Effect of subclinical infection on maintaining immunity against measles in vaccinated children in West Africa

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Summary

Background Despite a high coverage with measles vaccines in parts of west Africa, epidemics of measles occur with reduced severity in an increasing proportion of older children who have been vaccinated. We examined the effect of exposure to natural measles on immunity in vaccinated children.

Methods Our study was carried out in 1992 during an epidemic of measles in Niakhar, a rural area of Senegal with about 27,000 inhabitants who mostly live in compounds that include several households; within each household people live in different huts. Vaccine coverage in Niakhar was 81% at the time of our study. We measured haemagglutinin-inhibiting antibody at exposure and twice thereafter (after 4–5 weeks and at 6 months) in 36 vaccinated and 87 unvaccinated children. The frequency of measles and subclinical measles—defined as a four-fold or greater rise in antibody titre without clinical signs or symptoms—was related to intensity of exposure according to whether the index case was in the same hut, household, or compound.

Findings Clinical measles occurred in 20 (56%) of 36 unvaccinated children and in one (1%) of 87 vaccinated children. Subclinical measles occurred in 39 (45%) of 86 vaccinated children who were exposed to measles and in four (25%) of 16 unvaccinated children. The frequency was inversely related to pre-exposure antibody concentration (p=0.001 for trend) and directly related to intensity of exposure (p=0.002 for trend). Antibody concentrations in subclinical cases increased on average by 45-fold and remained raised for at least 6 months.

Interpretation Increased antibody titre after subclinical measles may be common in vaccinated children in West Africa where the intensity of exposure is high. As measles vaccination coverage increases, the circulation of wild measles will decrease, and vaccine-induced antibody is less likely to be boosted. Thus, new epidemics, albeit milder in form, may occur in vaccinated areas which should be recognised in campaigns to eradicate measles.


Introduction

Natural measles infection induces lifelong immunity as shown during an epidemic in the Faroe Islands when only inhabitants who had had measles in an epidemic 65 years earlier escaped infection. However, the assumption that live measles vaccine also induces lifelong protection or immunity against disease has been revised after outbreaks among high school and university students in the USA during the 1980s who had been vaccinated 15–20 years earlier. These observations accord with evidence that although measles antibodies persist for at least 16 years after vaccination, concentrations may fall below the putative protective concentration of 125 mIU/mL in a few people, which results in measles on exposure. Such a low concentration of antibodies is, however, now rare in the USA where live measles vaccine is given at age 15 months with a second dose recommended at school age. By contrast, in Senegal, west Africa, where children are vaccinated in infancy, we found that during a measles epidemic in 1987–90, the proportion of vaccinated children with this low antibody concentration was 13%; after exposure the attack rate in this group was 38%, compared with 82% in unvaccinated children. In this region, although measles is common in vaccinated children, the case fatality rate is much lower than in children who have not been vaccinated, which suggests that residual cellular immunity, conferred by vaccination, still persists after antibody concentrations have waned.

The role of natural measles in subclinical boosting of vaccine-induced measles antibody or of cellular immunity needs further documentation, especially in west Africa where such data are scarce. The most thorough study of such increased antibody titres is by Chen and colleagues. They found that during an outbreak of measles among vaccinated college students in Boston, USA, a rise in antibody concentration without overt measles was common in students with low concentrations of pre-exposure antibody. A large-scale study in China showed that subclinical measles boosted antibody responses in vaccinated children and that this increase lasted longer and was higher than in children who were revaccinated. Mulholland argued that in developing countries where measles is controlled by high levels of vaccine coverage, a second dose may be needed in adolescence to boost waning immunity, particularly for young mothers, who if previously vaccinated in infancy would have little antibody to transfer to their infant. In the western region of the Gambia, where measles vaccine coverage has been 84% for the past 10 years, we may be beginning to see these changes. In an outbreak of measles in 1997, of 835 cases, 175 (21%) occurred in infants, 434 (52%) were in children aged 1–9 years, and 225 (27%) were in those older than 10 years. Only 25 (14–3%) infants were vaccinated, whereas the proportion with a documented vaccine history rose to 60% in the children aged 1–9 years (Whittle H, unpublished). These data suggest a...
vaccine efficacy of only 71% and waning immunity, since previous data indicate that more than 95% of children respond to standard measles vaccination. Similarly, data from rural Senegal suggested waning immunity because vaccine efficacy declined from 100% to 66% for standard Schwarz measles vaccine over 10 years.

During an outbreak of measles in a part of Senegal with high vaccine coverage, we examined antibody changes in relation to vaccination status and to intensity of exposure.

Methods
Study population
Our study took place between December, 1991, and August, 1992, during an outbreak of measles in Niakhar, Senegal, a rural area with about 27,000 inhabitants who mostly belong to the Sereer ethnic group and live in large compounds. Within a compound there are several households, a self-defined social unit with a household head and common storage and cooking facilities; within a household people sleep in different huts. Niakhar has three dispensaries—two public and a private one—by the Catholic church. From 1984 to 1990, infant and childhood mortality in Niakhar was 112 per 1000 and 253 per 1000, respectively, most infant mortality was due to diarrhea, malaria, respiratory infections, measles, and malnutrition. In a survey carried out in 1990, 3% of the children aged 2–4 years were wasted (weight-for-height of less than −2 on z scores) and 31% were stunted (height-for-age of less than −2 x z scores). The surveillance system in Niakhar is based on weekly visits by 12 fieldworkers to all the 1800 compounds to obtain information on births, migrations, marriages, deaths, and infections. There were measles vaccination campaigns in Niakhar in 1986–87 during the accelerated phase of the Expanded Programme on Immunisation (EPI). From July, 1987, BCG, diphtheria, pertussis, tetanus, poliomyelitis, measles, and yellow fever vaccines were offered systematically in immunisation sessions organised once a month at each of Niakhar’s three health centres as part of measles and pertussis vaccine trials. The coverage for measles vaccine among children aged 1–2 years born in Niakhar increased from 36% in 1986 to 81% in 1992.

Measles surveillance and exposure
The study we report here, which examines household contacts of known cases, was part of a larger study to assess the long-term efficacy and effect on mortality of high-titre measles vaccine given during a trial undertaken in Niakhar between 1987 and 1990. The trial began active surveillance for acute cases of measles in Niakhar. When a fieldworker was told about a case of suspected measles, the project physician was called to examine the child. During the visit, information was sought on how the case had contracted measles and contacts were traced. Thus, new cases of measles were found by routine surveillance and through active follow-up of contacts by the physician. At the first visit to a compound, a census was made of all children aged younger than 15 years. If parents gave their consent, a blood sample was taken by finger prick from cases and from exposed children aged younger than 7 years who had no history of measles infection. Samples were also taken from children who developed measles and from uninfected contacts 4–5 weeks after the onset of symptoms and again 6 months later.

Clinical examination and case definition
Compounds with suspected cases of measles were visited at least twice a week for the first 4 weeks to observe the development of symptoms, to detect new cases as soon as possible, and to provide treatment. During each visit, the presence and severity of the following symptoms were recorded: Koplik spots, rash, desquamation, conjunctivitis, stomatitis, cough, respiratory symptoms, diarrhea, and temperature. At the end of each examination, the clinician assessed whether the child had probable, possible, or no measles. With further follow-up, cases of possible measles were reclassified as either probable or no measles. All children with a clinical diagnosis of probable measles had a typical morbilliform rash of acute measles, a typical desquamating rash of measles in the recovery phase, or both.

A child who developed measles more than 6 days after the first case (index case) in the same compound was classified as a secondary case. Cases with an interval of less than 6 days were judged co-index cases. As we have previously described, secondary cases and exposed children were classified according to the intensity of contact with a measles case: sleeping in the same hut (high), living in the same household but not sleeping in same hut (intermediate), or living in the same compound but not in the same household (low).

The study was approved by the Senegalese Ministry of Health and by the Gambia Government/Medical Research Council (MRC) ethical committee. The purpose of the study was explained to parents and guardians of the children before consent was obtained for a blood sample. In West Africa vaccination during epidemics is not standard practice. Since our project was designed to examine vaccine efficacy, we ensured that all cases received adequate treatment.

Measurement of measles antibody titles
We tested blood samples for measles haemagglutinin-inhibiting antibodies at the MRC Laboratories, the Gambia. The sensitivity of this test was 15–52 mIU per mL. Since the test started with a 1/2 dilution, the minimum detectable titre was 31.25 mIU per mL. We defined acute infection as a four-fold increase in titre together with clinical features of measles. Children who had a four-fold or greater increase in titre between exposure and convalescence but who did not have clinical measles according to the physician were judged to have had subclinical measles.

This analysis was limited to children aged from 7 months to 6 years at the time of exposure, since younger children could have been protected by maternal antibodies. We excluded seven children who had a four-fold or greater decrease in titre between exposure and convalescence because they may have had an early increase in antibody titre with a subsequent decline in antibody.

We identified 55 index cases in 51 compounds and 161 contacts who had a blood sample collected at the time of exposure. 123 (76%) of the contacts had a second sample collected about 1 month after exposure and 90 (73%) had another sample collected 6–9 months after exposure. Of the 123 children who had a blood sample taken both at exposure and 1 month later, 21 (17%) developed clinical measles. All children with clinical measles had a significant increase in titre between the samples taken at exposure and thereafter, apart from one child who already had a high titre when tested after the onset of symptoms. Of the 102 children with paired samples who did not develop clinical measles, 43 (42%) had subclinical measles as indicated by a four-fold or greater increase in haemagglutinin-inhibiting antibody and no clinical symptoms.

The 55 index cases and the 123 contacts with serial antibody measurements had a similar sex distribution.
ARTICLES

Table 1: Clinical and subclinical measles after exposure by age at exposure and vaccination status

The mean age of the index cases was older than that of contacts: 51 (SD 27) versus 36 (18) months (p=0.009). Ten (18%) of the 55 index cases had been vaccinated, compared with 87 (71%) of the 123 contacts (relative risk 0:27 [95% CI 0:11–0:66], p<0.0001). The low vaccine coverage in the contacts compared with the regional average of 81% in infants aged 1–2 years is because of the inclusion of young infants who had not been vaccinated (table 1). There may also be a natural bias towards the children who had not been vaccinated in the compounds of measles cases. Among the 123 contacts there was no significant difference between those exposed in the compound, household, or hut in terms of sex, mean age, percentage vaccinated, proportion seronegative, antibody titre of seropositive children at contact, and timing of first blood sample in relation to exposure and nutritional status (data available from the authors, on request).

Vaccination status

Table 1 shows the rates of clinical and subclinical measles by age and vaccination status. Attack rates were related to vaccination status: measles was 53-70 (6-81–423-56) times more likely in children who had not been vaccinated than in those who had been vaccinated. Subclinical measles tended to be more likely in vaccinated than in unvaccinated children (relative risk 1-76 [0-73–4-29]). In the univariate analysis, rates of clinical measles were not significantly related to age, sex, or to the time between the first blood sample and the onset of the first case in the compound. None of the children who had measles died.

Table 2: Clinical and subclinical measles after exposure by titre of measles haemagglutinin-inhibiting antibody at exposure and vaccination status

Antibody concentration at exposure

Table 2 shows that clinical attack rates were highest in unvaccinated children with no detectable antibody; the presence of antibody in unvaccinated children probably reflects undocumented vaccination or previous subclinical measles. Among vaccinated children, the likelihood of developing subclinical measles was strongly and inversely related to antibody concentration at exposure (p<0.0001 for trend). No cases of subclinical measles occurred in children with an antibody titre of log, 8 or more.

Intensity of exposure

Table 3 shows that among unvaccinated children the likelihood of developing clinical measles tended to be higher for children who lived in the same household than for those who lived in the same compound (2-57 [0-75–8-81]). This tendency was particularly strong when we limited the analysis to unvaccinated children without pre-exposure antibodies. In these children, the attack rate increased from two cases among seven exposed children in the same compound to seven cases among ten exposed children in the same household, and to nine cases among ten exposed children in the same hut (p=0-01 for trend). The likelihood of developing subclinical measles among vaccinated children was also significantly related to intensity of exposure (p=0-002 for trend). This trend was even stronger when we limited the analysis to children with antibody titres lower than 1-64 (p<0-001 for trend) (data not shown). The antibody titre 1 month after exposure among children who did not develop measles was also related to intensity of exposure: mean titre (log.) 5-7 (SD 3-7) for the 29 children in the same compound as the case, 6-5 (2-8) for the 24 children in the same household, and 7-4 (2-7) for the 49 children in the same hut (p=0-04).

We also analysed the determinants of clinical and subclinical infection in a multivariate logistic regression model (table available from authors, on request). In the final analysis, clinical infection was significantly related

Table 3: Clinical and subclinical measles after exposure by intensity of exposure and vaccination status

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Table 4: Geometric mean antibody titres at exposure and 1 month and 6 months after exposure for children with clinical measles, subclinical measles, and no measles

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Duration of antibody response after exposure

Table 4 shows that antibody in subclinical measles was boosted on average by 45-fold to concentrations similar to those of children who had had measles and that this increase in antibody persisted for at least 6 months after exposure. Although antibody titres fell over time, the mean titre in the 29 children with sub-clinical measles 6 months after exposure was still log 2-8 (2-7) higher than the mean titre at exposure (p<0.001, paired t test).

Discussion

We found that clinical attacks of measles occurred mostly among children who had not been vaccinated and lived in the household or hut of the index case (high degree of exposure). These findings accord with data obtained from Guinea Bissau and the situation in Niakhar in 1983-86 when vaccine coverage was inadequate and the case fatality rate was 6-5% and dependent on the intensity of exposure. During 1983-86, secondary cases in the compound were 1-9 times more likely to die than the index cases, and children in the same hut were 3-6 times more likely to die than index cases. By contrast, in 1992 with increased coverage and improved treatment in the home, the case fatality rate was 1-6%. The fall in the case fatality rate is unlikely to reflect a change in vitamin A status, since such supplementation was not part of treatment. A change in the virulence of the virus is an unlikely explanation, because although genetic analysis has revealed variability in the haemagglutinin and nucleoprotein genes, the virus behaves in a monotypic way in relation to infectivity and pathogenicity.

We showed that subclinical measles was common in immunised children and the frequency of the attacks was related to post-vaccination antibody titres. Thus, 88% of vaccinated children with haemagglutinin-inhibiting titres of 1/2 or less showed a boost in antibody, which fell to 60% in those with pre-exposure titres between 1/4 and 1/32, and to zero in those with high titres above 1/128. As in the case of clinical measles, subclinical episodes were probably related to exposure, with lowest exposure in the compound (17%) and highest exposure in the same hut: as the index case (58%). Other less likely explanations are a familial trend towards similar antibody concentrations or that nutritional state, which varied according to family, was the underlying determinant. This explanation seems improbable because antibody responses to measles vaccines are normal in children with moderate malnutrition.

We have no data to suggest that minor symptoms such as fever and headache were common in subclinical attacks, as reported by Chen and colleagues in Boston. Similarly, we could not answer the important issue of whether clinical and subclinical attacks follow exposure to subclinical measles since all contacts had blood samples collected immediately after the identification of the first clinical case in the compound and not after the subclinical cases. A reasonable assumption is that the increase in antibody titre during subclinical measles is the result of systemic replication of the virus, which is greatest among those with low pre-exposure antibody concentrations who then encounter a high degree of exposure. Whether this event is associated with shedding of infectious virus is unknown and of obvious importance if measles is to be eradicated.

We also examined the magnitude and duration of the increase in antibody titre after exposure in children who had and had not been immunised. Children with clinical measles had a large increase that was sustained for 6 months. Subclinical measles in vaccinated children boosted antibody to similar concentrations, although these fell by four-fold over 5 months. We have no local data on the concentration and duration of measles antibody in children who were revaccinated. In Bin and colleagues' study in China, children were revaccinated 3, 5, 10 years after primary immunisation and the increase in haemagglutinin-inhibiting antibody after reimmunisation was low, irrespective of the time between doses and the antibody concentration at vaccination. They also reported that the boosting effect was short lived since antibody dropped to original concentrations within 1-2 years; decay was particularly rapid in those whose primary response to the first immunisation was poor. In that study, like ours, vaccinated children exposed to natural measles had a substantial rise in antibody that lasted for at least 3 years. Thus, exposure to natural measles that leads to subclinical measles may be a more effective way to boost antibody than reimmunisation, which may have a short-lived response, especially in children who have had their primary immunisation in infancy.

Little is known about antibody persistence after vaccination in west Africa where malaria and other infections are rife. Cohen and co-workers found a rapid turnover of γ-globulin in Gambian adults with synthesis rates seven times higher than in Europeans. We found measles antibody concentrations 5-7 years after vaccination to be higher when taken in the rainy season than in the dry season. Perhaps malaria and other infections cause fluctuations in antibody responses to vaccines with an overall acceleration of decay.

A possible criticism of our small study is that vaccine efficacy against clinical disease was high and that there is little cause for concern. This argument ignores data from the 1997 outbreak in the Gambia and previous data from Senegal and Guinea Bissau where vaccine efficacy ranged from 65% to 70%. Moreover, our main focus was to examine young children vaccinated within the previous 3 years who had high antibody concentrations. A decrease in antibody concentrations and decline in vaccine efficacy will mainly occur among older children. If we compare vaccinated and unvaccinated children with no antibodies, the vaccine efficacy was 91%. In a previous study, we found the vaccine efficacy for this group of older children was about 50% and the secondary attack rate was 48%. These findings contrast with reports from developed countries where long-term efficacy remains high. Perhaps young age at vaccination, a high intensity of exposure, and a more rapid decline in antibody concentration account for the differences in west Africa.

The Gambia was one of the first countries to interrupt measles transmission through the introduction of yearly
campaigns to immunise children aged 6 months to 6 years. Strategies have evolved to interrupt transmission and eventually eliminate measles by keeping the number of susceptible people below a critical minimum, which in some populations may be as low as 3%. The basic plan consists of three phases. The catch-up phase involves one immunisation of children aged 1–14 years. The keep-up phase involves routine immunisation at age 12 months. The follow-up campaign is done every 4–5 years to reduce the accumulation of susceptible infants and children aged 1–4 years. This strategy has been successful in the elimination of measles in Cuba and the English speaking Caribbean. However, in west Africa political instability and economic strictures has made it difficult to implicate or sustain all three components of the plan. Thus, in countries with good routine immunisation, but no catch-up phase or regular follow-up campaigns, measles still occurs in widely spaced epidemics. The trigger may be an imported case of measles which initiates infection in the pool of susceptible infants who were only briefly protected by low concentrations of antibody transferred from vaccinated mothers whose antibodies are no longer boosted by natural exposure. Another large and growing group of susceptible people are older children who have missed immunisation or vaccinated children who, in the absence of boosting of immunity by natural measles or by revaccination, become infected in the face of intense exposure in crowded huts and households.

Contributors
The study was planned by all authors except Henrick Jensen and was written by Hilton C Whittle who also supervised the laboratory work. Badara Samb did the fieldwork under the guidance of Peter Aaby and Francois Simondon. John Bennett advised on the design, analysis, and presentation of the study. Henrick Jensen and Peter Aaby did the statistical analyses.

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