia and cardiac arrythmia. She was treated with corticoid and antibiotics (Bactrim) and supplemented in iron, in addition to standard treatment (Aspirin, Pyralvex, Aureomycine, Mebendazole). The following day she was better and corticoid was stopped. Her health worsened at night and she was transferred the following morning to the Fatick hospital where she died at night.

She was an in-migrant in the study area, therefore she was not eligible to be called by the team. She could have been vaccinated, had she come spontaneously.

Death 5 : 17-051-58656 F 30/10/87 died on 03/10/89 (23 months) at day 13.

Secondary case in compound, she was seen before the rash for the first time on September 5; she developed measles on September 22, infected by a boy living in the same hut; she was seen on September 29 with pneumonia; she was treated with antibiotics (Ampicillin); the physician was notified that her health had worsened on October 3; unfortunately his car was not working that day and we he came to transfer her at night, the child was already dead.

The child was eligible for vaccination during the project but her mother refused to bring her at the 3, 5 and 10 months sessions when called.

A-1.2 LIST OF NON-CASES WITH AT LEAST 4 FOLD INCREASE IN ANTIBODY TITER OR WITH VERY HIGH TITERS DURING EXPOSURE TO MEASLES.

Case 1 : booster to a vaccinated child

VC=01-007 Id=61439 M born 01/10/88 exposed 15/06/89 -> 08/07/89
vaccinated at 5 months with EZ-HT vaccine on 21/03/89
blood samples R-21-045 21/03/89 titer= 2^4
M-00-581 20/06/89 titer= 2^4 (non converter)
R-26-903 08/08/89 titer= 2^13 (booster)

Case 2 : booster to a vaccinated child

VC=06-001 Id=54190 F born 05/11/85 exposed 07/11/88 -> 04/01/89
vaccinated at 8 mo with standard vaccine on 28/07/86
blood samples M-00-227 10/01/89 titer= 2^8
M-00-264 03/02/89 titer= 2^12 (booster)
R-26-903 08/08/89 titer= 2^13 (booster confirmed)

Case 3 : high titer to a vaccinated child

VC=20-003 Id=50319 M born 19/09/83 exposed 07/11/88
vaccinated at 3 years with standard vaccine on 20/12/86
blood samples M-00-198 30/11/88 titer= 2^13 (high titer)

Case 4 : high titer to a vaccinated child

VC=20-003 Id=50319 M born 19/09/83 exposed 07/11/88
vaccinated at 3 years with standard vaccine on 20/12/86
blood samples M-00-198 30/11/88 titer= 2^13 (high titer)

Case 5 : high titer to a child who had measles earlier

VC=20-014 Id=50321 F born 23/04/79 exposed 17/12/88 -> 28/12/88
had measles on 31/03/83
blood samples M-00-216 20/12/88 titer= 2^12 (high titer)

Case 6 : 4 fold increase to a 3 months old child

VC=20-014 Id=61200 F born 03/09/88 exposed 17/12/88 -> 28/12/88
vaccinated after exposure with EZ-HT vaccine on 16/02/89
blood samples M-00-220 20/12/88 titer= 2^0 (no detectable)
R-20-030 16/02/89 titer= 2^4 (4 fold increase)
R-25-859 27/07/89 titer= 2^4 (not converter)

Case 7: booster to a vaccinated child

VC=22-012 Id=57941 F born 25/02/87 exposed 19/12/89
vaccinated at 6 months with the EZ-HT vaccine on 20/08/87
blood samples R-02-370 20/08/87 titer= 2^1
R-04-857 29/10/87 titer= 2^3 (seroconverter)
R-06-400 10/12/87 titer= 2^5
M-00-962 27/12/89 titer= 2^13 (booster)

Case 8: high titer to a vaccinated child

VC=22-012 Id=30734 M born 09/05/78 exposed 19/12/89
vaccinated at 3 years with the standard vaccine on 15/04/81
blood samples M-00-959 27/12/89 titer= 2^13

Case 9: high titer to a vaccinated child

VC=22-038 Id=31034 F born 10/01/78 exposed 25/11/89 -> 09/12/89

vaccinated at 2 years with the standard vaccine on 15/05/80
blood samples M-00-819 30/11/89 titer= 2^13

Case 10: high titer to child of unknown vaccination status

VC=22-040 Id=31066 M born 16/11/77 exposed 21/12/89 -> 30/12/89
unknown status
blood samples M-00-968 28/12/89 titer= 2^13

Case 11: high titer to a child of unknown status

VC=22-042 Id=31080 M born 30/06/76 exposed 19/12/89 -> 18/12/89
unknown status
blood samples M-00-857 15/12/89 titer= 2^13

Case 12: high titer to child of unkown previous measles status

VC=22-066 Id=52508 F born 03/04/84 exposed 14/11/89 -> 27/11/89
unknown prior measles status
blood samples M-00-782 21/11/89 titer= 2^13

Case 13: high titer to child of unknown vaccination status

VC=22-098 Id=31844 M born 05/04/77 exposed 20/12/89 -> 30/12/89
unknown vaccination status
blood samples M-00-953 20/12/89 titer= 2^13

Case 14: booster to vaccinated child

VC=22-107 Id=60441 F born 31/01/88 exposed 16/01/90
vaccinated with the EZ-HT vaccine at 5 months on 16/06/88
blood samples R-12-089 16/06/88 titer= 2^2
R-17-089 24/11/88 titer= 2^5 (seroconverter)
M-00-980 03/01/90 titer= 2^0 (decay)
M-01-378 24/01/90 titer= 2^10 (booster)

Case 15: high titer to vaccinated child

VC=23-035 Id=56824 M born 30/04/86 exposed 28/11/89 -> 07/12/89
vaccinated with standard vaccine on 08/01/87
blood samples M-00-828 01/12/89 titer= 2^13

Case 16: high titer to child of unknown status

VC=23-035 Id=30988 M born 14/12/75 exposed 28/11/89 -> 07/12/89
unknown status
blood samples M-00-884 20/12/89 titer= 2^13

Case 17: high titer to a child of unknown vaccinated status

VC=23-070 Id=32494 F born 06/04/72 exposed 02/08/88 -> 16/08/88
unknown vaccination status
blood samples M-00-152 05/08/88 titer= 2^13

A-1.3 : VACCINE FAILURES AMONG PROJECT CHILDREN (1)

Case 1 : SW-HT

VC=29-020 Id=58087 M born 24/02/87 (cohort 01)

Vaccinated at 25 weeks with SW-HT vaccine on 20/08/87;
blood sample taken at vaccination R-02-390 titer(3)= 500 miu
2 blood samples taken on 29/10/87 R-04-946 titer(2)= 250 miu
and on 10/12/87 R-06-456 titer(1)= 125 miu
does not fit the definitions of seroconverter or seroresponder;

Developed measles on 22/10/88 (14 months after vaccination);
case outside of study area; no blood sample was taken;
seen at Diohine dispensary and in Pikine dispensary;
seem to have had a normal course of disease;
physician has seen desquamation + cough on 10/12/88 (J50);
not confirmed.

Case 2 : EZ-HT

Vc=31-020 Id=61507 M born 30/09/88 (cohort 20)

Vaccinated at 19 weeks with EZ-HT vaccine on 15/02/89;
blood sample taken at vaccination R-20-969 titer(4)=1000 miu;
no other blood sample at 10 months;

Developed measles on 13/05/89, 2 months after vaccination;
had a normal course of disease; maximum score= 9 (J5);
single case in compound; probably infected at the village well.
2 blood samples taken on 17/05/89 M-00-511 titer(3)=500 miu
and 09/06/89 M-00-562 titer(3)=500 miu
No evidence of increase in antibodies;
not confirmed.

Case 3 : EZ-HT

Vc=16-031 Id=60044 M born 29/12/87 (cohort 11)

Vaccinated at 21 weeks with EZ-HT vaccine on 25/05/88
blood sample taken at vaccination R-11-948 titer(2)= 250 miu
no other blood sample at 10 months;

Developed measles on 31/08/89, 15 months after vaccination
had a normal course of disease although attenuated; maximum score=12 (J4);
Third case in compound, although co-index, probably infected by a visitor;
3 blood samples taken on 30/08/89 M-00-703 titer(3)= 500 miu
and 11/10/89 M-00-722 titer(13)=512000 miu
and 15/11/89 R-29-172 titer(13)=512000 miu
Directly confirmed.

Case 4 : SW-HT

VC=23-017 Id=60519 F born 09/04/88 (cohort 15)

Vaccinated at 21 weeks with SW-HT vaccine on 08/09/88;
blood sample taken at vaccination R-15-412 titer(2) = 250 miu
1 blood samples taken on 16/02/89 R-20-018 titer(1) = 125 miu
does not fit the definitions of seroconverter or seroresponder.

Developed measles on 26/11/89, 14 months after vaccination;
single case in the compound;
had a normal course of disease; maximum score= 17 (J6);

2 blood samples taken on 01/12/89 M-00-833 titer(3) = 500 miu
27/12/89 M-00-896 titer(11)= 128,000 miu
Directly confirmed.

Case 5 : SW-HT

Vc=21-035 Id=60528 F born 22/04/88 (cohort 15)

Vaccinated at 19 weeks with SW vaccine on 08/09/88;
blood sample taken at vaccination R-15-396 titer(0)< 125 miu
other blood sample at 10 months R-20-010 titer(1)= 125 miu
does not fit the definition of seroconverter;

Developed measles on 09/12/89, 15 months after vaccination;
had a normal course of disease; maximum score= 17 (J6);
secondary in compound (third case, generation B);
2 blood samples taken on 30/11/89 M-00-799 titer(0)< 125 miu
and 12/01/90 M-00-926 titer(11)= 128,000 miu
Directly confirmed.

Case 6 : EZ-HT

Vc=21-035 Id=57885 M born 06/03/87 (cohort 02)

Vaccinated at 22 weeks with EZ vaccine on 13/08/87;
blood sample taken at vaccination R-01-205 titer(3)= 500 miu
other blood sample at 10 months R-05-180 titer(3)= 500 miu
other blood sample at 12 months R-07-559 titer(4)=1000 miu
does not fit the definition of seroconverter;

Developed measles on 21/12/89, 28 months after vaccination
had a normal course of disease although attenuated, maximum score=7 (J7);
Secondary case in compound (seventh case, generation C);
2 blood samples taken on 30/11/89 M-00-800 titer(0)< 125 miu
and 17/01/90 M-00-942 titer(10)= 64,000 miu
Indirectly confirmed.

Case 7 : EZ-HT

VC=16-023 Id=61356 F born 25/09/88 (cohort 20)

Vaccinated at 20 weeks with EZ-HT vaccine on 15/02/89;
blood sample taken at vaccination R-20-949 titer(?)=
and at 10 months R-25-825 titer(?)=
seroconverter status unknown;

Developed measles on 07/01/90 (6 months after vaccination);
secondary case in compound (sixth case, generation C);
had a normal course of disease, maximum score=7 (J10);
1 blood sample taken on 02/02/90 M-01-310 titer(13)=512,000 miu
Indirectly confirmed.

Case 8 : SW-HT

Vc=22-142 Id=60669 M born 19/05/88 (cohort 16)

Vaccinated at 22 weeks with SW-HT vaccine on 20/10/88;
blood sample taken at vaccination R-16-556 titer(0)< 125 miu;
and at 10 months R-21-146 titer(1)= 125 miu
does not fit the definition of seroconverter;

Developed measles on 16/01/90, 14 months after vaccination;
had a normal course of disease; maximum score= 9 (J5);
secondary case in compound (third case, generation B);
2 blood samples taken on 12/01/90 M-00-920 titer(0)< 125 miu

and 13/02/90 M-01-340 titer(?)
evidence of increase in antibodies unknown;
Not confirmed.

Case 9 : SW-HT

Vc=17-080 Id=60269 M born 21/02/88 (cohort 13)

Vaccinated at 21 weeks with SW-HT vaccine on 20/07/88
blood sample taken at vaccination R-13-170 titer(4)= 1000 miu
and at 10 months R-18-722 titer(0)< 125 miu
does not fit the definitions of seroconverter or seroresponder.

Developed measles on 05/03/90, 19 months after vaccination
had a normal course of disease, maximum score=17 (J6);
Index case in compound, probably infected by
1 blood sample taken on 10/03/90 M-01-756 titer(?)
Not confirmed.

Case 10 : EZ-HT

VC=17-037 Id=61905 M born 26/12/88 (cohort 23)

Vaccinated at 20 weeks with EZ-HT vaccine on 17/05/89;
blood sample taken at vaccination R-23-415 titer(?)=
seroconverter status unknown;

Developed measles on 26/03/90 (10 months after vaccination);
secondary case in compound (fourth case, generation B);
had a normal course of disease, maximum score=6 (J32);
1 blood sample taken on 21/03/90 M-01-699 titer(?)=
Not confirmed.

Case 11 : Standard

VC=23-012 Id=57983 F born 04/04/87 (cohort 3)

Vaccinated at 45 weeks with the standard vaccine on 18/02/88;
blood sample taken at vaccination R-08-679 titer(0)< 125 miu
and at 25 months on 18/05/89 R-23-566 titer(?)
seroconverter status unknown;

Developed measles on 28/06/90 (14 months after vaccination);
secondary case in compound (fifth case, generation B);
had a normal course of disease, maximum score=11 (J8);
2 blood samples taken on 21/06/90 M-02-551 titer(?)=
and on 26/07/90 M-02-125 titer(?)=
Not confirmed.

A-1.3 LIST OF VACCINE FAILURES AMONG OTHER CHILDREN

Personal identification					Vaccination			Measles		Confirmation of case		
Vil	Conc	Ident	S	Date of birth	n	Date	Age (mo)	Date	Age (ye)	Score max	Blood samples	Confir mation
ORSTOM campaigns, 1981-1983												
3	1	11614	F	21/04/80	1	27/02/82	22	07/05/89	9	7	3-> ?	no
					2	16/12/86	79	(revaccinated)				
4	36	9692	F	08/10/77	1	02/03/83	64	12/02/90	12	11	?	no
8	7	12270	M	22/08/82	1	09/03/83	6	04/03/89	6	16	0-> 9	dir
National EPI campaign, 1986-1987												
5	25	12347	F	11/11/82	1	31/12/86	49	11/06/89	6	10	?-> 8	no
7	53	52121	M	29/01/84	1	17/02/87	36	06/03/90	6	7	?	no
8	7	54290	F	03/03/85	1	20/02/87	23	09/03/89	4	11	0->10	ind
8	7	56294	F	03/09/86	1	25/03/87	6	27/03/89	2	12	0->	ind
10	17	50308	F	01/06/83	1	16/02/87	44	18/10/89	6	16	?	ind
11	33	54382	F	29/05/85	1	13/03/87	21	10/05/89	3	?	?	no
17	31	56485	M	22/03/86	1	10/01/87	9	28/03/90	4	?	?	no
17	73	50811	M	29/12/83	1	10/01/87	36	16/03/90	6	17	?	no
19	154	56626	M	10/07/86	1	07/01/87	5	03/08/88	2	11	?->13	no
20	3	56646	F	04/09/86	1	30/01/87	4	03/12/88	2	12	0->11	dir
20	14	50901	F	09/12/83	1	20/12/86	36	28/12/88	5	11	0->10	dir
21	127	56719	F	06/04/86	1	19/02/87	10	04/12/87	1	99	?	no
22	52	31225	F	31/05/83	1	26/12/86	42	02/09/89	6	12	0->11	dir
22	52	31229	M	30/03/83	1	26/12/86	44	04/09/89	6	12	0->11	dir
22	81	56762	F	16/08/86	1	08/01/87	4	22/02/90	3	11	?	no
Other Vaccinations												
3	2	50281	F	04/06/83	1	03/09/85	27	18/05/89	5	11	6->	no
					2	16/12/86	42	(revaccinated)				
4	50	53912	F	25/09/82	1	21/03/86	41	28/05/89	6	9	0->10	dir
6	1	54190	F	05/11/85	1	28/07/86	8	04/01/89	3	11	8 12	dir
16	3	22801	F	17/07/78	1	01/04/83	56	19/02/89	10	12	0 ?	no
16	24	23067	M	23/11/78	1	15/12/79	12	27/03/90	11	7	?	no
16	58	23438	M	06/07/78	1	08/04/83	57	26/02/89	10	7	?-> 9	no
17	45	24987	F	26/12/78	1	15/03/83	50	29/03/90	11	17	?	no
21	102	52351	M	21/04/84	1	15/12/85	19	15/01/89	5	99	?	no
21	105	29927	F	15/07/82	1	15/12/85	41	15/01/89	7	99	?	no
22	3	30621	M	30/09/83	1	15/01/86	27	30/12/89	6	99	0->10	no
23	9	32548	F	15/11/80	1	11/11/83	35	19/07/88	7	11	0->13	dir

ANNEX 2

VACCINES UTILIZED : 1987-1989

1. Measles vaccines

Producer/ Brand	No batch	Date received	Date expiry	No vials	No doses	Date end	No doses not used
A) Project vaccines							
Edmonston-Zagreb	81/3	15/03/87	30/06/89	750	B1	23/06/89	0
(EZ-HT)	137	06/01/89	01/10/90	1400	B1	30/10/90	
Mérieux (SW-HT)	0980	15/03/87	30/11/88	750	B1	30/10/88	487
Mérieux (Standard)		15/03/87	01/03/89	750	B1	17/02/89	
		01/03/89	01/03/90	500	B1		
Mérieux (Placebo)		15/03/87	01/03/89	750	B1	17/02/89	
		01/03/89	01/03/90	50	B10		
B) Other vaccines							
RIMEVAX	M102G11A	07/09/87	01/03/89	250	B5	17/02/89	290
		16/11/87	01/03/89	500	B5	17/02/89	
MORBILUAX	32A07	31/11/88	31/05/89	500	B10	19/05/89	360
	32A02	26/04/89	13/06/90	500	B10		

1. BCG vaccines

Producer/ Brand	No batch	Date received	Date expiry	No vials	No doses	Date end	No doses not used
Pasteur FR	03A86	10/08/87		500	B10	08/09/87	
	04A86	07/09/87		200	B20	15/03/88	
	165A86	16/11/87	01/06/89	800	B20	22/07/88	
	162B86	27/10/88	01/06/89	1200	B20	14/02/89	
		10/11/88	01/06/89	1000	B20	20/06/89	400
		26/04/89	01/04/90	500	B10		

3. DPTP vaccines

Producer/ Brand	No batch	Date received	Date expiry	No vials	No doses	Date end	No doses not used
Mérieux		10/08/87		1500	B20	18/01/88	
	B0022	07/09/87	01/01/89	400	B20	18/10/88	
	B0022	16/11/87	01/06/89	1600	B20	18/10/88	
	B0105	27/04/88	01/02/89	1200	B20	27/01/89	120
	B1232	02/02/89	01/11/89	2600	B20		

4. Yellow-fever vaccines

Producer/ Brand	No batch	Date received	Date expiry	No vials	No doses	Date end	No doses not used
Pasteur-Dakar	1051	10/08/87		500	B20	24/11/87	
	1038	16/11/87	31/03/88	600	B20	15/03/88	
	1042	16/11/87	31/03/88		B20	15/02/88	
	1073	16/11/87	31/10/88		B20	22/07/88	
	1089	27/04/88	25/01/88	600	B20	13/12/88	
	1103	10/11/88	24/08/88	100	B10		

5. Tetanus-toxoid

Producer/ Brand	No batch	Date received	Date expiry	No vials	No doses	Date end	No doses not used
Behring	2701375	10/08/87	03/09/89	1000	B20	17/07/88	
Berna	35892	10/11/88	07/11/89	1000	B20	03/05/89	
Torlak Institute	147	27/04/88	01/07/89	1800	B20	11/01/89	
	162	26/04/89	01/10/90	1800	B20		

ANNEX 3

MEDICAL DRUGS UTILIZED : 1987-1989

Name / DCI	Date up-date	Number received	Cost (CFA)	Price /unit	Origin	Not used
Ampicilline	07/89	18,968	234,171	12.34	MSF/LAB/SIP	1,000
Acide Acetyl-Salicylique						
(500 mg)	07/89	23,000	31,842	1.38	MSF/SIP	8,000
(75 mg)	07/89	45,000	18,128	0.40		19,000
Butyl-scopolamine	08/88	200	6,340	31.70	MSF	156
Chloroquine	07/89	63,000	163,723	2.59	MSF/SIP	4,000
Chloramphenicol	07/89	2,760	25,235	9.14		0
Co-trimoxazole	07/89	14,400	183,143	12.71	MSF/LAB	3,800
Dexamethasone	07/89	1,450	13,370	9.22	MSF/LAB	30
Diazepam	07/89	690	17,135	24.83	MSF/SIP	300
Fanasil	07/89	5,000			SIP	5,000
Acide Folique	07/89	10,400	11,640	1.12	MSF/LAB	100
Fumarate Fer	07/89	70,000	72,000	1.02	MSF/SIP	38,500
Griséofuline	07/89	3,000	11,385	3.79	MSF	2,000
Iduviran	07/89	44	20,057	455.84	LAB	0
Indométacine	08/88	1,020	855	0.85	MSF	750
Mebendazole	07/89	12,456	76,950	6.17	MSF/LAB	4,072
Metronidazole	07/89	19,000	82,000	4.31	MSF/LAB	3,340
Nystatine, 10000	07/89	5,000	28,625	5.72	MSF	1,700
Nystatine, 50000	07/89	1,200	13,790	11.49	MSF	900
Nystatine, pomade	07/89	150	25,028	166.85	MSF	97
Paluject	02/87	200	3,222	16.11	SIP	0
Peni-G	07/89	50	4,726	94.52	PNA	0
Phenobarbital	07/89	4,000	4,985	1.44	MSF	1,000
Praziquantel	07/89	240	49,530	206.37	MSF	120
Pyralvex	07/89	113	68,232	603.82	LAB	21
Retinol	07/89	200	5,850	2.92	LAB	0

Name / DCI	Date	Number received	Cost (CFA)	Price /unit	Origin	Not used
Tetracycline 3%	07/89	990	146,433	147.91	MSF/SIP	261
Tetracycline 1%	07/89	2,090	166,120	79.48	MSF/SIP	150
Tetracycline	07/89	11,184	86,589	7.75	MSF/SIP	5,088
KMNO4	07/89		7,632		PNA	
Cotton	07/89		13,500		PNA	
Compresses	07/89		18,805		PNA	
Alcool	07/89		27,854		PNA/LAB	
Sparadrah	07/89		30,140		PNA	

ANNEX 4

TECHNICAL NOTE

Computations of age :

Age in difference of months = (12*year+month) - (12*year+month of birth)
Age in months = int((date - date of birth)/30.4375)
Age in weeks = int((date - date of birth)/7)
Age in years = int((date - date of birth)/365.25)

Computations of periods at risk:

Person-days at risk : PDS = sum(date of end - date of beginning)
Person-months at risk: PMS = PDS/30.4375
Person-years at risk: PYS = PDS/365.25
Rates RAT = Events / PYS
Probability (from rate) PRO = n*RAT/(1+(n-a)*RAT)
where n = duration of period,
a = mean duration lived by those who failed

Computations of GMT in international units:

$GMT = 62.5*2^x$
where x is the mean reciprocal of dilutions.

Coefficient of variations of rates and ratios:

Rate computed from PYS (m) $CV^2 = 1/E$
Probability (p) $CV^2 = (1-p)/E$

Variance of logarithms of rates and ratios:

Log(rate) VAR = 1/E
Log(proba) VAR = (1-p)/E

(where E is the number of events).

ANNEX 5

LIST OF PERSONNEL

1) INVESTIGATORS

Michel Garenne, PhD. Project Director. Head UR Population et Santé. Senior Researcher at ORSTOM, Dakar. Now Associate Professor of Demography, Harvard School of Public Health. Boston.

Odile Leroy, MD, MA. Assistant Director. Member UR Population et Santé. ORSTOM. Now Medical Officer, in charge of measles vaccines, Pasteur Mérieux, Paris.

Jean Pierre Beau, MD. Member UR Population et Santé. ORSTOM. Senior Researcher at ORSTOM, Dakar. In charge of verbal autopsies and treatment of malnourished children.

Ibra Sène, MD. Head Circonscription Médicale de Fatick, Senegal. In charge of supervising the field work and treatment of sick children.

Hilton Whittle, MD. Senior researcher, Medical Research Council, Fajarah near Banjul, The Gambia. In charge of the laboratory work.

Abdourahmane Sow, MD. Head Infectious Diseases Department, Fann Hospital, Dakar. Now at WHO/GPA. In charge of case assessment and treatment of severely sick children.

2) MEMBERS OF THE DATA MONITORING AND SAFETY COMMITTEE AND OF THE SCIENTIFIC COMMITTEE (SC).

Ministry of Public Health, Senegal

Colonel Sy, Dr. Directeur de l'Hygiène et de la Protection Sanitaire. Dakar.
Commandant Fode Diouf. Chef du Service des Grandes Endémies. Dakar

Task Force for Child Survival

John V. Bennett, MD. Task Force for Child Survival.
Hector Traverso, MD. Task Force for Child Survival.
M. Giordano. Task Force for Child Survival (adm).
Tom Ortiz. Task Force for Child Survival (adm).
Roger Bernier, MD. Centers for Disease Control (SC).
Laury Markowitz, MD. Centers for Disease Control (SC).

ORSTOM representatives at DMSC

Mr Bernard Dalmayrac, Head Centre ORSTOM de Dakar.
Mr Galat, Senior researcher at ORSTOM, Dakar.

3) OTHERS AND CONSULTANTS

Olivier Fontaine, MD. Participated to the writing of the protocol.
Susan Zimicki, MPH. Participated to the writing of the protocol.
Ibrahima Sarr, PhD. Head Census Bureau, Dakar.
Awa Marie Coll, MD. Replaced Dr Sow when he left in Sept 1989.
Michel Cadoz, MD. Visited and invited at SC.
Peter Aaby. Visited and invited at DMSC.

3) DAKAR STAFF

Michel Ndiaye
Takhy Diop
Emile Ndiaye
Antoine Ndour
Ousmane Ndiaye
Emilie Ndiaye

4) FIELD STAFF

FIELD PHYSICIANS AND MIDWIFE

Jean Paul Mouliat Pelat (Sep 87-Jul 89)
Ibra Sène (Jan 87-Aug 87)
Fred Mutika (Sep 87-Oct 87)
Ibrahima Diallo (Nov 87-Dec 87)
Badara Samb (Jan 88-Oct 90)
Ablaye Yam (Mar 88-Oct 90)
Aminata Simaga (Mar 89-Jul 89)
Marie Emanuelle Ezan (Sep 89-Oct 90)

LABORATORY ASSISTANT

Frank Giry (Bioforce)
Tofène Ndiaye

SUPERVISORS

Ernest Faye
Pape Niokhor Diouf

FIELD WORKERS

Saliou Diouf
Ngor Sine
Samba Diatte
Bassirou Fall
Samba Diouf
Latyr Faye
Djib Diouf
El Hadj Diouf
Waly Diafate
Ousmane Faye
Abdou Diouf
Raphael Dogue
Moussa Sarr

DRIVERS

Ousseynou Ndiaye
El Assane Faye
Etienne Ndong

OTHER NIAKHAR STAFF

Khady Sene
Marie Bakhoum
Pierre Tine

ANNEX 6

LIST OF VILLAGES OF THE STUDY AREA

Darou
Diokoul
Kalome Ndofane
Ngalagne Kop
Ngane Fissel
Ngayokheme
Sass Ndiafadji
Sob

Bary Ndondol
Datel
Lambaneme
Mbinondar
Mboyene
Ndokh
Ngangarlame
Nghonine
Poudaye
Toucar

Dame
Diohine
Gadiak
Godel
Khassous
Kothioh
Leme
Logdir
Meme
Mocane Ngouye
Ngardiame
Poultok Diohine

ANNEX 7

LABORATORY PROCEDURES

All samples were analyzed at the MRC laboratory in Fajarah, The Gambia. The laboratory uses international standards for antibody assays which have been standardized against the WHO international reference preparation for measles antibody.

The test used to measure decay of antibodies or change in antibody levels following measles or exposure to measles was the measles hemagglutination inhibition test (HAI). IgM and IgG measles antibodies were not tested separately for previous experience using either HAI or ELISA methods to quantify these classes of antibody have not proved helpful in differentiating primary vaccine failure (i.e. no antibody response after vaccination) from secondary vaccine failure (infection following a decline in antibody response after vaccination).

A micromethod was used. Sera obtained by fingerprick were taken into a serum separator tube (Microtainer, Becton Dickinson), spun at 6000 g for 3 minutes to separate serum from red cells and stored at - 16°C until used. Serum was decomplemented in the microtainer tube at 56°C for 1/2 hour and thereafter absorbed overnight in another tube with 1/3 volume of packed green monkey cells. 25 l of serum was diluted in an equal volume of phosphate Buffered saline (PBS) containing 1% Bovine serum albumin and 0.1% sodium azide in non-sterile microtiter plates. 25 l of phosphate buffered saline containing 4 hemagglutination units of Tween either extracted measles hemagglutinin (Behringwerke) is added to an equal volume of each dilution of serum and incubated at 37°C for 3 hours then 25 l of a 0.5% suspension of green monkey cells is added to each of the wells. After standing for 3 hours at room temperature the plates are left overnight at 4°C and read by eye in the morning. The starting dilution was 1:2, which detects 125 m.i.u measles HAI/ml.

ANNEX 8

EXCERPTS FROM CONTRACT

Article VI. Project Officer

Roger Bernier, Lauri Markowitz and Hector Traveso are hereby designated Co-Project Officers for this contract. Roger Bernier will serve as the Principal Co-Project Officer and is responsible for guiding the technical aspects of the project collaboratively with the Co-Project Officers. The Co-project Officers shall not make any commitments or authorize any changes which effect the contract price, terms or conditions: any such changes shall be referred to the Contracting Officer for action.
(NB : after 1988, John Bennett served as Principal Co-Project Officer).

Article VI. Project Director

Work and services will be conducted under the direction of Michel Garenne. The TFCS reserves the right to approve any necessary successor to the Project Director.

Article XX. Data

A copy of the data tape will be given to the Project Officer at completion of the study. All information of whatever nature resulting from work being performed with the data collected under this contract will be submitted to the Project Director for written approval prior to publication or dissemination.

Article XXI. Blood samples

Blood samples taken during the course of the study will remain property of the contractor. Blood samples that will not be used for the direct interest of the study will be made available to other researchers for further studies. The use of these blood samples will be restricted to those whose project of research has been accepted in written by the Project Director. A special provision of blood samples will be made for use by the Project Officers. All information of whatever nature resulting from work being performed with the blood samples collected under this contract will be submitted to the Project Director for written approval prior to publication or dissemination.

ANNEX 9

LIST OF FIGURES

LIST OF CHARTS