The Niakhar High-Titer Measles Vaccine Trial, 1987-1990

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This book is dedicated to *Sophie*, my wife, for her love and patience, and her help in preparing this book; to my sons *Sacha* (who designed the cover page) and *Basil*e; and to my daughters, *Clémence* and *Raphaëlle*—young children who once suffered from the complex situation caused by the high-titer measles vaccine trial.

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FOREWORD

This book presents the methodology and main findings of the trial of two high-titer measles vaccines conducted in Niakhar, Senegal, from 1986 to 1990 by a group affiliated to the French Institute of Scientific Research Overseas (ORSTOM), Unité de Recherche Population et Santé. ORSTOM was later renamed Institut de Recherche pour le Développement (IRD). A report was published in 1991, as soon as possible after the end of the field work. It was a comprehensive report aiming at making results available to policy makers and to vaccine producers as quickly as possible. The study was subsequently followed by scientific and ethical controversies. This book presents the study as it was reported in 1991, with the addition of two chapters: Chapter 1 provides a general introduction to measles, including mortality from measles, measles vaccines, and measles control; and Chapters 10 and 11 provide a summary of the scientific and ethical debates and political discussions which followed the trial. Other chapters (2–9) are basically identical to the original report, with some minor edits.

SUMMARY OF MAIN FINDINGS

A randomized 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 5 months of age: Edmonston-Zagreb (EZ-HT) and Schwarz (SW-HT). Results were compared to the performance of the Standard measles vaccine (low-titer, Schwarz strain) 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. 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 to 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, Standard). The randomized groups were comparable in various social, familial, and health characteristics. Due to vaccinations and medical services provided during the study period, mortality of infants and children was significantly reduced during the study period.

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 that of the SW-HT vaccine. There was a significant increase in antibody titers among seropositive children after the EZ-HT and SW-HT vaccines. However, there was no clear evidence of seroconversion among children with high levels of maternal antibodies (1,000+ miu) in any of the vaccine groups. Furthermore, the geometric mean titer of antibodies 5 months after the high-titer vaccines was lower than 5 months after the Standard vaccine.

Clinical 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 the high-titer vaccines than after the Standard vaccine: there were 5.2 times more failures after the EZ-HT vaccine and 8.3 times more 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. The 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 years after vaccination and during the rainy season. There were no significant differences in mortality by sex. However, the last 8 cohorts were followed for a period too short to verify this effect. Morbidity was monitored only until the age of 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.

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.

PREFACE

DR. PIERRE CANTRELLE[1]

(*TRANSLATED FROM FRENCH. TEXT WRITTEN IN 1991*)

In West Africa, as in other parts of the world, a specific name is given by local populations to measles, a disease usually well identified by them and distinguished from other eruptive diseases. In comparison with other pathologies, this knowledge allows for reliable studies of measles morbidity and mortality at population level through interviews.

In West Africa, measles was shown to be a major cause of morbidity and mortality. Its severity is probably higher than it once was in Europe. Populations were well aware of the severity of the disease: they considered as a survival advantage the fact that a child successfully passed the measles test. Medical circles also noticed the severity of the disease: for example, in 1930, measles was reported as a serious problem among the Tuaregs by colonial physicians. In the 1950s, reports from colonial health services in Burkina Faso (then Upper Volta), who gathered information from medical districts, pointed out that "every year a heavy toll is paid to measles."

However, the total burden of the disease remained unknown. Indeed, health services statistics provided information on causes of death in district hospitals, but they did not represent mortality in rural environments. Because illnesses and deaths occurred mostly at home, few cases came to the hospitals and relatively few deaths were notified, so that the severity of the disease was poorly reported by health services.

The measurement of the measles burden was enabled by population-based representative surveys collecting family reports on morbidity and mortality, and focusing on a few obvious diseases, such as measles.

The demographic survey conducted in the Senegal Valley in 1957–1958 made it possible for the first time to obtain estimates of measles mortality in a rural population of sub-Saharan Africa. Considering

[1] Dr. Pierre Cantrelle (M.D. and Demographer) initiated population research on measles in Senegal and at the Niakhar field site.

the magnitude of the evidence, the reaction of pediatricians was to challenge the fact, with the argument that "if it were true, it would be known"!

Further proof of the findings of the Senegal Valley survey was provided by surveys conducted in Burkina Faso in 1960 and in Nigeria. At that time, a newly developed vaccine became available. At the request of the Minister of Health of Burkina Faso, preliminary studies were carried out in that country in 1961 with the Edmonston-B vaccine. These were followed by the first mass vaccination campaign against measles in Burkina Faso in 1962.

The vaccine was proposed in Senegal at about the same time, as in other member countries of the OCCGE.[2] The vaccine was administered as a trial in Senegal in 1963 in the Sine-Saloum region, the Niakhar and Tattaguine districts. However, the safety of the first vaccine was not considered to be sufficient since it induced severe reactions and the Ministry of Health gave up this vaccine, and also because a new vaccine, originating from a further attenuated Schwarz strain, had just been developed. A new study was carried out in 1965 in the nearby Khombole pilot area with the new vaccine. Then, in 1966, the Niakhar area, where the Sine-Saloum demographic survey was in place, benefited from a pilot vaccination campaign, preceding the first mass vaccination campaign conducted in Senegal in 1967.

The effects of these first campaigns were impressive: they stopped the spread of epidemics and reduced the incidence of the disease, which resulted in a significant decrease in the number of measles visits in rural clinics. And it was in Senegal that the impact of first vaccination campaigns was properly measured, not only on period mortality, but also on cohort survival. Vaccination, by suppressing the disease, showed that the impact of measles was even higher than expected if only the deaths directly attributed to it were taken into account. Thus, it was shown that such a health program can be decisive for inducing a decline in mortality, and this was obtained with a single-shot vaccination that ensured lasting protection, life-long in principle. In addition, the advent of measles vaccination changed the nature of the determinants of the disease and its severity.

Did the notions of transmission and prevention exist in local populations? In Khombole, Senegal, where a pilot pediatric clinic was in place, it was found that quarantine was often practiced spontaneously by

[2] OCCGE stands for "Cooperation and Collaboration Organization for Fighting Main Endemic Diseases." It was an institution active in francophone countries of West Africa from 1960 to 1998.

families when an epidemic occurred, hoping to isolate children from the contagion. The effect of this measure was to delay the age of contracting the disease, and it is known that children become less vulnerable as they grow older than 2 or 3 years. In urban areas, this practice was more difficult to apply because risks of contagion were more frequent, hence attacks of measles were earlier, on average.

Severity risk factors included age, associations with other pathologies, secondary cases versus primary cases, treatments, and traditional care.

Since vaccination became available, the critical issue is to ensure the continuity of the intervention. In Africa, when measles vaccination was proposed to a population, it was accepted without reservation, as mothers and the community both had experienced the severity of the disease. When witnessing its effectiveness, vaccination was regarded by the population as a new protective power, similar to traditional or magic protective powers, and apparently more powerful.

However, after the first national campaign, the health system did not have the means to maintain adequate vaccination coverage, in both quantity and quality, for the upcoming births. In Senegal, the result was that after a period of about 4 years, measles morbidity and mortality had returned to previous levels. The Sine-Saloum Demographic and Health Survey conducted in 1982 confirmed this point, as well as in the Sine study area (Niakhar) during the 1983–1984 period. This development has been roughly the same in other West African countries.

A new immunization program was undertaken in 1986 under the aegis of UNICEF, which had success similar to the first campaigns conducted 20 years earlier. It was again the Sine Demographic and Health Survey time-series that confirmed the fall in measles morbidity and mortality. This was also confirmed by the time-series of the civil registration in the city of Saint Louis. The question now is how to continue the program on a permanent basis, and the health system put in place seems to go in this direction.

Ultimately, the decisive step in the fight against this disease will be global eradication, as has been the case with smallpox, the last case of which was noted in 1979. It was in this perspective that this present study of vaccines given at an early age, described in the following pages, was conducted.

ACKNOWLEDGMENTS

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The authors warmly thank the Senegalese authorities who supported the project, in particular: M. Abdou Diouf, Président de la République du Sénégal; MM. Marie Sarr Mbodj, Thérèse King-Coly, and Assane Diop, Ministres de la Santé Publique; Dr. Colonel Mame Thierno Sy, Directeur de l'Hygiène et de la Protection Sanitaire; Dr. Fodé Diouf, Chef du Service des Grandes Endémies; Dr. AKM. Ndiaye, Directeur de l'ORANA; Dr. Pierre Cantrelle, UR Population et Santé; Mr. Bernard Dalmayrac, Chef du Centre ORSTOM; Mr. Jean Paul Gonzalès and Mr. Gérard Galat, ORSTOM; Mr. Charles Becker, ORSTOM & CNRS; Dr. John Bennett, the Task Force for Child Survival; and Dr. Roger Bernier and Dr. Laury Markowitz, Centers for Disease Control, Atlanta, GA. The authors are also deeply indebted to Prof. Neal Halsey (Johns Hopkins University) who conducted the Haiti study and who worked hard to verify and confirm the controversial results of this study.

The study would not have been possible without the active support of the Niakhar population and the local health professionals, in particular the nurses of Niakhar, Toucar, and Ngayokheme, the Catholic Sisters of Diohine, and the local authorities: M. le Gouverneur de Fatick, M. le Préfet de Fatick, MM. les Sous-Préfets de Niakhar et Tattaguine, and MM. les chefs des Communautés Rurales de Ngayokheme et Diarere.

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CHAPTER 1

BACKGROUND ON MEASLES AND ITS CONTROL

This chapter provides brief background information on measles, its lethality, and its control by vaccination.

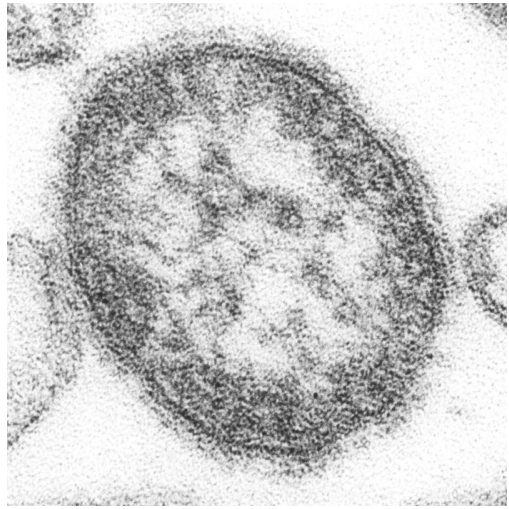
1.1 ORIGIN OF MEASLES

Measles is a severe infectious disease of humans caused by the Measles Virus (MeV), displayed on Figure 1.1. This virus is a single-stranded RNA virus, which belongs to the family of Paramyxoviridae, the same as mumps, parainfluenza and Respiratory Syncytial Virus (RSV)—all ubiquitous viruses spread by aerosols affecting humans [Enders 1996; Morgan & Rapp 1977].

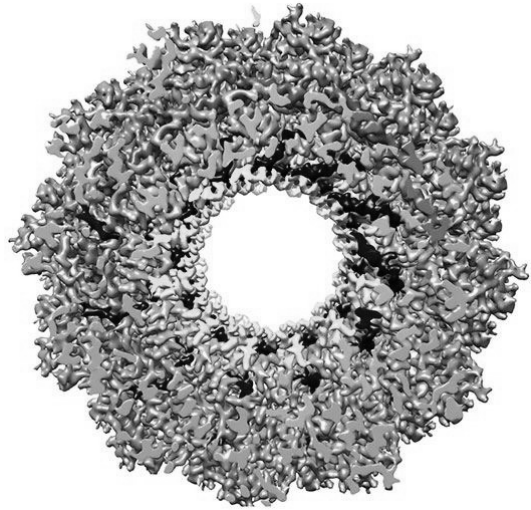
The measles virus belongs to the genus morbillivirus, as with many other viruses affecting domestic and wild animals, such as the Bovine Rinderpest Virus (BRV) affecting cattle and other cloven-hoofed animals, the Canine Distemper Virus (CDV) affecting dogs and related wild carnivores, the Feline Morbillivirus (feMV) affecting cats and wild felines, the *Peste-des-Petits-Ruminants* Virus (PPRV) affecting sheep and goats, the Equine Morbillivirus (EMV) affecting horses, the Cetacean Morbillivirus (CeMV) affecting dolphins and whales, and the Phocine Distemper Virus (PDV) affecting seals. MeV may also infect a variety of non-human primates, apes, and monkeys, through contact with humans [Enders 1996; Morgan & Rapp 1977].

From its genetic structure, the virus closest to MeV seems to be the BRV, the source of large and highly lethal epidemics among cattle (cattle plague or *peste bovine*). It is therefore likely that the measles virus adapted to humans during domestication of cattle, which occurred at various times in the ancient world from 10,000 to 5,000 BC. According to their genetic structures, the two viruses seem to have diverged some 5,000 years ago, although divergence is difficult to assess for RNA viruses. This reinforces the theory of passage from BRV to MeV at the time of cattle domestication [Norrby et al. 1985].

Figure 1.1: Photos of the measles virus



1a: Electron microscope photograph of the measles virus. Source: Centers for Disease Control, USA.



1b: Reconstruction of the nucleocapsid of the measles virus, from a high-resolution electron microscope. Source: CNRS, Grenoble, Institute of Structural Biology, France.

The measles disease was first described by a Persian doctor named Abu Bakr Muhammad ibn Zakariyâ, more often called Ibn Razi or Rhazes in Europe, who worked in Baghdad around 900 AD [Rhazes 1848]. Ibn Razi was the first to explain how to distinguish measles from smallpox, although he thought that they were two different aspects of the same illness. Measles probably existed among humans before that time and it has been argued that the plague that struck Athens in 430 BC, described by Thucydides, could have been due to measles. Similarly, a serious disease outbreak that occurred in Roma in 165 AD, reported by the Roman doctor Galen, could have been due to measles. The English term "measles" was first used in Europe in the 14th century. The word stems from "miser" which referred to the wretchedness of lepers. It was described in England by Syndenham as early as the 17th century. Numerous outbreaks of measles were later reported and analyzed in Europe and elsewhere. The first systematic investigation of an epidemic was conducted in the Faroe Islands in 1846, a striking observation of high mortality in virgin soil epidemics, and measles was still a major concern for public health in the early 20th century [Fuller 1730; Gastel 1973; Panum 1847; Sydenham 1666; Debré & Joannon 1926].

Measles caused large-scale and highly lethal epidemics in human populations until vaccines were developed in the early 1960s (see below). Measles was one of the causes (together with smallpox) of the huge population decline in the Americas after the arrival and invasion of Europeans: some 90% of the population disappeared in less than a century after the landing of Christopher Columbus, partly because of infectious diseases (mainly measles and smallpox) and partly because of the destruction of the American Indian economic and political systems [Black 1992; Stannard 1992].

1.2 MEASLES EPIDEMIOLOGY

In human populations, the measles virus is transmitted from person to person through aerosols (droplets) or direct contact. Transmission rates are high, so that epidemics are easy to detect, with a large number of cases occurring at about the same time. Since transmission rates are high, most people are affected in infancy or childhood. The mean age at infection is about 4 years, ranging from 6 months to 15 years, with only a few cases occurring earlier or later. Infants are usually protected by maternal antibodies until 6–11 months, so cases occurring in the first 6 months are rare (see below for more details). By the age of 15 years, some 95% to 99% of children have already been infected in unvaccinated

populations, so that primo-infections occurring in adulthood are rare, except in isolated populations where the virus is not circulating, as in small islands or small isolated communities.

The primo-infection is immunogenic; that is, infected children are protected by antibodies generated during infection. This natural immunity lasts for many years, and is boosted by regular exposure to unvaccinated populations, so that children contract clinical measles usually only once during their life, although some rare cases of double infections have been documented. The matter is more complex in vaccinated populations: firstly, immunity induced by the vaccine appears be less potent and lasts for a shorter duration than the natural infection, and secondly, and more importantly, exposure to the natural virus tends to disappear in vaccinated populations, so that the booster effect of natural exposure vanishes. As a consequence, vaccinated children become susceptible again when they age, unless they are revaccinated at regular intervals, and cases are often found in early adulthood (such as college students in North America) and sometimes among older people.

The dynamics of natural measles epidemics are well documented and well understood. A simple SIR (Susceptible/Infected/Recovery) model is able to reproduce the observed dynamics of measles epidemics in large populations [Anderson & May 1982, 1985, 1991; McLean & Anderson 1988a, 1988b]. These dynamics are typically chaotic, with large annual fluctuations in the number of cases and with a relatively constant proportion of susceptibles (about 50% of children under the age of 15 years in unvaccinated populations), which allow the virus to circulate continuously. The net reproduction rate (R_0) of measles transmission was estimated at high values (ranging from 4 to 10, depending on the population dynamics), which makes measles one of the most transmissible infectious diseases of humans. The minimum size of population able to sustain measles transmission was estimated at 500,000, so that measles circulates in large and connected populations typical of ancient Europe and Asia. In contrast, measles does not occur regularly in small isolated islands or in remote communities. In these cases, measles can only be imported from outside, and when it occurs it tends to have different dynamics and a huge mortality because of the large number of susceptibles of all ages, the rapid dynamics of the transmission, and the high level of exposure [Black 1966].

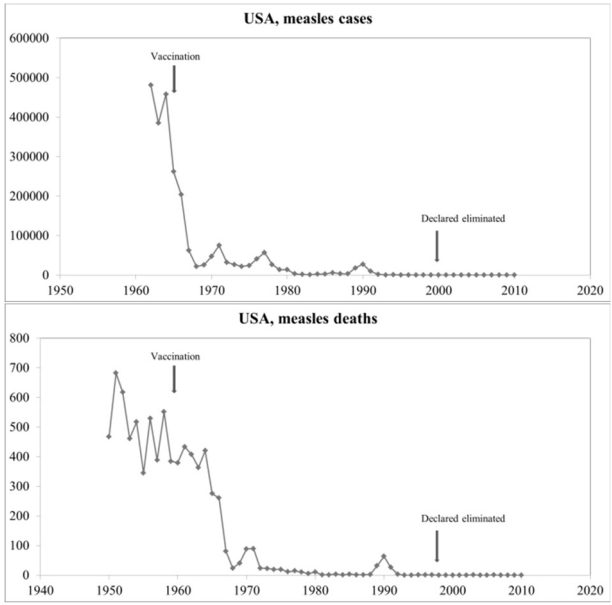
In the case of semi-isolated communities (as in the Niakhar study), measles is not transmitted continuously. It is always imported from places with larger populations where transmission is continuous, in this case from Dakar, the capital city of Senegal, or from other nearby towns.

Once in the community, it is transmitted as in a large population, usually every year, often with a seasonal pattern. The seasonal pattern seems to be due to the ability of the virus to remain infective in droplets for longer periods in certain climatic conditions of temperature and humidity [Anderson & May 1991; Gershon 1990].

1.3 MEASLES IN VACCINATED POPULATIONS

Large-scale vaccination radically changes measles epidemiology. Firstly, it protects vaccinated children, so that not only do they not become infected but also they no longer transmit the disease. After mass vaccination campaigns, transmission is often stopped for several years. Furthermore, when vaccination coverage is high, measles virus transmission is cut. When vaccination coverage is very high, transmission of the virus is fully controlled in the population, so that it does not occur anymore, unless imported from outside from other unvaccinated populations. Mathematical models of disease transmission showed that a 90% coverage with a fully efficient vaccine (100% vaccine efficacy) is enough to reduce the net reproduction rate (R_0) to a value lower than 1, and therefore to guarantee full control in the short term and eradication in the long term [Anderson & May 1982, 1985, 1991]. This is what typically happened in the USA, where the systematic vaccination of children for 40 years led to full control (no more endogenous transmission), and where the few remaining cases were sporadic and always imported from abroad. Mass vaccinations started in 1963 in the USA, and by 1970, incidence and mortality were already reduced to small numbers compared with the pre-vaccination period, with only sporadic spikes in 1971, 1977, and 1990 (Figure 1.2). Measles was declared ‘eliminated’ from the USA in the year 2000, and after that date the number of cases became very small and the number of deaths became almost nil, with all index cases being imported from abroad and outbreaks of secondary cases being of a very small size (a few cases each time) [Gay et al. 2004; Orenstein et al. 2004]. These successful campaigns were then applied to other countries in the Americas, and by the year 2016, PAHO declared measles eliminated from the continent. A similar observation was made in England and Wales [Ramsay et al. 2003].

Figure 1.2: Incidence and mortality of measles in the USA 1950–2010



Source: Centers for Disease Control, USA

1.4 MEASLES CLINICAL FEATURES

Clinical features of the disease are typical and usually easy to diagnose [Katz 1972]. After viral invasion, the virus replicates quickly and within 10 days induces a high fever (39°C or more), rhinitis (coryza, running nose), conjunctivitis (infected eyes), and coughing, and a few days later a typical maculo-papular rash that starts from the face and invades the whole body. The rash disappears within about one week, and is followed by extensive desquamation. Another feature is the Koplik's spots, a rash that occurs inside the mouth and is pathognomonic (characteristic) of measles, although it does not always occur or is not always visible, and lasts only a day or two. In general, the sequence of clinical events, the typical rash, and the desquamation, as well as the epidemiologic context, make measles easy to diagnose, an important feature for field work and vaccine trials. Biological confirmation can be done by measuring rising measles antibodies during the course of infection (see Chapter 8 for details).

1.5 MEASLES PATHOLOGY

The pathology induced by measles infection is complex and often severe, requiring hospitalization and sometimes causing death. The virus initially infects respiratory epithelial cells from the nose to the lower part of the respiratory tract, in particular dendritic cells in the lung. These cells drain into nearby lymph nodes (primary viremia) and infect lymphocytes leading to viral replication (secondary viremia). Infected cells circulate in the blood and spread around the body, infecting a variety of organs such as skin, lung, liver, spleen, thymus, and brain. This infection induces a strong cell-mediated immune reaction, characterized by production of many cytokines such as Interferon-α (Inf-α) and Interleukin-2 (Il-2), the cause of the rash [Gentilini & Duflo 1986; Gershon 1990; Morgan & Rapp 1977]. The complex immune reactions are better understood now; they evolve over time (1 to 12 weeks), and seem to involve numerous Th1 and Th2 reactions, and a great variety of responses that promote B-cell development. The first immune response (T-cells) is designed to ensure clearance of the RNA virus, while the second set (B-cells, antibodies) is designed to guarantee long-term immunity [Fisher et al. 2015; Griffin 2010, 2016].

Complications of measles infection are numerous, and the most common are the following [Gentilini & Duflo 1986; Reinert et al. 1984; Wilson et al. 1961]:

- Hyperthermia: the viremia that occurs before the rash may induce severe hyperthermia (very high fever), which may cause death if untreated.
- Respiratory infections (bacterial superinfection): pneumonia, bronchitis, laryngitis. These occur typically 7–14 days after the rash. In some cases, in particular in immuno-depressed subjects, measles may induce giant cell pneumonia.
- Diarrheal diseases: measles often induces diarrheal infections, especially in developing countries with poor hygiene, which may be due to a variety of bacteria (salmonella, shigella, staphylococcus) or parasites (amoebiasis). These occur typically 14–21 days after the rash, and are often an immediate cause of death by dehydration, or can lead to malnutrition.
- Eye complications: conjunctivitis and keratitis, which may lead to blindness in severe cases.
- Ear complications: otitis media is common among children.

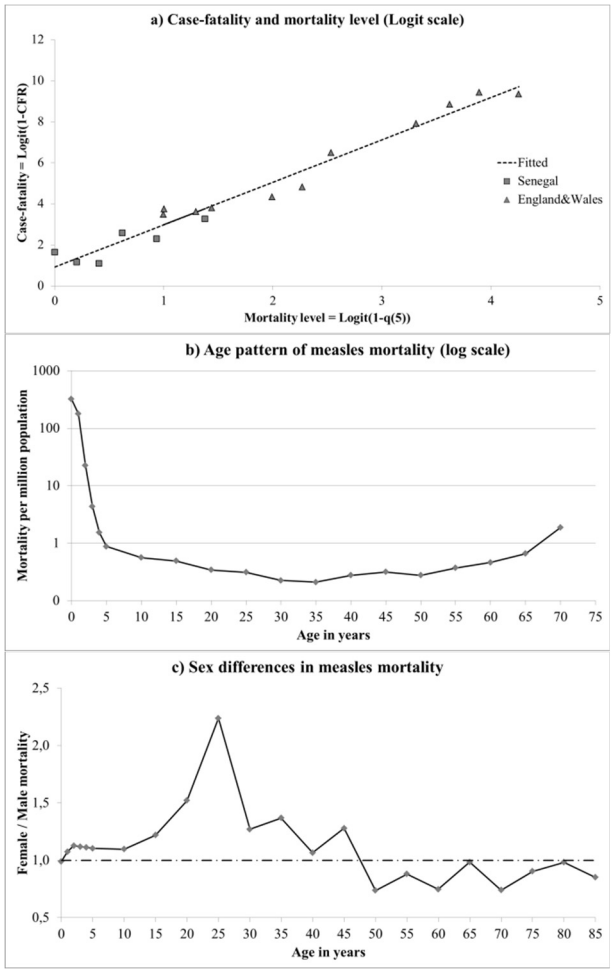
- Neurological complications: encephalitis, seizures, consciousness disorder, etc. These occur typically 2–30 days after the rash, and may lead to neurologic sequelae when severe.
- A long-term neurological complication is Subacute Sclerosing Pan-Encephalitis (SSPE), a fetal disease caused by persistent measles virus infection. SSPE develops several years after primo-infection.
- Immunological: measles induces short-term immunological abnormalities, and in some cases long-term immunological defects leading to Systemic Lupus Erythematosus (SLE) or Multiple Sclerosis (MS).
- Nutritional: severe measles infection often leads to acute malnutrition (marasmus, kwashiorkor) in poorly nourished populations of developing countries.
- Interactions with other infectious diseases: measles may exacerbate the severity of concurrent childhood diseases, in particular pertussis (whooping cough), tuberculosis, malaria, and HIV/AIDS.

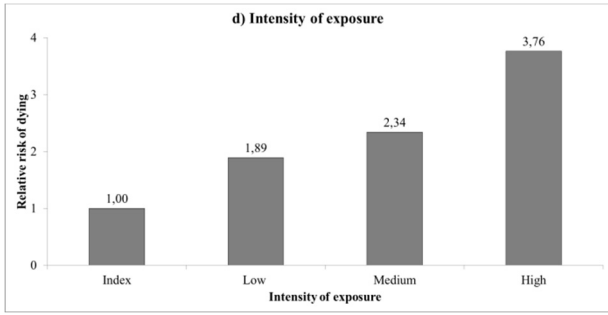
1.6 MEASLES MORTALITY

Measles mortality, or more precisely its case-fatality, is a complex issue [Barkin 1975]. At population level, it depends on the underlying level of mortality (the higher the level of mortality in the population, the higher the case-fatality), on age (higher case-fatality for very young children and for the elderly), and on gender (higher case-fatality for girls and young women, from the age of 1 to 50 years). At the individual level, case-fatality is higher among immuno-depressed people, malnourished children, and children with concurrent infection. In addition, the intensity of exposure at the time of transmission seems to have an effect on case-fatality: children more closely exposed to index cases have higher case-fatality, most likely because they receive a higher viral dose [Garenne & Aaby 1990; Garenne 1994b].

The following figures illustrate these complex patterns (see Figure 1.3). Panel (a) displays the relationship between case-fatality and level of mortality in England and Wales (1957–1964) and in Senegal (1963–1989); Panel (b) displays the age pattern of measles case-fatality in countries with reliable statistics before 1965; Panel (c) displays the sex differences in measles case-fatality, from the same data as in Panel (b); Panel (d) displays the effect of intensity of exposure, from the Niakhar study. All this information will be used in this study.

Figure 1.3: Patterns of differential mortality from measles in the world





Sources: (a) Cause of death statistics, England & Wales 1957–1964; and Niakhar data 1963–1989; (b,c) World Health Statistics, 37 countries, 1950–1964; (c) Cause of death statistics, cited in Garenne [1994b]; (d) Niakhar data, cited in Garenne & Aaby [1990].

1.7 MEASLES VACCINES

The development of measles vaccines was made possible by the experimentation of the measles virus on kidney cells by John Enders and Thomas Peebles at the Harvard Medical School, Children's Hospital in Boston, Massachusetts [Enders & Peebles 1954; Enders et al. 1960; Enders 1962; Katz et al. 1960, 1962; McCrumb et al. 1962; Preblud & Katz 1988]. This innovation paved the way to the attenuation of the wild virus, and within a few years to the development of the first vaccine in 1961. These early vaccines were tested in 1961 in the USA, Europe, and West Africa, in particular in Senegal in Tattaguine, an area close to Niakhar. The first vaccines were licensed in 1963 in the USA, but induced some severe reactions [Griffin et al. 2008]. They were followed by further attenuated vaccines, licensed in 1966 in the USA, and imitated by other producers in Europe, Russia, Japan, China, and elsewhere using different strains and vaccine-producing techniques for attenuation (see Chapter 2 for details on vaccine strains and producing techniques).

1.8 IMPACT OF MEASLES VACCINATION IN THE WORLD

Within a few years after 1966 the measles vaccine was administered throughout the world. Notification of measles cases is officially compulsory in most countries, however the data remain deficient, and available data are weak. However, data collected by the World Health Organization (WHO) indicate an impressive decline by some 96% in reported incidence between 1974 (5.6 million cases notified) and 2015 (195,762 cases notified), obviously a direct effect of increasing vaccination