Protective efficacy of high-titre measles vaccines administered from the age of five months: a community study in rural Senegal

Badara Samb[1], **Peter Aaby**[1,2], **Hilton Whittle**[3], **Awa Marie Coll Seck**[4] and **François Simondon**[1] [1]*ORSTOM, Dakar, Senegal;* [2]*Epidemiological Research Unit, Statens Seruminstitut, Copenhagen, Denmark;* [3]*MRC Laboratories, Banjul, The Gambia;* [4]*University of Cheikh Anta Diop, Dakar, Senegal*

Abstract

Using data on incidence and secondary attack rates, we examined the protective efficacy of high-titre Edmonston-Zagreb (EZ) and Schwarz (SW-HT) measles vaccines administered at 5 months. Control children were assigned to placebo at age 5 months and standard Schwarz (SW-std) measles vaccine at 9–10 months of age. A large proportion of measles cases was verified serologically. Though high-titre vaccines seemed to be protective before 10 months of age, a significant reduction in disease could not be demonstrated due to low incidence of measles. After 10 months of age, SW-std given at 10 months gave a vaccine efficacy of 100% and induced better protection than SW-HT ($P=0{\cdot}030$) and EZ-HT ($P=0{\cdot}128$) administered at 5 months. In studies of secondary attack rates in the compound, vaccine efficacy was 91% (75%–97%) for EZ-HT, 85% (40%–96%) for SW-HT, and 100% for SW-std. Attack rates were correlated with intensity of exposure ($P=0{\cdot}0006$), being much higher for children exposed in the same hut than for those living in the same compound but in a different household (relative risk=3·36 [1·32–8·57]). The attack rate was significantly lower among vaccinated than unvaccinated children with no detectable measles antibody (relative risk=0·41 [0·18–0·93]). In rural areas with a high coverage in the surrounding community, a single dose at 9–10 months may provide sufficient protection. Since high-titre vaccines have been associated with higher mortality than SW-std, further improvements in measles control before 9 months may require two-dose strategies with standard vaccines.

Introduction

There has been increasing concern about measles infection before the normal age of vaccination (AABY & CLEMENTS, 1989; AABY *et al.*, 1990a; DABIS *et al.*, 1988; LOENING & COOVADIA, 1983; TAYLOR *et al.*, 1988). Measles before 9 months of age is connected with a high case fatality ratio (CFR) and it seems also to be connected with a significant delayed mortality (AABY *et al.*, 1986, 1990b; GARENNE & AABY, 1990). Several studies have shown that high-titre Edmonston-Zagreb measles vaccine (EZ) is capable of inducing measles antibodies even in the presence of maternal antibodies (MARKOWITZ *et al.*, 1990; TIDJANI *et al.*, 1989; WHITTLE *et al.*, 1988a, 1990). Since seroconversion is usually considered to be equivalent to protection, the World Health Organization (WHO) has recommended the use of EZ from the age of 6 months in areas with a high incidence before 9 months of age (WHO, 1990). However, there have been few studies of the protective efficacy of early measles vaccination with high-titre vaccines (AABY *et al.*, 1988).

The present study in rural Senegal compared high-titre EZ and high-titre Schwarz vaccine (SW-HT) given at 5 months of age with standard Schwarz measles vaccine (SW-std) administered at the age of 10 months (WHO, 1990). EZ was initially recommended for use in urban areas with a high incidence before 9 months of age. However, a uniform vaccination policy would clearly be an advantage from an administrative point of view. We therefore wanted to examine whether these high-titre vaccines could contribute to improved control of measles also in rural areas which have a lower incidence before 9 months of age than urban areas.

After completion of the study, long-term follow-up of study children demonstrated increased mortality for recipients of high-titre vaccines. It has therefore been recommended that high-titre measles vaccines should no longer be used (EPI [Expanded Programme on Immunization], 1992). However, we thought it worthwhile to document the vaccine efficacy (VE) of high-titre measles vaccines and SW-std.

Subjects and Methods

The study was carried out in Niakhar, Senegal, in a rural area with a population of about 25 000 which had been under demographic surveillance since 1983 (CANTRELLE, 1969). The area is inhabited by Sereer who live in large compounds. The population, the demographic surveillance system (GARENNE *et al.*, 1987), and the epidemiology of measles there (GARENNE & AABY, 1990) have been described in detail elsewhere. The surveillance system was based on a weekly visit by field assistants to all compounds in the study area to get information on births, migrations, deaths, and infections (measles and whooping cough).

Address for correspondence: Drs Badara Samb and Peter Aaby, ORSTOM, B.P. 1386, Dakar, Senegal.

Study of high-titre measles vaccines

All children born of mothers resident in the study area between 1 February 1987 and 31 January 1989 were included in the study. Children were allocated at random to receive either EZ, SW-HT or placebo at 5 months of age. Parents were advised to bring their children for one of the monthly vaccination sessions at the nearest of the 3 health centres in the study area in the 3rd, 5th and 10th months after birth. At 3 months of age, children received bacillus Calmette-Guérin (BCG) and diphtheria, tetanus, pertussis and polio (DTP-IPV), at 5 months the second dose of DTP-IPV, and at 10 months the third dose of DPT-IPV and yellow fever vaccine. At the 5 months vaccination (mean age 5·1 months) children received EZ, SW-HT or placebo. The study was 'blind' between 5 and 10 months of age. Children in the placebo group as well as children who had not previously attended for vaccination were offered vaccination with SW-std when they were 10 months old (mean age 10·1 months). Children belonging to the study cohort who did not attend for vaccination at 5 months also remained under surveillance although they had not entered the study. Children who remained vaccinated were called for vaccination at a health centre during 2 campaigns, and at the end of the study period (September–December 1990) all children were visited at home by a physician. Measles vaccination was offered to those who had still not received measles vaccine; 55% (138/248) accepted.

Blood samples were collected at 5 and 10 months of age from children included in the study. Recipients of high-titre vaccine found to be serologically negative at 10 months of age were offered revaccination against measles; 5 children (1%) in the EZ and 31 (10%) in the SW-HT thus received a second vaccination with either EZ or SW-std. Revaccinated children were excluded from the analysis of VE from the time of revaccination. Blood samples were not collected from the children who had received SW-std.

When blood samples from the first vaccinated children were analysed, it became clear that SW-HT gave lower

seroconversion rates than EZ (unpublished observations). Children in the last 8 month cohorts (born between 1 June 1988 and 31 January 1989), were therefore allocated to receive only EZ or placebo at 5 months of age. Thus there were 3 groups during the first 16 month cohorts but only 2 during the last 8 month cohorts. As a consequence, there were fewer children in the SW-HT group than in the other 2 groups.

Vaccines

EZ-HT and SW, kindly provided by the Institute of Immunology, Zagreb, (EZ, lots 81 and 137) and Institut Mérieux, Lyon (SW-HT), were given in a minimum dose of 100 000 plaque-forming units (pfu). SW-std had a titre of 6000 50% tissue culture infective doses ($TCID_{50}$). All measles vaccines were administered subcutaneously. Samples of the vaccines used in the field were routinely controlled at the Medical Research Council (MRC) Laboratories in Fajara, The Gambia.

Measles surveillance and clinical examination

As soon as a field assistant was informed of a case of suspected measles in the weekly visit to all compounds, the project physician was called to examine the children. At the first visit, a census was made of all children under 15 years of age in the compound. Whether children lived in the same hut as the index case, in the same household but not the same hut, or in the same compound but not in the same household, was recorded (GARENNE & AABY, 1990). If the parents consented, a blood sample was taken from all cases and from exposed children without a parental history of measles infection. Convalescence samples were collected about 4–5 weeks after the beginning of symptoms from children who developed measles.

All 55 cases with a clinical diagnosis were seen by a project physician and had a typical rash and/or typical desquamation. Eleven further cases were reported by parents, usually the mother. Previous studies in this area have shown maternal diagnoses of measles to be very reliable (AABY, 1992). Most of these cases had occurred outside the study area.

Serology

Blood samples were analysed for measles haemagglutination inhibition (HAI) antibodies at the MRC Laboratories in The Gambia (WHITTLE *et al.*, 1988b). The sensitivity of this test is 62·5 milli-international units (miu). Since the test starts with a 1:2 dilution, the minimum detectable level is 125 miu. A four-fold increase in paired samples was considered proof of acute measles infection. Protection in relation to antibody level was analysed for children who had a blood sample collected within 10 d of the onset of symptoms in the index case in the compound.

Vaccine efficacy

The protective efficacy against measles infection was examined by comparing incidence of measles in the different groups and by determining protection against infection after known exposure at home to an index case of measles. Children were considered to be vaccinated from 14 d after administration of vaccine at 5 or 10 months of age. Vaccine efficacy (VE) was defined as (1−relative risk of incidence [vaccinated/unvaccinated])×100.

In the study of incidence, comparison was made for 2 periods, between 5 and 9 months of age and from 10 months of age, when most of the children had received a high-titre or SW-std vaccine. Incidence was calculated as number of cases in relation to the number of person-years-at risk (PYR). PYR was calculated from 14 d after vaccination to the special survey in the autumn of 1990, the day of death, the day of migration, the day of measles infection, or the date of receiving a second dose of measles vaccine, whichever came first. Since study design was different for the first 16 and the last 8 monthly cohorts, the analysis of incidence has been standardized for these 2 periods.

The secondary attack rate (SAR) following exposure was assessed for different study groups taking intensity of exposure into consideration (GARENNE & AABY, 1990). All exposed children who developed measles experienced the onset of symptoms within an interval of 8–19 d if they belonged to the first generation of cases infected in the compound. Cases occurring in later generations within the compound were also counted as secondary cases. Cases were classified according to the closest exposure. Two children exposed twice with an interval of 6–12 months were counted only the first time they were exposed.

In the analysis of incidence, we used only the unvaccinated children in the placebo group as controls, since there could be an association between not attending for vaccination and being exposed outside the study area. In the study of secondary attack rates, however, we also used the unvaccinated children in the group which had not entered the study. There is no reason to believe that susceptibility to measles is either higher or lower when exposed at home for children who did not receive the first vaccination than for other children in the community.

Statistics

Relative risk (RR) and Greenland-Robins approximate 95% confidence interval (CI) were calculated using the EpiInfo program (Version 5·01a).

Results

Study children and vaccine coverage

During the study period 2467 children were born in the area. At the 5 months vaccination, 2177 children were eligible for inclusion in the study. Of these children, 72·9% received a vaccine at 5 months: 624 received EZ, 321 SW-HT and 634 the placebo. Nine received the wrong vaccine and were excluded from the study. Of the control children still in the study at the 10 months vaccination, 78·7% (480/610) received SW-std. At 2 and 3 years of age, coverage in the control group had increased to 86·8 and 90·4%, respectively.

Table 1. Incidence of measles per 1000 person-years-at-risk according to age and vaccine group; children with a clinical diagnosis of measles only. Niakhar, Senegal, 1987–1900[a]

Vaccine group[c]	No. of cases per 1000 PYR[b] by time of exposure 5–9 months	≥10 months
EZ	4·0 (1/251·4)	4·3 (4/929·7)
SW-HT	0·0 (0/127·6)	8·8 (5/568·5)
Placebo[d]	11·7 (3/255·5)	19·1 (3/156·8)
Placebo/SW-std[e]	–	0·0 (0/826·5)
Not in study[d]	16·4 (4/244·6)	57·1 (28/490·3)
Not in study/SW-std[e]	–	0·0 (0/397·6)

[a]As only the first 16 of the 24 monthly birth cohorts in the study received SW-HT (see note c), the analyses of vaccine efficacy have been adjusted according to whether the child belonged to cohorts 1–16 or 17–24. Hence, some vaccine efficacies cited in the text are not directly deducible from the Table. The calculation of vaccine efficacy has been standardized for the 2 age intervals in the Table. Four measles cases occurred before the children received measles vaccination; 2 cases occurred among 12 children excluded because they received the wrong vaccine or were vaccinated at an incorrect age, and one case was excluded because it had received 2 measles vaccines.

[b]PYR=person-years-at-risk.

[c]EZ=Edmonston-Zagreb vaccine; SW-HT=Schwarz high-titre vaccine; SW=std=standard Schwarz vaccine.

[d]Children not immunized against measles.

[e]Children immunized with the SW-std measles vaccine.

Measles cases

Fifty-five of the study children were diagnosed with clinical measles between the beginning of the study in July 1987 and the autumn of 1990, most of them during an epidemic between September 1989 and May 1990. Four cases were infected before they had received their 5 months vaccination. After 5 months of age, 5 children in the EZ group (2, 1, 1, 1 and 0·6 years old and 5 in the SW-HT group (2, 1, 1, 1, 1 years old) caught measles, whereas none of the recipients of SW-std were diagnosed with measles. None of these children died of acute measles. One vaccinated case was excluded from the analysis because the child apparently had received 2 measles vaccines. The remaining 40 cases occurred among unvaccinated children. Of the 55 cases, 28 had 2 blood samples collected in the acute and convalescence phase of the disease, the rest had only one blood sample (20) or refused to give a blood sample (7). Of the 28 children with 2 blood samples, 24 (86%) had a four-fold increase in the HAI titre; these included 2 of the 3 children in the EZ group and all 3 children in the SW-HT groups with 2 samples. Three cases had the same $\log_2$ titre in both samples (3-3, 3-3, 5-5) and one had no antibody in either sample. With 3 of the 4 cases without an increase in titre, there were other verified cases in the compound. The case who had no antibody has been maintained in the analysis since not all cases were examined by haemagglutination assay and the condition for inclusion was a clinical diagnosis.

Vaccine efficacy based on incidence of measles

The incidence in the different age and vaccine groups is shown in Table 1. The unvaccinated children who did not enter the study had a higher risk of contracting infection than children in the placebo group who never received measles vaccine (RR=2·4, CI=1·0–6·1). If children with a parental diagnosis of measles were included, the difference in incidence was even greater (RR=2·7, CI=1·2–5·9).

Comparison of recipients of high-titre vaccines and unvaccinated children. There were too few cases between 5 and 10 months of age to determine VE confidently. Considering both high-titre groups together compared with the placebo group, VE was 71% (−114% to 96%) ($P<0·43$). Compared with recipients of placebo who had not been vaccinated against measles, EZ had a protective efficacy of 75% (10%–93%) ($P=0·055$) and SW-HT one of 11% (−886% to +92%) ($P=0·720$), if the periods both before and after 10 months of age were considered.

Comparison of recipients of high-titre vaccines and SW-std vaccinated children

Compared from 10 months of age, SW-std had a VE of 100% ($P=0·003$, Fisher's exact test) compared with the unvaccinated children. SW-std given at 10 months of age also provided significantly better protection than SW-HT administered at 5 months of age ($P=0·030$, Fisher's exact test) and tended to be better than EZ administered at 5 months of age ($P=0·128$). The protective efficacy remained essentially unchanged when cases with a parental diagnosis only were included (data not shown).

Table 2. Secondary attack rates after exposure in the compound according to age, intensity of exposure and vaccine group; only children with a clinical diagnosis. Niakhar, Senegal, 1987–1990

Age and place of exposure	Attack rate (%) (no. of cases/no. exposed)[a] EZ	SW-HT	SW-std	Placebo and unvaccinated
5–9 months				
Compound	–	0·0 (0/1)	–	0·0 (0/4)
Household	–	–	–	60·0 (3/5)
House	0·0(0/4)	–	–	100·0 (3/3)
≥10 months				
Compound	0·0 (0/9)	0·0 (0/6)	0·0 (0/10)	33·3 (3/9)
Household	18·2 (2/11)	16·7 (1/6)	0·0 (0/12)	80·0 (4/5)
House	6·7 (2/30)	14·3 (1/7)	0·0 (0/32)	83·3 (15/18)

[a]EZ=Edmonston-Zagreb vaccine; SW-HT=Schwarz high-titre vaccine; SW-std=standard Schwarz vaccine.

Vaccine efficacy based on the secondary attack rate

There was a highly significant tendency towards increasing SAR with intensity of exposure in the unvaccinated group ($P=0·0006$; χ^2 for linear trend=11·9) (Table 2). Children exposed in the same hut had a 3·36 times higher risk (1·32–8·57) ($P=0·002$) of developing measles than did children living in the same compound but in a different household. The VE standardized for age and intensity of exposure was 91% (75%–97%) ($P<0·0001$) for recipients of EZ administered at 5 months of age, 85% (40%–96%) ($P=0·0002$) for SW-HT administered at 5 months of age, and 100% ($P<0·0001$) for SW-std given at 10 months of age (Table 2). In compounds with at least one case confirmed serologically, the attack rate among unvaccinated children in the same household was 95% (19/20). The only child who did not develop measles had a titre of 4000 miu 3 d after exposure, even though the child had no history of measles infection or vaccination against measles.

After 10 months of age, when the different measles vaccines could be compared, recipients of SW-std tended to have better protection than those who had received SW-HT ($P=0·104$, Fisher's exact test) or EZ vaccine ($P=0·109$, Fisher's exact test).

Antibody levels and protective efficacy

Of the 169 study children exposed after the age of 5 months, 111 (66%) had provided a blood sample within 10 d of exposure (date of first symptom in the index case in the compound). All except one of the children who developed measles were negative in the initial HAI test. One child in the EZ group, who was a secondary case in the household, had a titre of 500 miu 9 d after exposure and 10 d before the child developed the first symptoms of clinical measles. In the convalescence phase, the child had a titre >256 000 miu.

The attack rate was significantly lower among vaccinated children with no detectable antibody (4/12) than among unvaccinated children with <125 miu antibodies (18/22) (RR=0·41, CI=0·18–0·93), $P=0·008$, Fisher's exact test).

Discussion

One of the major objectives of this study was to assess the protective efficacy of high-titre measles vaccine between 5 months and the normal age of vaccination. The observed measles incidence of 0·5% between 5 and 10 months of age was clearly lower than the incidence of 2·15% expected from previous data (GARENNE & AABY, 1990), probably due to the effect of vaccination campaigns launched by the Ministry of Health and UNICEF in 1987 and the herd immunity provided by the higher vaccination coverage (AABY *et al.*, 1990a) resulting from the project. The reduced rate of measles at 5–10 months of age among recipients of high-titre measles vaccine (2·6/1000 PYR), as compared with those immunized only after 10 months of age (11·7/1000 PYR) also contributed to this effect, though statistically significant protection could not be shown. Thus the study had no power (15%) to demonstrate the expected VE (85%) of high-titre vaccines between 5 and 10 months of age. However, both high-titre measles vaccines provided a reasonable VE in the secondary attack rate studies. Thus there is reason to think that these vaccines provide clinical protection before the normal age of vaccination, as was found in Guinea-Bissau (AABY *et al.*, 1988).

The evaluation of high-titre vaccines, in particular of SW-HT, may well have been too favourable because several of the children with unmeasurable antibodies were revaccinated and in the exposure study children without

antibodies were clearly more likely to contract measles. Furthermore, in the incidence calculation after 10 months of age the recipients of high-titre vaccines were compared with children who had not been vaccinated with SW-std and these children may have had a higher risk of contacting measles. Since EZ provided a better antibody response than SW-HT (our unpublished observations), the EZ is more likely to improve control of measles infection than high-titre Schwarz vaccine.

No other community study from Africa has provided serological confirmation of a large number of cases, presumably due to the difficulties in timing when the first sample is taken late in the acute phase. In the present study, in which most of the exposed children provided a blood sample before exposure, significant increases in titre could be demonstrated in most paired samples. The one child vaccinated with EZ whose clinical diagnosis was not confirmed serologically was an index case who infected no one and the exclusion of this case would not affect the results obtained for protection after exposure at home.

The recipients of SW-std tended to be better protected after 10 months of age than the recipients of high-titre vaccines, though the difference was not statistically significant in the comparison between EZ and SW-std. This result is contrary to other studies, which have indicated better protection after early EZ vaccination than after SW-std vaccination (AABY *et al.*, 1988) and better seroconversion after early EZ vaccination than after SW-std vaccination at 9 months (TIDJANI *et al.*, 1989). The fact that children in the control group received SW-std at 10·1 instead of 9 months may have improved the performance of the standard vaccine in the present study.

The potential benefits of early measles vaccine with high-titre vaccines are related both to protection before the normal age of vaccination and to the possibility of better protection than with SW-std after 9 months of age (AABY *et al.*, 1990a). The consequence of the low incidence before 10 months of age and of the better protection in the SW-std group was that high-titre vaccines prevented few cases compared with the placebo/SW-std group in spite of the lower measles immunization coverage in this group. In the present study, the interval between giving the high-titre vaccine and the standard vaccine was 5 months, whereas it would be only 3 months in the normal situation when a change is made from vaccination at 9 months to 6 months of age (WHO, 1990). In such situations, the benefits of high-titre vaccine may be less. In areas with a low incidence of measles, and as long as a single dose strategy is maintained, good coverage with the standard vaccine at 10 months may be as effective for measles control as the introduction of early vaccination with high-titre measles vaccine if SW-std has a better VE after 9 months of age. Thus the crucial issue for measles vaccine strategy is the relative VE after 9 months of age for SW-std and high-titre vaccines.

Since high-titre vaccines have been protective before 9 months of age (AABY *et al.*, 1990a) and SW-std was better than high-titre vaccines after 10 months of age in the present study, two-dose strategies need to be considered. However, such strategies presuppose that the second dose can stimulate protective immunity equivalent to that obtained by vaccinating for the first time with SW-std at 9 months.

In this rural area the incidence before 10 months of age was low. Hence, the major arguments for introduction of high-titre measles vaccines in rural areas also may be the simplification of vaccine policy and the possibility of obtaining better coverage at 6 months of age than at 9 months. However, since high-titre vaccines have been found to be associated with higher mortality than SW-std vaccine in Guinea-Bissau (AABY *et al.*, in press; EPI, 1991) and Senegal (AABY *et al.*, 1991; GARENNE *et al.*, 1991) it has been recommended that high-titre measles vaccines no longer be used (EPI, 1992). It may require two-dose strategies with standard vaccines to improve the control of measles before 9 months of age.

Acknowledgements

Financial support was provided by the Task Force for Child Survival, Atlanta, Georgia, USA; the Expanded Programme on Immunization, WHO, Geneva; and the Unité de Recherche Population et Santé, ORSTOM, Dakar, Senegal. We are grateful to Dr Michel Garenne, who initiated the project, Dr Odile Leroy, who worked in the first part of the project, Dr John Bennett (Task Force for Child Survival), and Dr Lauri Markowitz (Centers for Disease Control, Atlanta, Georgia, USA), for their support and comments.

References

Aaby, P., Bukh, J., Hoff, G., Leerhøy, J., Lisse, I. M., Mordhorst, C. H. & Pedersen, I. R. (1986). High measles mortality in infancy related to intensity of exposure. *Journal of Pediatrics*, **109**, 40–44.

Aaby, P. (1992). Influence of cross-sex transmission on measles mortality in rural Senegal. *Lancet*, **340**, 388–391.

Aaby, P., Jensen, T. G., Hansen, H. L., Kristiansen, H., Thårup, J., Poulsen, A., Sodemann, M., Jakobsen, M., Knudsen, K., da Silva, M. C. & Whittle, H. (1988). Trial of high-dose Edmonston-Zagreb measles vaccine in Guinea-Bissau: protective efficacy. *Lancet*, **ii**, 809–811.

Aaby, P., Knudsen, K., Jensen, T. G., Thaarup, J., Poulsen, A., Sodemann, M., da Silva, M. C. & Whittle, H. (1990a). Measles incidence, vaccine efficacy and mortality in two urban African areas with high vaccination coverage. *Journal of Infectious Diseases*, **162**, 1043–1048.

Aaby, P., Bukh, J., Kronborg, D., Lisse, I. M. & da Silva, M. C. (1990b). Delayed excess mortality after exposure to measles during the first six months of life. *American Journal of Epidemiology*, **132**, 211–219.

Aaby, P., Samb, B., Simondon, F., Whittle, H., Coll Seck, A. M., Knudsen, K., Bennett, J., Markowitz, L. & Rhodes, P. (1991). Child mortality after high-titre measles vaccines in Senegal: the complete data set. *Lancet*, **338**, 1518.

Aaby, P., Knudsen, K., Whittle, H., Thårup, J., Poulsen, A., Sodeman, M., Jakobsen, M., Brink, L., Gansted, U., Permin, A., Jensen, T. G., Lisse, I. M., Andersen, H. & da Silva, M. C. (in press). Long-term survival after Edmonston-Zagreb measles vaccination: increased female mortality. *Journal of Pediatrics*.

Cantrelle, P. (1969). *Etude démographique dans le région du Sine-Saloum (Sénégal); état civil et observation démographique. Travaux et document 1*. Paris: ORSTOM.

Dabis, F., Sow, A., Waldman, R. J., Bikakouri, P., Senga, J., Madzou, G. & Jones, T. S. (1988). The epidemiology of measles in a partially vaccinated population in an African city: implication for immunization programmes. *American Journal of Epidemiology*, **127**, 171–178.

EPI (1991). Safety and efficacy of high titre measles vaccine at 6 months of age. *Weekly Epidemiological Record*, **66**, 249–251.

EPI (1992). Consultation on studies involving high titre measles vaccines. *Weekly Epidemiological Record*, **67**, 357–361.

Garenne, M. & Aaby, P. (1990). Pattern of exposure and measles mortality in Senegal. *Journal of Infectious Diseases*, **161**, 1088–1094.

Garenne, M., Maire, B., Fontaine, O., Dieng, K. & Briend, A. (1987). *Risques de décès associés à différents états nutritionnels chez l'enfant d'âge préscolaire*. Dakar: ORSTOM.

Garenne, M., Leroy, O., Beau, J. P. & Sene, I. (1991). Child mortality after high-titre measles vaccines: prospective study in Senegal. *Lancet*, **338**, 903–907.

Loening, W. E. K. & Coovadia, H. M. (1983). Age-specific occurrence rates of measles in urban, peri-urban, and rural environments: implications for time of vaccination. *Lancet*, **ii**, 324–326.

Markowitz, I. E., Sepulveda, J., Diaz-Ortega, J. L., Valdepino, J. L., Albrecht, P., Zell, E. R., Stewart, J., Zarate, M. L. & Bernier, R. H. (1990). Immunization of six months old infants with different doses of Edmonston-Zagreb and Schwarz measles vaccines. *New England Journal of Medicine*, **322**, 580–587.

Taylor, W. R., Mambu, R. K., ma-Disu, M. & Weinman, J. M. (1988). Measles control efforts in urban Africa complicated by high incidence of measles in the first year of life. *American Journal of Epidemiology*, **127**, 788–794.

Tidjani, O., Grunitsky, B., Guerin, N., Levy-Bruhl, D., Lecam, N., Xuereff, C. & Tatagan, K. (1989). Serological effects of Edmonston-Zagreb, Schwarz, and AIK-C measles vaccine strains given at ages 4–5 or 8–10 months. *Lancet*, **ii**, 1357–1360.

Whittle, H., Hanlon, P., O'Neill, K., Hanlon, L., Marsh, V., Jupp, E. & Aaby, P. (1988a). Trial of high-dose Edmonston-Zagreb measles vaccine in The Gambia: antibody response

and side-effects. *Lancet*, ii, 811–814.
Whittle, H. C., Mann, G., Eccles, M., O'Neill, K., Jupp, L., Hanlon, P., Hanlon, L. & Marsh, V. (1988b). Effects of dose and strain of vaccine on success of measles vaccination of infants aged 4–5 months. *Lancet*, i, 963–966.
Whittle, H. C., Campbell, H., Rahman, S. & Armstrong, J. R. M. (1990). Antibody persistence in Gambian children after high-dose Edmonston-Zagreb measles vaccine. *Lancet*, 336, 1046–1048.
WHO (1990). Global advisory group. *Weekly Epidemiological Record*, 65, 6–11.

Received 28 May 1992; revised 5 January 1993; accepted for publication 6 January 1993

Announcements

Annual International Course on Identification of Arthropods and other Insects of Medical and Veterinary Importance
18 April–13 May 1994: London, UK

Further information can be obtained from: Dr M. J. R. Hall, Medical and Veterinary Division, Department of Entomology, The Natural History Museum, Cromwell Road, London, SW7 5BD, UK; phone (0)71-938-9451, fax (0)71-938-9395/8937.

Tuberculosis—Towards 2000
International Conference—Pretoria, South Africa
13–17 March 1994

A scientific conference and workshops on the short-term future of tuberculosis in the developing world, with particular emphasis on Africa.

Further details from The Secretariat, Tuberculosis—Towards 2000, MRC National Tuberculosis Programme, Private Bag X385, Pretoria 0001, South Africa; phone +27 12 324 1680, fax +27 12 325 5970.

The Dr Albert Dubois Prize for Tropical Pathology

The third quinquennial award of this prize will be made in 1994 by the *Fondation Docteur A. Dubois, Académie Royale de Médecine de Belgique.*

The prize is worth 500 000 Belgian francs (about 12 500 ECU), and is intended to promote clinical, experimental or epidemiological research in tropical human and veterinary pathology.

Entries should be submitted *not later than 31 May 1994* to l'Académie Royale de Médecine de Belgique, 1 rue Ducale, B-1000 Brussels, Belgium. Further information can be obtained from the Secretary of the *Fondation* at the same address.