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Sir,

I read with great interest your document on "Scientific Dishonesty & Good Scientific Practice". It is a very comprehensive review of an important issue.

As proposed in your § 3.7.5 (p 77), I would like to draw your attention to the case of one of your nationals who was working in a developing country: Mr. Peter Aaby, formerly working at the Institute of Ethnology and Anthropology at the university of Copenhagen and now at the Staten Serum Institute, who has conducted field work in Guinea Bissau and has been recently involved in other work in Senegal.

Mr. Aaby's behavior during the crisis associated with the Edmonston-Zagreb vaccine has been rather controversial, raising issues about scientific dishonesty and unethical behavior. I detail the facts in the following pages.

Problems with *good scientific practice* were already raised during the earlier work done by Mr. Aaby on malnutrition and its relationship with measles mortality [1]. I was never able to replicate Mr. Aaby's findings that malnutrition was not a risk factor for measles mortality: in fact I found the opposite, as did all my colleagues throughout the world. Here again, Mr. Aaby's findings were based on inappropriate data collection and inappropriate analysis. Fortunately, this case did not have much importance: virtually nobody believed it, and new findings associated with vitamin A supplementation confirmed the major role of malnutrition in measles mortality.

However, the case of the Edmonston-Zagreb vaccine could have had disastrous implications. If the strategy recommended had been implemented, it could have caused the death of many millions of children in developing countries.

I have had many opportunities for friendly and productive interactions with Mr. Aaby between 1983 and 1989, when I was working in Senegal. We were seeing each other about twice a year, as European researchers working nearby one another. I have always appreciated his capacity to search for new explanations and to go more in depth in the understanding of topics related with measles. We even wrote a paper together [2]. Therefore, I was extremely disappointed by his very *controversially political* attitude during the case of the Edmonston-Zagreb.

I have been affiliated with ORSTOM a French research institution for a number of years. I am now working as an Associate Professor of Demography at the Harvard School of Public Health, an institution deeply concerned with misconduct in science. However, I act here as an independent researcher. I attach my CV for further information.

Please feel free to contact me if needed.

Yours sincerely,

Michel Garenne

enc.

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Mr. Peter Aaby and the case of the Edmonston-Zagreb vaccine.

Background

Regular measles vaccines (the standard or low-titer Schwarz vaccine) are usually given to children at 12-15 months [3], an age where most maternal antibodies have waned. In Africa, where maternal antibodies seem to wane somewhat faster, this age has been lowered to 9 months after a classical study conducted in Machakos, Kenya [4-5]. However, this leaves a small window of a few months between the age at which some children become susceptible (4 months) and the age at vaccination (9 months). The strategy of using high titer measles vaccines has been developed in order to overcome this problem.

First trials of the High-Titer Edmonston-Zagreb (EZ-HT) vaccine showed a good seroconversion, even among children vaccinated at 4-5 months [6-17]. No significant side effects within a few weeks after vaccination were noted by any of the investigators. The only study on clinical efficacy available in 1989 was that of Mr. Aaby in Guinea Bissau [11], which is analyzed in more depth below. In 1987-90, M. Garenne and colleagues conducted a comprehensive study of the immunogenicity, safety and clinical efficacy of the high titer vaccines for WHO, under the auspices of the Task Force for Child Survival, an organism closely related to the Centers for Disease Control in Atlanta [18-21].

In the Spring of 1989, Mr. Aaby warned Garenne and Colleagues that he found a clustering of child deaths among female recipients of the EZ-HT vaccine. However, the results were not statistically significant. The data from Senegal did not reveal any excess mortality at that time. This was the situation when M. Garenne left Senegal to take a position at Harvard, in November 1989.

In April 1990, Mr. Aaby was visiting in Boston for other reasons, and Garenne and Aaby compared their data on survival after the EZ-HT vaccine. This time, there was a trend towards excess mortality in Senegal as well as in Bissau and when pooled together, the results were statistically significant. The WHO was informed at that time, by Mr. Aaby, on behalf of both investigators.

For reasons which were originally external to the trial, a person named François Simondon was nominated in Senegal for another vaccine trial on pertussis, although Garenne was still officially the Principal Investigator of most projects in Senegal, including the measles projects, according to a formal agreement between Harvard and ORSTOM. For reasons unknown, Mr. Simondon decided to massively vaccinate the study area with the EZ-HT vaccine in May 1990, without prior authorization of the investigators and of the Ministry of Health. As a result Garenne asked for his immediate replacement, with the support of the Scientific Commission at ORSTOM. However, due to internal politics at ORSTOM, Garenne was asked to not go back to Senegal and to choose a person to replace him for the follow-up of the measles vaccines. A few days later, at the fourth meeting of the Data Monitoring and Safety Committee (DMSC) in June 1990, Garenne agreed that Mr. Aaby would replace him in Dakar, only because he knew that Aaby was very much concerned with the excess mortality after the EZ-HT vaccine and he thought that he would immediately stop the use of this vaccine. Unfortunately, this was not the case and this is where things really went wrong.

1) Vaccinations during the summer of 1990 in Senegal.

Mr. Aaby had already written to WHO, and had presented the results of the excess mortality at an informal session of the meeting or the International Epidemiological Association, in Helsinki in July 1990. However, he decided with Mr. Simondon, without informing the co-investigators and without seeking for the authorization of the Ministry of Health of Senegal, to have again a mass vaccination during the summer of 1990 with the EZ-HT vaccine. The number of persons vaccinated at that time has been kept secret. There was no rationale for this: the routine vaccination was normally done with the standard Schwarz vaccine, and he was among the few people to know that the vaccine was seriously increasing the risk of death of children. Garenne learned this only in late October 1990, a few days before the next meeting of the DMSC.

2) Relationship with the Ministry of Health of Senegal

The day before the fifth meeting of the DMSC (November 1990), Garenne sent a telefax to the group, with detailed information on the excess mortality, which was at this point significant in the Senegal trial, urging them to stop the use of the vaccine and to inform officially the Minister of Health, under the responsibility of whom the project was placed. They *refused to present* the data to the representative of the Ministry of Health and decided to continue using the vaccine. Garenne learned this the following day and directly informed the Ministry of Health that there was highly significant evidence that the vaccine was increasing the risk of death of children,

and not reducing it as normally expected with regular vaccines [22-23]. In retaliation, Mr. Aaby, Mr. Simondon and the representative of the Task Force for Child Survival decided to call WHO in Geneva, asking for a formal intervention. WHO sent its representative in Dakar to the Ministry of Health, asking to continue the use of the EZ-HT vaccine in the study area. Fortunately, the people at the Ministry of Health knew about Garenne's work: they knew his prior work in Senegal, they trusted him and refused to yield to outside pressures. The use of the EZ-HT vaccine was immediately stopped in Senegal by decision of the Minister of Health (November 1990).

After this episode, the WHO decided to gather an expert meeting in Geneva, in early March 1991. All investigators were invited, among them Mr. Aaby, Dr. Markowitz (CDC), Dr. Halsey (Johns Hopkins) and Dr. Garenne, who had conducted the largest trials. Mr. Aaby presented a confusing summary of several trials, and very few details about his own trials. Dr. Garenne was given the opportunity to present his own material, but was too quickly criticized by Dr. Markowitz, without being given an appropriate amount of time to answer to the criticisms. In other words, the meeting was very *unsatisfactory*. Garenne was under strong pressure to withdraw his findings and to *keep quite about them.* On the other hand, Dr. Halsey seemed to be very much impressed by the results and decided to stop immediately any use of the EZ-HT vaccine and to investigate the case with his own data, which was the *correct answer* to the very alarming results presented at the meeting.

Since WHO did not seem to take the findings seriously, and after extensive consultations with colleagues at Harvard and in France, Garenne and colleagues decided to publish the data as they were in the Lancet [19].

3) Reactions of Aaby and colleagues to the publication

The reaction of Mr. Aaby to this publication was surprising. A normal reaction would have been to echo the findings by showing his findings from Bissau, which were quite similar, although not significant by themselves. Instead, together with Mr. Simondon and others, they tried to manipulate the data in order to reduce the statistical significance [24]. As explained in the reply by Garenne et al. [25], it was *not statistically correct* to not use a life table analysis, since cohorts had not had the same exposure to risk of death. It was startling to see them using of the differences by sex for arguing to continue using the vaccine, and disturbing to see biostatisticians such as Mr. Knudsen, also a Danish national, signing an article like this. They had the statistical expertise and knew what they were doing.

4) Atlanta meeting

After the publication of Garenne et al., Dr. Halsey found private funds in France to conduct a follow-up of his study in Haiti, where he had used the same vaccines as the ones in Senegal (same batch). He found the same excess mortality, and reported it to WHO. The WHO decided to organize another meeting in Atlanta, in June 1992, and to have an independent expert review the data (Dr. Paul Fine in London). There was no longer any problem: Garenne was recognized to be right and the WHO stopped its recommendation to use the vaccine worldwide [26].

Note that, assuming a uniform excess of mortality as found in the Senegal study, and a total number of 250 million doses, as proposed by WHO in 1990, the strategy of using the EZ-HT vaccine could have caused the death of 18 million children. It would have been an international disaster.

5) Information of families and care of vaccinated children

Note that at this point, the families of children vaccinated with the EZ-HT vaccine have still not be officially informed. Garenne informed them indirectly, but he did not have the official authority at this point. More importantly, despite many requests and proposals made by the previous investigators (Garenne et al.), surviving children who received the EZ-HT vaccine are not given appropriate care, when they should, not speaking about financial compensations, for which provisions were made in the original protocol.

6) Aaby's view on clinical efficacy

The comprehensive Senegal study showed that not only the vaccine was extremely dangerous, but also had a relatively poor clinical efficacy: it had three times more vaccine failure than the standard vaccine given at 10 months of age, and that its immunogenicity in presence of maternal antibodies had been strongly overestimated [18, 20, 21]. The data on clinical efficacy published by Mr. Aaby and colleagues [11] suggested that the regular vaccine was hardly efficacious, whereas most investigators throughout the world find a 95% efficacy, and that the EZ-HT was almost perfect. How could this result be found? A more careful analysis of the publication reveals flaws in the study design as well as in the analysis:

- the children were not vaccinated at the same age: many were vaccinated beyond age 9 months, which made any comparison with other vaccines worthless;
- there was no serological confirmation of measles cases;
- the number of vaccine failures was very small: no conclusion could be drawn from this; the confidence intervals of protective efficacy were not computed;
- the statistical analysis is questionable: the estimates from the survival analysis announced in the statistical methods were not presented; how can one have a life table analysis with no case of failure as in the EZ group?

Comments

Mr. Aaby is an excellent politician. In fact, his background was in political anthropology. But, is this going to make him a "good scientist"?

Recently, in December 1992, Mr. Aaby has been excluded from ORSTOM, after many requests from the Scientific Commission and from the Researchers Union. However, he still continues to publish the work of Garenne and colleagues under his own name, the same work that they are publishing at the same time. This will obviously create major legal problems with the publishers: it violates the copyrights and the international contracts prepared to protect the rights of the investigators.

It is probably true that all of this would never have happened if normal administrative, scientific and ethical procedures had been respected at the level of WHO as well as at ORSTOM [27, ,28]

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* Attached to document.

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TRIAL OF HIGH-DOSE EDMONSTON-ZAGREB MEASLES VACCINE IN GUINEA-BISSAU: PROTECTIVE EFFICACY

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Summary In a randomised study of 558 children in an urban African community, the protective effect of the Edmonston-Zagreb (EZ) measles vaccine given in a dose of 40 000 plaque forming units from the age of 4 months was compared with the effects of a standard dose (6000 tissue culture infectious units) of Schwarz measles vaccine given from the age of 9 months. During two years of follow-up, all 14 clinical cases of measles occurred in the Schwarz group; 10 of the children contracted measles before vaccination and 4 after measles vaccination. Thus the EZ vaccine provided significant protection against measles both before and after the usual age of vaccination. Among the children who were exposed to measles at home, those given EZ vaccine were better protected than either unvaccinated children or those given the Schwarz vaccine.

Introduction

SEVERAL previous studies in Bandim, a district of Bissau, Guinea-Bissau, have shown that the current strategy of measles immunisation does not control measles infection adequately.[1,2] Many children contract measles before 9 months of age[1] and in many the infection develops after they have received the Schwarz attenuated measles vaccine.[2] In this community, we have therefore examined whether the Edmonston-Zagreb (EZ) vaccine administered from the age of 4 months[3,4] controls measles better than the Schwarz vaccine given from the age of 9 months.

Subjects and Methods

Background

The child health project in Bandim was started in 1978. As part of the study, local assistants make monthly visits to all houses in the 8 zones of Bandim to register pregnancies, births, and deaths. Every third month, children under three years of age are called for weighing and vaccination in their neighbourhood. The work in Bandim has been supervised by Danish medical students. Other studies in Bandim have examined the measles case fatality rate and the impact of measles vaccination.[3,4] In January, 1985, just before the initiation of the EZ study, measles immunisation coverage with Schwarz vaccine was 84% (615 of 731) for children aged 12–35 months.

Study Design

The study began in February, 1985. Children born between Aug 1, 1984, and Sept 31, 1985, who had been registered in Bandim before 4 months of age were randomised to receive the EZ vaccine (EZ group) or the Schwarz vaccine (SW group). In addition to the Extended Programme of Immunisation (EPI) vaccines (BCG, diphtheria/pertussis/tetanus, and poliomyelitis) from the age of 4 months the EZ group received EZ measles vaccine and the SW group received an inactivated poliomyelitis vaccine (IPV) (kindly donated by Institut Merieux). From the age of 9 months, children in the EZ group received IPV and those in the SW group were given the Schwarz measles vaccine. Children were called for vaccination every month until they received these vaccines. If not vaccinated before age 9 months, children of both groups then received only one vaccine, this being either the EZ or the Schwarz measles vaccine. Blood samples taken by finger prick were collected before the first (at age 4 months or over) and second vaccinations (at 9 months or over) and again at 18 months.

We followed the vaccinated children to assess the protection conferred against measles and to measure their serological responses. Measles vaccinations were noted on the health card, and other health centres were asked not to revaccinate the child against measles. Children vaccinated elsewhere against measles were excluded from the study. Since we could not guarantee that children in the control (SW) group would be vaccinated against measles if they moved out of the area, a double blind design was judged impossible.

Before the start and midway through the study (March, 1986), at meetings in each of the 8 zones of Bandim, the study was explained as a trial of two new and possibly better vaccines against measles and poliomyelitis. Before the first vaccination at 4 months, consent was obtained from the child's mother or guardian. Only one mother refused to have her child vaccinated, and 5 refused the collection of blood samples. The study was approved by Guinea-Bissau's Ministry of Health and by The Gambia Government/Medical Research Council ethical committee.

Vaccines and Serology

Children in the EZ group received a dose of 40 000 plaque forming units (pfu) of the EZ vaccine (lot 529)[4] and the children in the control group received a standard dose of the attenuated Schwarz measles vaccine (6000 tissue culture infectious units

ATTACK RATE AMONG CHILDREN EXPOSED TO MEASLES ACCORDING TO VACCINATION STATUS AND AGE: BANDIM 1985–87

—	No of cases/children exposed	
	In own household	In another household in same house
Unvaccinated (≥6 mo)	4/4 (100%)	3/5 (60%)
EZ (≥6 mo)	0/6 (0%)	0/14 (0%)
SW (≥ 9 mo)	2/4 (50%)	0/7 (0%)

[$TCID_{50}$]). Both vaccines were given subcutaneously. The potency of the measles vaccines stored in Bissau was assessed every 4–5 months and serum samples were analysed for haemagglutination inhibition (HAI) measles antibodies, both at the Medical Research Council laboratories in The Gambia.[7] Antibody responses after vaccination, which were satisfactory in both groups, will be reported elsewhere.

Measles Surveillance

Children aged 3–18 months were visited once every second week to obtain information on morbidity. Cases of measles were also identified at the local health centre. A large proportion of measles cases were found by systematic follow-up after exposure to non-study cases that had been already identified. The students visited at home all cases of suspected measles identified by the field assistants. Care was taken not to see the vaccination card and not to ask about the immunisation status of the child until a clinical diagnosis had been reached. Definite cases of measles only, according to the clinical criteria used in our study in The Gambia,[7] were accepted for analysis. 6 of the 20 such cases in study children had not received the EZ or IPV vaccines when they contracted measles and have therefore not been included in the analysis.

Information was also collected about exposure to measles at home. Since in Bandim there are often several families living in the same house,[2,5] a distinction was made between exposure within the child's own household and exposure from a child in another household in the same house.

Statistical Methods

The whereabouts of the children in the study was under regular surveillance. This report is based on a final assessment early in June, 1987. The cumulative frequency of measles and survival have been estimated by survival analysis methods. Since all children were not vaccinated at the same time and many children moved during the study, duration of observation has been taken into consideration. In the analysis of measles morbidity and general mortality, observations were censored if the children moved or had been excluded for other reasons. We assumed that the children would have mounted an immune response by three weeks after vaccination—children were therefore assigned to groups from that date.

Results

Study Population and Vaccination Coverage

Among the 558 children in the study, 84% (234 in the EZ group and 235 in the SW group) received a vaccine within the auspices of the project; 26 children moved; 29 were vaccinated elsewhere; 8 were excluded for other reasons; 13 remained unvaccinated; and 13 died before being vaccinated. The distribution of those vaccinated and those excluded was closely similar in the two groups.* In the EZ group 25% had been vaccinated against measles by 4·8 months of age, 50% by 5·9 months, and 75% by 9·7 months. In the control group, these coverages were attained at 9·6 months, 10·9 months, and 13·0 months, respectively. The figures have been adjusted for the number of children who died or moved.

*Data available from authors on request.

Measles Before the Age of Measles Immunisation

All 10 children clinically diagnosed as having measles before vaccination were in the SW group and they had an HAI titre of 800 mIU/ml or more in blood samples collected at various intervals after diagnosis. 9 of the 10 cases occurred before 9 months of age, which is when the Schwarz measles vaccine is usually given. The cumulative frequency of measles in the SW group before vaccination against measles was 7·6%, which was significantly higher than the zero incidence in the EZ group ($p < 0·001$; log rank test).

Measles Infection after Measles Vaccination

Measles developed in 4 children in the SW group after they had received measles vaccine. None of the children in the EZ group had clinical measles before or after 9 months of age. 3 of the 4 cases of post-vaccination measles in the SW group had blood samples taken within a month of the clinical diagnosis. All 3 had antibody titres of 1600 mIU/ml or more. After the second vaccination the incidence of clinical measles was significantly higher in the SW group than in the EZ group ($p < 0·037$; log rank test).

Protection after Exposure

The table shows the attack rate among children exposed to a case of clinical measles in their own house. The attack rate among EZ-vaccinated children (zero) was significantly lower than that among unvaccinated children exposed either in their own household ($p = 0·005$; one-tailed Fisher's exact test) or to a child in a neighbouring household ($p = 0·01$; Fisher's exact test). The EZ group seemed to be better protected after exposure in their own household than did the SW group ($p = 0·13$, Fisher's exact test).

Mortality

There were no deaths among the 14 definite measles cases. However, another child given Schwarz vaccine who was not seen during his illness was said to have died of measles. The cumulative overall mortality from any cause between 4 and 24 months of age (Kaplan-Meier estimates) was 6·3% in the EZ group and 9·5% in the SW group.

Discussion

The main aim of the study was to evaluate whether the EZ vaccine given from 4 months onwards provided protection against measles before 9 months of age when children are normally immunised against this infection in developing countries. The data strongly suggest that it does. Furthermore, after exposure to measles at home the EZ vaccine, even when given at this early age, provided significant protection. Since many of the infants were not vaccinated on time at 4 and 9 months, the results of this study also show that significant protection against measles was conferred despite the delay in vaccination that occurs in most developing countries.

As seen before in Bandim,[2] protection against measles after immunisation with the Schwarz vaccine was not satisfactory since measles developed in 4 of the vaccinated children. Though further studies are needed, our results suggest that the EZ vaccine given in infancy may also provide better protection after 9 months of age than the Schwarz vaccine. The impact of measles in the Bissau urban area can be judged by the finding that 7·6% of the children in the SW group contracted measles before the age of

vaccination, in spite of high vaccination coverage both before and during the project. Nonetheless, the study probably underestimates the full effect of EZ immunisation since the project increased the overall efficiency of measles vaccination as well as immunising half the children in Bandim at an early age. These factors probably raised herd immunity, thereby reducing exposure to measles. The earlier study in Bandim showed increased herd immunity to be associated with a decline in measles mortality.[6] The only death from measles reported in the present study was a child who had received the Schwarz measles vaccine. By contrast, a total of 10 measles deaths occurred in a similar cohort of children in a neighbouring district in which the measles immunisation programme with the Schwarz vaccine from age 9 months had been implemented (unpublished). On the assumption that the frequency and case fatality rate was the same in the neighbouring district, we would have expected 12 deaths in the study cohort. Therefore, because of the study design, the case fatality rate was probably decreased in both vaccination groups; thus the non-significant difference in mortality shown between the groups may be an underestimate of the true difference.

The study in Bandim was designed to test the effect of EZ vaccination in a hyperendemic area where measles has a high acute and a high delayed mortality rate.[8] However, the high rates were not seen here, probably because earlier immunisation with the EZ vaccine improved coverage. Epidemiological studies are needed to establish the immediate effect of measles vaccine on child mortality. The long-term effect should also be examined since measles infection is associated with an excess delayed mortality.[8] However, it now seems justified to use the EZ vaccine at an early age where risk of infection is high and where there are no other means of protection; for example, in hospitals, refugee camps, and other institutions as well as during campaigns to control major outbreaks.

In a general immunisation programme, it is best to use one type of measles vaccine and one schedule for all circumstances. Therefore studies of the EZ vaccine are needed where there is a low risk of measles transmission. The protective effect of EZ measles vaccine should prove to be at least as strong and as longlasting as that of the Schwarz vaccine before a general shift to the EZ vaccine is recommended. The duration and level of antibody responses in the absence of boosting due to exposure to cases will also need investigation. Furthermore, the results of some studies of Schwarz measles vaccine have shown increased frequencies of fever and diarrhoea after immunisation.[9] Since the EZ vaccine is apparently more effective than the Schwarz vaccine,[3,4] it could have side-effects that would be unacceptable in an area with little risk of early measles. Further epidemiological studies of the two vaccines are therefore needed.

The Bandim project has been organised jointly by the Ministry of Health, Guinea-Bissau, the International Medical Co-operation Committee (Denmark), and Danchurchaid. The vaccine study was supported jointly by the Danish Council for Development Research, the Danish Medical Research Council, and the Danish Social Science Research Council. We thank Dr P. Medina, Secretary General of the Ministry of Health, for his interest in our work, and Mr Eugenio Pereira, Mr Calilo Djalo, Mrs Maria Isabel Camala, Mrs Nina Martins, Mrs Candida Nanque, Mrs Carolina Monteiro, and Mrs Natividade Monteiro for assistance in the collection of data.

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References at foot of next column

TRIAL OF HIGH-DOSE EDMONSTON-ZAGREB MEASLES VACCINE IN THE GAMBIA: ANTIBODY RESPONSE AND SIDE-EFFECTS

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Summary In a randomised trial, infants living in a large village in The Gambia were immunised either at 4 months of age with 40 000 plaque forming units (PFU) of the Edmonston-Zabreb (EZ) measles vaccine or at the usual age of 9 months with 6000 $TCID_{50}$ of a conventional Schwarz measles vaccine. Measles developed in 2 of 119 children who received the EZ vaccine, in 1 before and in the other after 9 months of age. In the Schwarz group measles developed in 7 of 120 children—in 5 before and in 2 after 9 months of age. Serological responses measured at 5 months after vaccination and at 18 months of age were satisfactory in both groups although in the Schwarz group levels were on average 2-fold higher than in the EZ group. The frequencies of fever, cough, vomiting, and diarrhoea were no higher in the EZ vaccinees in the 3 weeks following vaccination than in age-matched non-immunised controls. Long-term morbidity as assessed by clinic attendances and weight at 18 months of age was much the same in the two groups. The EZ measles vaccine is thus safe and clinically and serologically effective when used in a high dose to immunise young Gambian infants.

Introduction

WE and others have argued that the present policy of immunisation of children at 9 months of age to control measles is failing in urban areas of the developing world because of the constant influx of cases and susceptible children from other areas.[1,2] A substantial proportion of infants living in urban areas contract severe measles before 9 months of age,[3-5] either in crowded slums or at hospitals and clinics where infectious children come in contact with unimmunised infants.[6] The measles case fatality rate can be very high among such infants. In Bissau 54% of affected infants, who were secondary cases, died.[7] The delayed effect

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Measles control

The severity of measles in developing countries is well recognized. This disease is also an important cause of morbidity in industrialized countries. Unfortunately, in some of the latter countries, health workers and the general public persist in the belief that natural measles disease is preferable to immunization. Such beliefs should be dispelled, and the importance of measles immunization in all countries reinforced.

Measles before the age of 9 months continues to be a major cause of morbidity and mortality in a number of developing countries. At the same time, measles immunization has altered the epidemiological patterns of disease so that an increasing proportion of cases occurs in older age groups. The introduction of measles vaccine strains which are effective before the age of 9 months offers a means to address the first problem. A variety of control measures will be helpful in addressing the second, among them the identification and immunization of susceptible populations.

Measles immunization before 9 months of age

Sufficient data are now available to recommend that "high titre" Edmonston-Zagreb (EZ) measles vaccine be administered at 6 months of age or as soon as possible thereafter in countries in which measles before the age of 9 months is a significant cause of death. "High titre" is defined as 5.0 $\log_{10}$ infectious units when the titre has been measured in parallel with the WHO International Reference Reagent for measles vaccine and corrected appropriately. It is anticipated that increasing supplies of this vaccine will become available for use in developing countries over the next 1 to 2 years, in part through UNICEF. High titre EZ vaccine should preferentially be offered to those countries with the most severe measles problems in young infants.

Before EZ strains produced elsewhere are accepted for use at 6 months of age, they should be shown to be comparable in this age group with respect to reactogenicity and immunogenicity to the strain produced by the Institute of Immunology in Zagreb. Most studies have involved countries in Africa and the Americas. Further studies are encouraged in other areas of the world.

In countries where high titre EZ vaccine will be used, HIV-infected infants (symptomatic as well as asymptomatic) should also receive it.

Evaluation of the impact on overall measles incidence and mortality following the introduction of high titre EZ vaccine should receive high priority. Programmes should be prepared to investigate apparent vaccine failures and adverse events in recipients of this vaccine.

In countries where measles before the age of 9 months is not a significant problem or high titre EZ vaccine is not available, currently recommended schedules of immunization should be retained using any strain of measles vaccine meeting WHO Requirements. These vaccines should have a minimum potency of 4.0 $\log_{10}$ infectious units. This recommendation does not preclude further research on immunization schedules to improve measles control using currently available vaccines.

Measles control in older children

Some countries with moderately high coverage levels have reported outbreaks in older children or even young adults. This is an expected consequence of immunization programmes whose target age group has been children under 2 years of age (under 1 year of age in most developing countries) in which 100% uptake has not been reached. Another expected result of high coverage levels is an increase in the proportion of cases which occur among children previously immunized (vaccine failures). Neither occurrence necessarily indicates programme failure. Even in countries currently reporting increased numbers of cases in older children, the present immunization programme has succeeded in reducing overall incidence and mortality rates.

Lutte contre la rougeole

Nul ne songe à nier la gravité de la rougeole dans les pays en développement. Cette maladie est également une cause importante de morbidité dans les pays industrialisés. Malheureusement, dans certains de ceux-ci, les agents de santé et le public lui-même persistent à croire que la maladie naturelle est préférable à la vaccination. Il faut dissiper ces idées fausses et insister, dans tous les pays, sur l'importance de la vaccination contre la rougeole.

La rougeole demeure la cause principale de morbidité et de mortalité avant l'âge de 9 mois dans plusieurs pays en développement. En même temps, la vaccination antirougeoleuse a modifié le tableau épidémiologique de la maladie de sorte qu'une proportion croissante de cas surviennent dans les groupes plus âgés. L'introduction de souches de vaccin antirougeoleux efficaces avant l'âge de 9 mois serait un moyen de résoudre le premier problème. Plusieurs mesures de lutte contribueraient à résoudre le second, notamment le recensement et la vaccination des populations vulnérables.

Vaccination antirougeoleuse avant l'âge de 9 mois

On dispose désormais de données suffisantes pour recommander d'administrer le vaccin antirougeoleux Edmonston-Zagreb (EZ) à « titre élevé » à l'âge de 6 mois ou dès que possible après cet âge dans les pays où la rougeole est une importante cause de décès avant l'âge de 9 mois. On entend par « titre élevé » 5,0 $\log_{10}$ unités infectieuses lorsque le titre a été mesuré parallèlement au réactif international de référence OMS pour le vaccin antirougeoleux et dûment corrigé. Des stocks de plus en plus importants de ce vaccin devraient être mis à la disposition des pays en développement d'ici 1 ou 2 ans, par l'intermédiaire de l'UNICEF notamment. Le vaccin EZ à titre élevé devrait être proposé de préférence aux pays confrontés aux problèmes les plus graves de rougeole chez les jeunes enfants.

Avant que des souches d'EZ produites ailleurs puissent être administrées à l'âge de 6 mois, elles devront avoir fait la preuve d'une réactogénicité et d'une immunogénicité comparables dans ce groupe d'âge à celles des souches produites par l'Institut d'Immunologie de Zagreb. La plupart des études effectuées jusqu'ici ont porté sur des pays d'Afrique et des Amériques. Des études devraient être effectuées également dans d'autres régions du monde.

Dans les pays où le vaccin EZ à titre élevé sera utilisé, les nourrissons infectés par le VIH (symptomatiques ou asymptomatiques) devront également être vaccinés.

L'évaluation des effets sur l'incidence globale de la rougeole et sur la mortalité par rougeole de l'introduction du vaccin EZ à titre élevé devra recevoir la priorité. Des programmes devront être mis sur pied afin d'étudier les échecs apparents de la vaccination et les manifestations indésirables chez les personnes vaccinées.

Dans les pays où la rougeole ne constitue pas un problème important avant l'âge de 9 mois et dans les pays où le vaccin EZ à titre élevé n'est pas disponible, les schémas de vaccination actuellement recommandés devront être maintenus en utilisant toutes les souches de vaccin antirougeoleux répondant aux normes de l'OMS. Ces vaccins devront avoir une activité minimale de 4,0 $\log_{10}$ unités infectieuses. Cette recommandation n'exclut pas de nouvelles recherches sur les schémas de vaccination destinés à améliorer la lutte antirougeoleuse au moyen des vaccins actuellement disponibles.

Lutte contre la rougeole chez les enfants plus âgés

Certains pays où les taux de couverture sont moyennement élevés ont signalé des flambées épidémiques chez des enfants plus âgés ou même chez de jeunes adultes, ce qui était une conséquence attendue des programmes de vaccination dont le groupe d'âge cible était les enfants de moins de 2 ans (et de moins d'un an dans la plupart des pays en développement) et qui n'ont pas atteint la barre des 100%. L'augmentation de la proportion de cas survenant chez des enfants déjà vaccinés (échecs de la vaccination) est également un résultat prévisible des niveaux de couverture élevés. Aucun des 2 scénarios ne signifie nécessairement que le programme a échoué. Même dans les pays qui notifient actuellement un nombre plus élevé de cas chez des enfants plus âgés, le programme de vaccination en cours a réussi à réduire les taux d'incidence et de mortalité globaux.

Child mortality after high-titre measles vaccines: prospective study in Senegal

MICHEL GARENNE ODILE LEROY JEAN-PIERRE BEAU
IBRAHIMA SENE

The use of Edmonston-Zagreb high-titre (EZ-HT) vaccine at age 6 months has been recommended for countries in which measles before the age of 9 months is a substantial cause of death, but little is known about the long-term effects of high-titre live measles vaccines given early in life. In a randomised vaccine trial in a rural area of Senegal, children were randomly assigned at birth to three vaccine groups: EZ-HT at 5 months (n=336); Schwarz high-titre (SW-HT) at 5 months (n=321); and placebo at 5 months followed by standard low-titre Schwarz vaccine at 10 months (standard: n=358). All children were prospectively followed for 24–39 months in a well-established demographic surveillance system. Child mortality after immunisation was significantly higher in the two groups which received high-titre vaccines than in the group given the standard vaccine. The relative risk of death was 1·80 (95% confidence interval [CI] 1·18–2·74; p=0·007) in the EZ-HT group and 1·51 (0·97–2·34; p=0·07) in the SW-HT group compared with the standard group. The three vaccine groups were comparable as regards various social, family, and health characteristics, and there was no difference in mortality between children who received the standard vaccine and those who were eligible for the trial but did not take part for various reasons. The higher risk of death in the two high-titre vaccine groups remained significant in multivariate analyses. These findings suggest a need to reconsider the use of high-titre measles vaccines early in life in less developed countries.

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Introduction

Measles is a leading cause of child mortality and morbidity in less developed countries.[1,2] It is rare in infants under 4 months old owing to the protection afforded by transplacentally acquired maternal antibodies. In less developed countries the majority of infants become susceptible shortly after the age of 4 months. Measles case-fatality rates are highest at younger ages, especially between 4 and 12 months.[3]

In developed countries low-titre, live, attenuated measles vaccines are safe, immunogenic, and effective when given in the second year of life. In less developed countries, the profile of maternal antibodies differs somewhat,[4,5] and the usually recommended age for vaccination is 9 months.[6] However, this strategy leaves open a window of high risk of death from measles between the ages of 4 and 9 months.

The live Edmonston-Zagreb (EZ) vaccine[7] produces a better immunological response than standard vaccines even when given as early as 4 months of age.[8–10] Two possible explanations for the better performance of this vaccine are the strain and the titre, often 10–100 times higher than that of standard vaccines. Several vaccine trials have compared the immunological responses and adverse reactions after Edmonston-Zagreb vaccines of low, medium, and high titres with those of other measles vaccines of the same titres in children younger than 9 months.[11–16]

The use of Edmonston-Zagreb high-titre vaccine has been recommended "at age 6 months in countries in which measles before the age of 9 months is a significant cause of death".[17] However, little is known about the long-term effects of high-titre live measles vaccines given early in life.

Subjects and methods

The study area was located near Niakhar, in the department of Fatick in central Senegal. It included 30 villages, inhabited by about 25 000 people of Sereer origin. A comprehensive demographic surveillance system based on yearly censuses and weekly visits to households to register vital events was in progress before the study started and has been maintained since.

A randomised vaccine trial of the efficacy, safety, and immunogenicity of two high-titre live measles vaccines, Edmonston-Zagreb (EZ-HT) and Schwarz (SW-HT), was carried out in 1987–89.[18] Although the primary objective of the study was clinical efficacy, a mortality surveillance was set up both to check safety and to evaluate the vaccination strategy. In addition to the routine surveillance system, independent checks on child deaths were made in October, 1990, and February, 1991. More details on the study area and on the data collection system can be found elsewhere.[19–21]

The study was approved by the Ministere de la Santé Publique, Dakar, Senegal; by ORSTOM authorities (Institut Français de Recherche pour le Développement en Coopération, Paris); and by the ethical committee of the British Medical Research Council, Fajarah, The Gambia. Oral informed consent was obtained from the parents of the participants; 20% of parents refused to allow their children to participate. During the 3 years of the project, vaccination was available to everyone, and free drugs and medical services were provided to all children and adults of the study population. As a consequence, overall mortality was substantially lower than during the 3 preceding years (1984–86).

Three measles vaccines were supplied by the manufacturers: EZ-HT (batch 81/3; titre 5·4 $\log_{10}$ plaque-forming units [pfu]; Institute of Immunology, Zagreb, Yugoslavia); SW-HT (batch 0980; titre 5·4 $\log_{10}$ pfu; Institut Mérieux, Lyon, France), and a Schwarz standard vaccine (titre 3·7 $\log_{10}$ pfu, Institut Mérieux). A placebo produced by Institut Mérieux as a standard vaccine preparation without the active particles was also used. The titre of the vaccines monitored throughout the project remained stable.

The study was carried out within the framework of the National Expanded Programme for Immunisation of Senegal. Children were vaccinated at ages 3, 5, and 10 months. At each session they received an injection of diphtheria, pertussis, tetanus vaccine and inactivated poliomyelitis vaccine; in addition they received BCG at 3 months and yellow fever vaccine at 10 months. High-titre measles vaccines were given only at 5 months (mean 22 [SD 2] weeks), and the standard measles vaccine was given at 10 months (after placebo at 5 months). By age 10 months all children who came to the three

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TABLE I--ENROLMENT, DURATION OF FOLLOW-UP, LOSS TO FOLLOW-UP, AND MORTALITY IN STUDY POPULATION

	Trial participants			Non-participants
	EZ-HT	SW-HT	Standard	
No assigned at birth	526	527	539	(−189)*
No enrolled at 5 mo	336	321	358	388
Person-months of follow-up	9522	9208	10 416	10 551
Mean (SD) duration of follow-up (mo)	28·3 (9·7)	28·6 (9·9)	29·1 (9·2)	27·2 (9·8)
No of non-accidental deaths during follow-up	50	42	32	35
No lost to follow-up	22	15	23	43

*Deaths and outmigrants before 5 mo.

TABLE II—SURVIVAL AFTER 5 mo BY VACCINE GROUP

Months of follow-up after vaccination (age)	Survival (SE) per 1000 survivors at 5 mo			
	Trial participants			Non-participants
	EZ-HT	SW-HT	Standard	
0 (5)	1000·0	1000·0	1000·0	1000·0
6 (11)	969·9 (9·4)	946·8 (12·6)	963·5 (9·9)	976·2 (7·9)
12 (17)	932·9 (13·8)	927·8 (14·5)	943·4 (12·3)	943·6 (12·0)
18 (23)	904·7 (16·3)†	902·0 (16·7)†	937·6 (12·9)	935·2 (12·8)
24 (29)	876·3 (18·3)*†	889·0 (17·7)	922·8 (14·3)	912·2 (14·8)
30 (35)	859·8 (19·4)*†	870·4 (19·2)†	910·6 (15·3)	901·2 (16·0)
36 (41)	831·8 (22·5)*†	858·6 (20·7)†	906·3 (15·9)	901·2 (16·0)

Significance of difference from standard group. *p < 0·05. †p < 0·10 (both two-tailed).

sessions were completely vaccinated. Children who missed a session could come later to complete their vaccination series.

At birth, children were randomly assigned by means of a computer random generator to one of three vaccine groups: EZ-HT vaccine at 5 months; SW-HT vaccine at 5 months; or placebo at 5 months and standard measles vaccine at 10 months (standard schedule). Some children born during the study period did not take part in the study because the parents refused, the 5 months vaccination was missed, or vaccination was contraindicated. These non-participants were eligible for regular vaccinations, including measles at 9–10 months, and were included in the surveillance for survival in the same way as the participants.

Criteria for inclusion in the study were: birth to a resident mother between Feb 1, 1987, and May 31, 1988; clinic attendance at 5 months for vaccination and parental agreement to participation; absence of any contraindication to measles vaccination (evolving infectious disease, history of convulsion, previous measles infection, or previous measles vaccination); and no revaccination with another measles vaccine between 5 and 10 months of age.

Investigators and field workers were unaware which type of measles vaccine had been given until the code was broken in June, 1989. Furthermore, the code was not revealed to the field workers who routinely recorded deaths or to the two physicians who reviewed the verbal autopsy questionnaires until the review was completed. Physicians and nurses who were treating patients in the local dispensaries knew nothing about vaccine assignment, because there was no mention of the type of measles vaccine on the health cards or on the dispensary register.

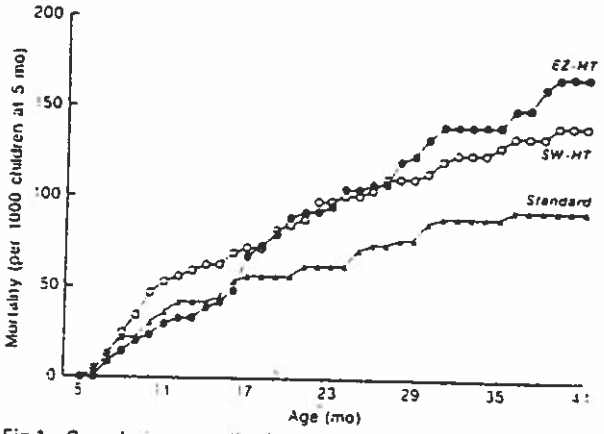

Fig 1—Cumulative mortality from 5 to 41 months, according to vaccine group.

Survival of children was analysed in a monthly life-table (Kaplan-Meier product limit estimates). Multivariate analyses were carried out with linear logistic regressions on age-specific death rates. Proportional hazard models were also tried, but they did not fit the situation well, because of the very strong seasonal pattern of mortality among children. Standard testing procedures were applied, and two-tailed tests were used.

Results

1015 children were included in the vaccine trial: 336 in the EZ-HT group, 321 in the SW-HT group, and 358 in the standard group; 388 children assigned at birth did not take part in the study (table I). By October, 1990, there was an excess of non-accidental deaths in both groups vaccinated with the high-titre vaccines (table I). There was only 1 accidental death—among the non-participants.

In a life-table analysis, children who received the EZ-HT vaccine at 5 months had significantly higher mortality at 41 months than children in the standard group (table II, fig 1): the relative risk of death was 1·80 (95% confidence interval [CI] 1·18–2·74; p = 0·007). Children who received the SW-HT vaccine at 5 months also had a higher mortality than children in the standard group (relative risk 1·51 [95% CI 0·97–2·34]; p = 0·07). There was no significant difference

TABLE III—COMPARISON OF VACCINE GROUPS ACCORDING TO CHARACTERISTICS OF FAMILY AND INFANT AT 5 mo

	Mean (SD)			
	Trial participants			Non-participants
	EZ-HT	SW-HT	Standard	
Age of mother (yr)	27·7 (6·5)	28·1 (7·8)	28·0 (7·3)	28·6 (7·0)
% of literate mothers	3·7 (1·2)	3·8 (1·2)	3·2 (1·0)	3·6 (1·1)
No of residents in compound	23 (14)	23 (18)	23 (18)	23 (19)
Distance to dispensary (km)	3·8 (2·3)	3·9 (2·5)	3·9 (2·6)	4·1 (2·3)
Mortality of older siblings of same mother (per 1000 livebirths)	313 (25)	309 (26)	313 (25)	297 (23)
% outmigrant children	6·5 (1·3)	4·7 (1·2)	3·9 (1·3)	11·1 (1·6)
Death rate in compound of residence (per 1000)	17·6 (20)	17·9 (25)	17·3 (23)	20·0 (25)
Infant at 5 mo				
Age at vaccination (wk)	21·6 (2·1)	21·6 (2·0)	21·5 (1·9)*	
Weight (kg)	6·45 (1·00)	6·46 (1·00)	6·40 (0·90)	
Height (cm)	63·0 (26·0)	63·3 (26·0)	63·2 (24·0)	
Left upper mid-arm circumference (mm)	132 (13)	132 (13)	132 (13)	

*With placebo vaccine; standard Schwarz vaccine given at 10 mo.

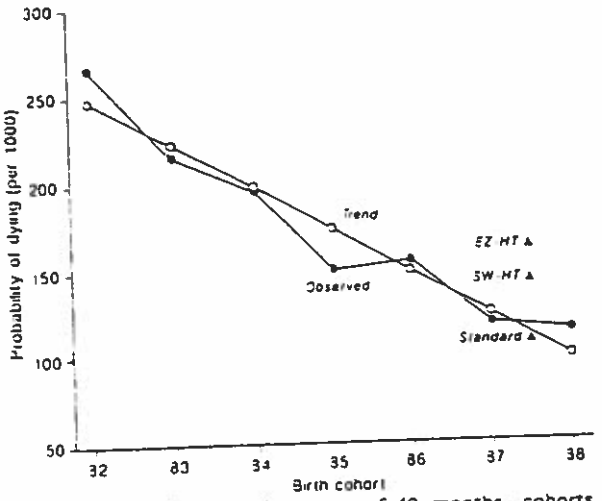

Fig 2—Trends in mortality at age 5–40 months, cohorts 1982–88.

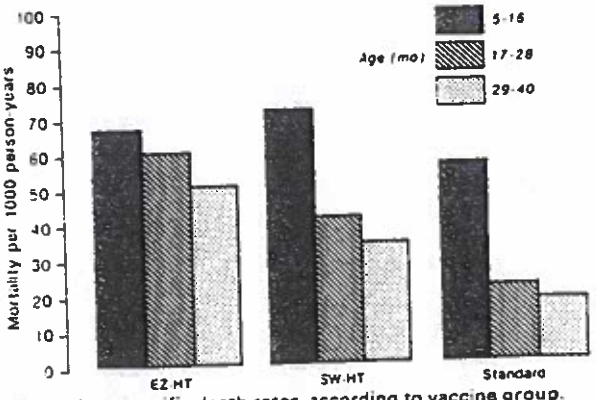

Fig 3—Age-specific death rates, according to vaccine group.

in cumulative mortality at 41 months between the EZ-HT and SW-HT groups (168 *vs* 141 per 1000 between 5 and 41 months) or between the standard group and the non-participant group (93 *vs* 99 per 1000).

Analyses to determine whether the vaccine groups were comparable showed that they were similar for the variables listed in table III and mortality in the randomised groups from birth to 4 months. Children in the non-participant group were also from families with a similar background. Children in the three vaccine groups were similar at 5 months in average age at vaccination, weight, height, and arm circumference (table III).

To exclude the possibility that mortality in the standard vaccine group was abnormally low, the mortality rates in the vaccine groups were compared with the rate predicted from trends in mortality since 1982 (fig 2). Extension of the trends predicts a mortality of 91 per 1000 during the study period compared with the 93 per 1000 found in the standard group.

There was no significant difference within the study group in mortality by sex: the relative risk of death (female/male) was 1·20 in the EZ-HT group ($p = 0·497$), 1·14 in the SW-HT group ($p = 0·636$), 0·64 in the standard group ($p = 0·195$), and 1·16 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.

The effect of various correlates of mortality was investigated in linear logistic regressions, which allowed a better fit of the mortality pattern with strong seasonal variation and changes with age. Periods of exposure to mortality were divided into 4-month periods corresponding to the three 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 effects of the vaccines (relative risks) remained stable with control for all other variables that were available: age, sex, age at vaccination, season, season of vaccination, measles antibody titre at 5 months, and seroconversion between 5 and 10 months of age. Odds ratios associated with high-titre vaccines remained stable in the various multivariate analyses. In the final model, the odds ratios were 1·71 ($p = 0·019$) for EZ-HT and 1·49 ($p = 0·093$) for SW-HT (table IV). The coefficient of the rainy season was always high and significant and was greater in the two HT-vaccinated groups than in the standard group. Sex, titre of antibodies at 5 months, and seroconversion between 5 and 10 months of age were not significant variables in any group.

The same multivariate analyses by vaccine group showed that the coefficient of age in the EZ-HT group was close to zero: this finding shows that mortality remained consistently high in the second and third year after the EZ-HT vaccine, whereas in other groups death rates declined substantially with age as would be expected (fig 3). The lack of decline in mortality rates with age of children is a cause for concern.

The finding of excess mortality in the vaccinated groups was possible for two reasons: the incidence of measles was low during the study period (69 cases among the study children), otherwise there might have been measles deaths between 5 and 10 months in the standard group (who received the placebo at 5 months); and 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.

Only verbal autopsies were available to evaluate causes of death. Few children died in hospital. Most of the deaths were apparently from common diseases of childhood (table V). In the EZ-HT vaccine group 9 deaths were attributed to kwashiorkor and 5 to viral diseases other than measles. 5 of 6 dysentery deaths and 8 of 10 deaths due to acute respiratory infections were in the SW-HT group. The only accidental

TABLE IV—RESULTS OF MULTIVARIATE LOGIT ANALYSIS OF DEATH RATES

Covariate	Estimate (SE)	t test	p (two-tailed)
Model 1: all combined			
Vaccine: EZ-HT	0·5382 (0·2295)	2·34·9	0·0192*
Vaccine: SW-HT	0·3994 (0·2376)	1·6800	0·0932†
Model 2: by vaccine			
Age (EZ-HT)	−0·0071 (0·0135)	−0·5287	0·5974 (NS)
Age (SW-HT)	−0·0383 (0·0166)	−2·3120	0·0214*
Age (standard)	−0·0405 (0·0190)	−2·1307	0·0338*

Standard = reference.
*$p < 0·05$. †$p < 0·10$.

TABLE V—DISTRIBUTION OF DEATHS BY REPORTED CAUSE

Probable cause	Trial participants			Non-participants
	EZ-HT	SW-HT	Standard	
Diarrhoea, dysentery	24	21	17	21
Malaria	8	6	7	2
Malnutrition	10	4	5	4
Acute respiratory	0	8	0	2
Measles	0	0	0	1
Other infectious diseases	5	1	1	3
Accident	0	0	0	1
Unknown	3	2	2	2
Total	50	42	32	36

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.

Discussion

The demographic surveillance system developed in Niakhar is an unusually reliable system of data collection that is unique in tropical Africa. Weekly visits to households ensure accuracy of dates of births and deaths, and yearly updating of maternity histories and full-scale census taking by roll call from computer printouts guarantees the complete recording of vital events.

Differences in mortality among the groups were tested by eight statistical procedures (life-table, death rate, probability of death, age-standardised death rates, linear logistic regression, proportional hazards, log-rank tests, and simulations). They showed a consistent level of significance of mortality differences from the standard vaccine group ($p = 0.007$ to 0·024 for the EZ-HT group and $p = 0.041$ to 0·102 for the SW-HT group).

The consistency of the data, both in the groups vaccinated with high-titre vaccines and in the groups not given the high-titre 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 group was very low ($p < 0.0001$).

Since the goal of the study was to compare two strategies—vaccination at 5 months with high-titre vaccines versus vaccination at 10 months with a standard vaccine—survival after 10 months was also investigated. The two groups receiving the high-titre vaccines at 5 months had a similar excess mortality between 10 and 41 months over that in the standard vaccine group. Relative risks of deaths were 2·50 (95% CI 1·52–4·13; $p = 0.0004$) in the EZ-HT group and 1·73 (1·00–2·98; $p = 0.56$) in the SW-HT group.

The fact that children who migrated out of the study area were removed (censored) at the time of their move did not affect the results. An attempt to find those who died after outmigration showed that their inclusion would not have affected the results. There were 11 deaths—3 in the EZ-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.

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

The prevalence of HIV infection was low in the study area: only 2 of 401 project children sampled at age 3 months had HIV antibodies, and neither died. A seroprevalence of 0·5% was found among pregnant mothers of the study area. Thus, HIV infections could not have had a role in this study.

Since the high-titre 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. Furthermore, both vaccines had high immunogenicity, high efficiency, and only mild side-effects.[14]

It is beyond the scope of this paper to document biological plausibility. However, previous studies suggest that interaction of live measles vaccines with child immunity is possible. Short-term effects of live virus vaccines on child immunity have been observed.[22–26] In a study in the Niakhar area, a low response to yellow fever vaccination was found when it was given in association with the EZ-HT vaccine (personal communication, Dr J-P. Gonzalès). The wild measles virus has severe adverse short-term effects on immunity and nutritional status of children, in particular on nitrogen metabolism[27] and vitamin A.[28] In addition, the wild measles virus can have long-term effects, such as subacute sclerosing panencephalitis.[29]

There was no reason to suspect excess mortality after measles vaccines in the study area: earlier findings there and in a nearby area[30] showed that survival was better among children vaccinated with a standard measles vaccine, even when it was given before 6 months of age. This finding suggests that the high titre may be the main cause of 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. This effect is partly due to the sample size, because the number of deaths was too small before that time for a significant relative risk to show, and partly because most excess deaths were concentrated in the high mortality age group, which lies from 18 to 41 months in this population.

A quick cost-benefit analysis suggests that the strategy of using high-titre vaccines early in life is not worth while: between 48 (SW-HT) and 75 deaths (EZ-HT) per 1000 children reaching age 5 months seemed to be associated with the use of high-titre vaccines. This number exceeds by far the reduction in mortality expected from the early vaccination, estimated to be 4 per 1000 children reaching age 5 months (incidence of 42/1000 between 5 and 10 months multiplied by case-fatality rate of 10%).

If these findings are confirmed in other settings, other strategies to reduce mortality from early measles should be developed. The low titre AIK-C vaccine seemed to produce a good immunogenic response at 6 months among Togolese children.[15] In Niakhar, the standard measles vaccines were safe, even when given at 4–6 months, and may well prevent deaths from measles. Since most complications of measles occur during the second and third weeks after onset, early treatment is possible. A systematic treatment of complications in the Niakhar study reduced the case-fatality rate among children below 3 years of age by 78%.

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Intestinal permeability, mucosal injury, and growth faltering in Gambian infants

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There is controversy over whether children in developing countries can catch up on their growth rates after bouts of diarrhoea. A factor influencing catch-up growth is the extent and duration of mucosal injury. To explore the relation between intestinal disease and growth performance, a non-invasive test of intestinal integrity, the lactulose:mannitol permeability test, was done regularly on children aged 2–15 months, whose growth was monitored over a mean of 7·5 months. The study revealed persistent abnormalities in the small bowel mucosa of 2–15 month old Gambian infants and a negative correlation between these abnormalities and growth. Up to 43% of observed growth faltering can be explained on the basis of these long-term intestinal lesions.

Lancet 1991; 338: 907–10.

Introduction

Whether diarrhoeal disease is responsible for the progressive deterioration of nutritional status so regularly observed in infants in developing countries remains a strongly debated issue.[1–4] That episodes of diarrhoea cause short-term faltering in both height and weight development is accepted. What is disputed is whether children are able to catch up with their expected growth trajectory after such episodes.

It is important to the argument that diarrhoea be regarded as a symptom, not a disease. Just as the pathophysiology of diarrhoea varies with precipitating agents, so will the impact of the illness on weight and height growth and the extent of mucosal injury. Episodes associated with a systemic inflammatory reaction can be expected to result in severe growth faltering during the acute phase of the illness, but in the absence of intestinal injury, catch-up growth could be rapid. In contrast, if the diarrhoea is accompanied by damage to the mucosa of the small intestine then full catch-up growth cannot be expected until such injury has been repaired.

Little is known about the time taken for restoration of normal mucosal structure and function following injury mainly because of difficulties in measuring intestinal status. Until recently mucosal damage could be assessed only by endoscopy and/or biopsy of the small intestine, but the introduction of non-invasive techniques for estimating specific aspects of mucosal function and integrity has enabled repeated measurements to be made even under field conditions.[5–7] Here we describe the use of one such method, the dual-sugar intestinal permeability test,[8] to assess small intestinal mucosal status of rural Gambian infants aged 2–15 months at risk of malnutrition. In this test, a low lactulose:mannitol ratio suggests mucosal normality

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treatment programme should be reviewed by an independent ethical committee, which could examine and agree the need for such treatment in individual cases. This approach would go a long way to meeting the objections of those who are fearful of misuse of the techniques and yet ensure that treatment can be made available to the very few people with highly distressing and damaging behaviour.

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Safety of high-titre measles vaccine

Measles vaccine has been in use in most developed countries for more than 20 years; its safety record is good and its protective efficacy is very satisfactory. Where high vaccine uptake rates are achieved the disease is generally well controlled, although sporadic cases, mainly from importations, and occasional outbreaks in poorly protected population groups, are still encountered. The usual recommendation is that the vaccine should be given at 12-18 months when maternally acquired antibodies have waned and maximum antibody responses can be assured. However, in many developing countries, where infants tend to lose maternal antibody earlier, where general resistance to infection is often poor, and where crowded living conditions lead to early exposure, measles commonly occurs in the second 6 months of life and is an important cause of death.[1,2] Consequently, since 1976 the World Health Organisation (WHO) has recommended that the vaccine should be given at 9 months—a compromise between the need to provide early protection and the inferior antibody response achieved by vaccination at an early age.[3] A high-titre vaccine (defined as more than 5·0 $\log_{10}$ infectious units) first produced in the Institute of Immunology, Zagreb, Yugoslavia, by further attenuation of the Edmonston strain (EZ vaccine) was found to induce a good antibody response when given as early as 4 months of age.[4] Since 1989, therefore, WHO has recommended the phased introduction of high-titre measles vaccine to be given at 6 months of age in countries with a high measles mortality under the age of 9 months.[5]

Evidence from several trials and from limited surveillance of the use of high-titre vaccines indicates that they are both safe and effective.[6–12] However, in this issue (p 903) investigators in Senegal report an excess mortality in infants who were followed for 24–39 months after being given one of two high-titre vaccines (EZ or Schwarz) at 5 months of age, by comparison with children given a placebo at 5 months followed by standard low-titre Schwarz vaccine at 10 months and with non-participants. This finding emerged from a study that was designed as a randomised controlled trial of two high-titre vaccines in a community with an established routine mortality surveillance system based on weekly household visits.

If the observed relation was causal, it will have profound implications for the continued use of high-titre measles, but there are good reasons for exercising caution before reaching such a conclusion: (*a*) the study was not designed to test a hypothesis about late mortality in recipients of the different vaccines, so methodological difficulties were encountered; (*b*) there was no significant difference in mortality during the first 6 months of follow-up; and (*c*), most important, there were various causes of death with no suggestion of a common pathogenesis.

A review of the Senegal evidence by an independent expert panel convened by WHO concluded that the results could not be used for decision-making and advised no change in the existing policy on use of high-titre vaccines.[6] Nevertheless, further careful monitoring of use of the vaccine and possible associated adverse events, including morbidity as well as mortality, is essential to confirm or refute the Senegal findings. WHO have asked all investigators conducting trials of high-titre vaccines to include evaluation of late events in their protocols. Further studies should include other high-titre vaccines, in particular the AIK-C strain.

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[24]

LETTERS to the EDITOR

Child mortality after high-titre measles vaccines in Senegal: the complete data set

SIR,—The Scientific Working Group concerned with the trial of high-titre measles vaccines (Oct 12, p 903) decided in February, 1991, that long-term mortality would best be analysed and reported after all 24 monthly cohorts of children had reached 36 months of age in February, 1992. Therefore, we were disturbed when this report was published, for it is biased to the high mortality found in the first 16 cohorts, whereas the later recruits, who to date have a lower mortality when vaccinated with a high-titre vaccine, have been excluded. We do not think that the study design legitimises the exclusion of the last 8 cohorts. The change to only one high-titre vaccine for the last 8 cohorts was based exclusively on the unsatisfactory antibody response to vaccination with high-titre Schwarz vaccine.

The study in Niakhar, Senegal, included children born during the 24 months February, 1987, to January, 1989, who attended a vaccination session at 5 months of age. The first 16 monthly cohorts were randomised to high-titre Edmonston-Zagreb (EZ), high-titre Schwarz (SW-HT), or placebo at 5 months and Schwarz standard (SW-std) at 10 months (controls). Because of an unsatisfactory serological response after SW-HT, the study design was changed to EZ or placebo/SW-std for the last 8 monthly cohorts. Between September and November, 1990, all children were visited at home (B. S., P. A.); survival information was also obtained on children who had moved out of the study area. This mid-term assessment was undertaken because preliminary results from Guinea-Bissau had suggested higher mortality for EZ vaccinees, especially girls, compared with controls.[1] The number of children included in the different groups in the Senegal study, person-years-at-risk (PYR) and the number of deaths observed between the first vaccination at 5 months and the evaluation in the autumn of 1990 are indicated in the table.

PERSON-YEARS-AT-RISK (PYR) AND DEATHS ACCORDING TO TYPE OF MEASLES VACCINATION AND COHORT FOLLOW-UP SEPTEMBER TO NOVEMBER, 1990 (NIAKHAR, SENEGAL 1987–90)

Type of vaccine	Deaths/children at risk (%) *(PYR)*		
	Cohort 1–16†	Cohort 17–24‡	Total
EZ	51/335 (15·2%) *(824·5)*	15/293 (5·1%) *(458·6)*	66/628 (10·5%) *(1283·1)*
SW-HT	41/322 (12·7%) *(790·1)*	..	..
Controls*	32/358 (8·9%) *(906·2)*	24/290 (8·6%) *(430·9)*	56/638 (8·8%) *(1337·1)*

*Placebo at 5 months of age and Schwarz standard measles vaccine at 10 months of age. †Children born February, 1987, to May, 1988. ‡Children born June, 1988, to January, 1989.

Compared with controls, EZ children had a relative risk (RR) of dying of 1·23 (95% confidence interval [CI] 0·86–1·75) (p = 0·257). The RR was the same if both high-titre vaccines were considered together. None of the children in the study died from measles. As in the Bissau study[1] the excess mortality occurred among females; female recipients of high-titre vaccines had a RR of 1·51 (CI 0·93–2·45) compared with female controls whereas there was no difference for the males (RR = 0·99). The survival results were unchanged when a Cox regression model was used to adjust for age, season, and length of follow-up, the mortality ratio (MR) being 1·24 (0·86–1·77) (p = 0·245) for EZ vaccinees compared with controls. The tendency towards higher mortality for the recipients of high-titre vaccines was marked for the first 16 monthly cohorts (MR = 1·75 [1·12–2·73] for EZ (p = 0·014) and MR = 1·46 [0·92–2·33] for SW-HT [p = 0·111]) but went in the opposite direction for the last 8 cohorts (MR = 0·59 [0·31–1·12], p = 0·105).

Interpretation of data from the first 16 cohorts is also complicated by divergent mortality in the control group who received standard measles vaccine; control girls had low mortality (about 7%) compared with control boys (about 12%) at 40 months of age (p = 0·18). Only longer follow-up in Niakhar and other areas can clarify the sex-specific impact of measles immunisation on mortality.

Routine use of high-titre vaccines has been suspended in the study area, and study children are being investigated for possible immunological problems.

There is reason for concern about the long-term safety of high-titre measles vaccine, based on studies from Guinea-Bissau and Senegal.[1] However, these concerns do not justify the premature and selective publication of data on this important matter.

The study was organised by UR Population et Sante, ORSTOM, Dakar, and Ministry of Public Health, Senegal, and has been supported financially by the Task Force for Child Survival, Atlanta, USA, and the WHO Expanded Programme on Immunisation.

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1. Expanded Programme on Immunization. Safety and efficacy of high titre measles vaccine at 6 months of age. *Wkly Epidemiol Rec* 1991; 66: 249–51.

[25]

*** This letter has been shown to Dr Garenne and his colleagues, whose reply follows.—ED. L.

SIR,—Mr Aaby and his colleagues argue that, in the comparison between treatment and control groups in the Senegal study, differences in mortality after high-titre measles vaccines are not significant when crude death rates for all 24 cohorts are combined and that the differences were inconsistent by sex. They conclude that the publication of the results was premature.

We found an excess mortality after vaccination with high-titre measles vaccines over a 3-year follow-up. There was significantly higher probability of death within 3 years of vaccination. The only proper way to estimate this probability is the life-table method, and failure to use this procedure may lead to false interpretations and can even reverse the risk ratio. An example is a comparison of mortality of two countries with different age structures: in 1983, Sao Tome

and Principe had the same crude death rate as Norway (10·2 per 1000) even though life expectancy there was 29·5 years less (50·0 *vs* 79·5). In the high titre measles vaccines study, mortality was falling rapidly with age and the cohorts were not exposed to the same duration, so the use of crude rates is incorrect and misleading. The statistical evidence was clear with life-table estimates, but inconclusive with crude rates:

Comparison*	RR (and 95% CI) Crude	Life table
5 mo. cohorts 1–16		
EZ-HT/S	1·70 (1·12–2·58)	1·80 (1·18–2·74)
SW-HT/S	1·42 (0·92–2·21)	1·53 (0·99–2·37)
5 mo. cohorts 1–24		
EZ-HT/S	1·23 (0·86–1·75)	1·41 (0·97–2·05)
10 mo. cohorts 1–16		
EZ-HT/S	2·32 (1·42–3·81)	2·50 (1·52–4·13)
SW-HT/S	1·64 (0·96–2·80)	1·73 (1·00–2·98)
10 mo. cohorts 1–24		
EZ-HT/S	1·54 (1·05–2·26)	1·94 (1·26–2·99)

RR = relative risk of death; CI = confidence interval.
*EZ-HT = high titre Edmonston-Zagreb vaccine, given at 5 months; SW-HT = high titre Schwarz vaccine, given at 5 months; S = standard, low-titre Schwarz vaccine, given at 10 months.

Furthermore, the most appropriate approach to study the long-term safety of these vaccines may be to compare mortality after 10 not 5 months, the period during which both treatments and controls were at equal risk (both were vaccinated against measles). For mortality restricted to this period risk ratios (RR) are even higher (see above). For the first 16 cohorts RR = 2·50 (95% CI = 1·52–4·13) for EZ-HT and 1·73 (1·00–2·98) for SW-HT; for the 24 cohorts, RR = 1·94 (1·26–2·99) for EZ-HT.[1] Including the last 8 cohorts, and combining the two HT vaccines did not change the results, mainly because the last 8 cohorts were exposed only for a short period to the risk of death and because most of the excess mortality was in the second and third year of life. In our paper we were conservative in presenting the data after 5 months, showing the balance of risks and benefits of vaccinating at 5 months with HT vaccines, and we showed that the risks exceeded by far the expected benefits. The absolute differences in mortality after 10 months are so large (8·9% for EZ-HT and 4·6% for SW-HT) that there was little doubt that the use of HT vaccines had to be stopped.

Mortality after HT vaccines was monitored every week for the 4 years of the trial and an independent check was made annually at the time of the census. Mortality data were presented to the Ministry of Public Health of Senegal about twice a year at meetings of the Data Monitoring and Safety Committee until the end of the study. The excess mortality did not exist in the first year of follow-up; it became significant only during the third year, and that is when the health authorities of Senegal decided to stop using the vaccine.

Mortality in the controls and in the non-participant group was described in detail in the paper. It is not usual to have a precise estimate of a long-term trend in age-specific mortality available. This was possible only because of the continuous demographic surveillance system in the study area. The level of mortality in the groups that did not receive the HT vaccine was clearly consistent with the trends previously noted.

The issue of sex differences is more complex. Since 1963 there was no evidence of sex differences in mortality from 5 to 41 months in this population. It is statistically correct to say that the differences between treatments and controls were significant for girls and not for boys. However, the difference was in the same direction and it was highly significant for both sexes combined. In statistical terms, this is best explained by considering the sex allocation of deaths as a random process in each group, as is done routinely for the study of sex ratios in the birth process. When this approach is adopted none of the differences by sex was significant in any of the vaccinated or unvaccinated groups, as expected.

Measles is one of the rare diseases for which there is a consistent excess in female mortality (about 20%).[2] The fact that, in both groups receiving the HT vaccines, females had a 14–20% higher mortality (non-significant) than males could be taken as an indication that the measles virus was operating here. To use the argument that the difference is only significant for females to justify continuing use of the vaccine is unacceptable.

We hope to learn more about the excess mortality after HT measles vaccines in the near future. We may learn more when all cohorts vaccinated with HT vaccines in Senegal, the 24 cohorts randomised and the 15 not randomised, reach 41 months. After extensive discussion and after sharing our data with many of our peers, we deemed it important to publish the results as they were and to alert the scientific community of our findings. Unfortunately four of the investigators in the Senegal study, who spent four years of their life on the project (two full-time, two part-time) were excluded from the Data Monitoring and Safety Committee as soon as the excess mortality became significant statistically, in April, 1990.

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Unusual presentation of *Mycoplasma pneumoniae* infection

SIR,—*Mycoplasma pneumoniae* is a well-known cause of community-acquired pneumonia, the number of cases now being seen in the UK is higher than usual due to the four-year epidemic cycle. Occasionally, infection presents in non-respiratory forms. We report two such cases.

An 11-year-old girl was admitted on July 29, 1991, with a 7-day history of fever and pain in the right ear. She did not have a cough or respiratory symptoms. A younger brother had had a cough which had cleared 7 days before the onset of the patient's symptoms, and her father had had a dry cough 2 days before her admission. On clinical examination bilateral cervical lymphadenopathy and an acutely inflamed and bulging right tympanic membrane were noticed. There was no neck stiffness. Chest X-ray was normal. Blood and urine cultures were negative. The patient was treated with co-trimoxazole but she became more drowsy and began vomiting. Lumbar puncture yielded clear CSF with 200 WBC/μl and 40 RBC/μl; protein 0·92 g/l; glucose 2·5 mmol/l. A 'Wellcogen' test for haemophilus type b, meningococcal, and group B streptococcal antigens was negative. Gram stain and culture of the CSF were negative. A brain scan was negative. Treatment was changed to intravenous cefuroxime and acyclovir.

A serum taken on admission had a titre of 160 for *M pneumoniae* antibody (gel particle agglutination); 3 days later the titre was 640. Intravenous erythromycin was therefore added but an immediate generalised rash developed after the first dose. Her treatment was then changed to chloramphenicol, penicillin, and acyclovir. *M pneumoniae* infection was confirmed by the detection of specific IgM at a titre of 16 (Norwich Public Health Laboratory). CSF and throat swab culture for *M pneumoniae* was negative. The patient responded to chloramphenicol and was discharged after 10 days. The father's *M pneumoniae* titre rose from 160 on Aug 2 to 640 on Sept 7; IgM weakly positive (titre).

A 10-year-old boy was admitted on July 23 with shortness of breath, dry cough, and fever of 5 days duration. He had also complained of a sore mouth for 2 days. He had conjunctivitis, swollen lips, infected gums, and small vesicles on both cheeks. An X-ray showed bilateral bronchial thickening consistent with infection. Blood and urine cultures were negative. Intravenous amoxycillin was given but his respiration and the conjunctivitis, stomatitis, and rash worsened. There was pain on micturition, with bullae and ulcers at the urethral meatus. Urinary retention necessitated catheterisation.

An admission serum sample was positive for *M pneumoniae* antibody at a titre of 160; 7 days later the titre was 1280. His IgM antibody titre was 16. Amoxycillin was replaced by erythromycin plus steroids and betamethasone eye-drops. He was discharged

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Safety of high titre measles vaccines

Introduction

A consultation was held in Atlanta, Georgia, United States of America on 16-17 June 1992 to review the accumulated safety data from studies involving the administration of high titre measles vaccines. The report of this consultation was presented to the WHO/EPI Research and Development (R&D) Group and the WHO/EPI Global Advisory Group, which both met in Jakarta, Indonesia in October 1992. The two groups endorsed the consultation's report and recommendations.

In view of the concerns about the safety of high titre measles vaccines, the R&D Group noted that all standard titre measles vaccines routinely supplied to countries through UNICEF tested to date have not exceeded a potency of 4.7 $\log_{10}$ infectious units per dose.

Reaching and sustaining high and timely coverage (>90%) with 1 dose of standard titre measles vaccine in all districts remains the first priority for all immunization programmes. The safety and efficacy of *standard titre* measles vaccines is emphasized.

The effect of the above endorsements is to rescind the recommendation of the Global Advisory Group meeting in Tokyo which first advised selective use of high titre measles vaccine, in certain circumstances, in October 1989.[1]

Summary

Unexpected results suggesting decreased survival when compared with standard titre vaccine administered at 9 months of age have been found in some field studies evaluating the performance of high titre measles vaccine. Analytical difficulties have arisen because the studies were

Programme élargi de vaccination (PEV)

Innocuité des vaccins antirougeoleux de titre élevé

Introduction

Une consultation, tenue les 16 et 17 juin 1992 à Atlanta, Géorgie, Etats-Unis d'Amérique, a été chargée d'examiner les données accumulées à partir des études sur l'innocuité des vaccins antirougeoleux de titre élevé. Le rapport de cette consultation a été présenté au Groupe recherche et développement (R&D) et au Groupe consultatif mondial du PEV/OMS qui se sont réunis à Djakarta, Indonésie, en octobre 1992. Les deux groupes ont approuvé le rapport établi et les recommandations formulées à l'issue de la consultation.

Considérant les inquiétudes exprimées au sujet de l'innocuité des vaccins antirougeoleux de titre élevé, le Groupe R&D a fait observer que tous les vaccins antirougeoleux de titre standard fournis normalement aux pays par l'intermédiaire de l'UNICEF et testés à ce jour avaient au maximum une activité de 4,7 $\log_{10}$ unités infectieuses par dose.

Pour tous les programmes de vaccination, la première des priorités consiste à assurer et maintenir une couverture élevée (>90%) et en temps voulu avec une dose unique de vaccin antirougeoleux de titre standard administrée dans tous les districts. Il est bien spécifié que les vaccins antirougeoleux *de titre standard* sont sans danger et efficaces.

Ceci a pour effet d'annuler la recommandation formulée par le Groupe consultatif mondial à sa réunion de Tokyo, qui, en octobre 1989, avait d'abord conseillé d'utiliser sélectivement le vaccin antirougeoleux de titre élevé, dans certaines circonstances.[1]

Résumé

Un certain nombre d'études réalisées sur le terrain aux fins d'évaluer le vaccin antirougeoleux de titre élevé ont abouti à des résultats inattendus, donnant à penser que la survie est plus faible avec ce vaccin qu'avec le vaccin de titre habituel administré à 9 mois. Des difficultés d'analyse sont apparues du fait que les études n'étaient

[1] Voir N° 2, 1990, pp. 8-9

not specifically designed to measure survival. Nonetheless, careful analysis of the results from all of the high titre vaccine trials showed decreased survival of high titre vaccine recipients, in areas with high background mortality rates, compared with recipients of standard measles vaccines at 9 months. No systematic biases could be found in the studies to explain these differences. Statistical analysis of these data suggested that the findings were unlikely to be attributable to chance alone.

The panel recommended that high titre measles vaccine derived from the original Edmonston measles vaccine isolate should no longer be recommended for use in immunization programmes. Further post-licensure field studies of new measles vaccines should take into account the results of these studies. Additional detailed epidemiological studies in populations that have received high titre vaccines and their controls were encouraged.

Background

In October 1989, the WHO/EPI R&D Group recommended the use of high titre Edmonston-Zagreb (EZ) measles vaccine for infants at 6 months of age, or as soon as possible thereafter, in countries where measles was a significant cause of death before the age of 9 months. This recommendation was endorsed by the EPI Global Advisory Group, and was based upon considerable data showing that *high titre EZ vaccine*[1] was safe and effective in 6-month-old infants and that vaccine cost was not an obstacle to implementation.

During 1990 there were reports from Senegal and Guinea Bissau of decreased survival (death occurring from a variety of causes) in infants who had received high titre measles vaccine before 9 months of age as compared with survival of infants receiving standard titre vaccine at 9 months of age. As a result of these reports, WHO/EPI organized a consultative meeting in Geneva on 21-22 February 1991. After reviewing and discussing the data, it was concluded that the information was not sufficiently persuasive to recommend a change in EPI policy. The consultation recommended to WHO/EPI that their policy to encourage use of high titre EZ vaccine should be continued according to guidelines that were developed at the 1989 Tokyo EPI Global Advisory Group meeting. WHO/EPI was also encouraged to continue to monitor survival among recipients of high titre measles vaccine.

Initially, because of problems of supply, it was not possible to implement the recommendation for vaccine use at 6 months of age. Subsequently other issues arose, including: the finding that high titre vaccine was more costly than expected; inconsistencies in the definitions of the titre of the vaccine; results from studies which did not confirm the high immunogenicity seen in earlier trials; and concerns about rare adverse events.

The October 1991 EPI R&D Group recommended reconvening the ad hoc panel to re-examine all the evidence relating to safety, immunogenicity and efficacy of high titre measles vaccines in infants less than 9 months of age. The secretariat was encouraged to expand the panel with additional immunologists, virologists, statisticians and a representative of the WHO Programme for Vaccine Development measles task force. The meeting was convened in Atlanta on 16-17 June 1992.

Summary of findings

The principal investigators from all of the high titre vaccine studies presented their results, including additional data not previously available in February or October 1991. In addition, data from all of the studies were independently ana-

[1] High titre EZ vaccine was defined in 1989 as 5.0 $\log_{10}$ or higher, but changed in 1990 to 4.7 $\log_{10}$ or higher per human dose.

pas expressément conçues pour mesurer la survie. Néanmoins, une analyse attentive des résultats obtenus avec tous les essais de vaccin de titre élevé a fait apparaître que la survie est plus faible chez ceux qui ont reçu un vaccin de titre élevé, dans des zones où les taux de mortalité générale sont importants, plutôt qu'un vaccin antirougeoleux standard, à l'âge de 9 mois. On n'a trouvé dans les études aucun biais systématique capable d'expliquer ces différences. L'analyse statistique de ces données a donné à penser que les constatations ne pouvaient probablement pas être imputables au seul hasard.

Le groupe d'experts a recommandé que les programmes de vaccination n'utilisent plus le vaccin antirougeoleux de titre élevé fabriqué à partir de la souche vaccinale originale Edmonston. Toute nouvelle étude de pharmacovigilance effectuée sur le terrain pour de nouveaux vaccins antirougeoleux devra tenir compte des résultats de ces études. Il a été vivement recommandé de procéder à d'autres études épidémiologiques détaillées parmi les populations ayant reçu des vaccins de titre élevé, ainsi que chez leurs témoins.

Historique

En octobre 1989, le Groupe R&D du PEV/OMS a recommandé l'utilisation du vaccin antirougeoleux Edmonston-Zagreb (EZ) de titre élevé chez les nourrissons de 6 mois, ou dès que possible après cet âge, dans les pays où la rougeole est une importante cause de décès avant l'âge de 9 mois. Cette recommandation, approuvée par le Groupe consultatif mondial du PEV, était fondée sur un très grand nombre de données attestant que le *vaccin EZ de titre élevé*[1] était sans danger et efficace chez l'enfant de 6 mois et que le coût du vaccin ne constituait pas un obstacle à son utilisation.

En 1990, des rapports en provenance du Sénégal et de Guinée-Bissau faisaient état d'une diminution de la survie (mortalité due à des causes diverses) chez les nourrissons qui avaient reçu un vaccin antirougeoleux de titre élevé avant l'âge de 9 mois par rapport à ceux qui avaient reçu un vaccin de titre standard à 9 mois. A la suite de ces rapports, le PEV/OMS a organisé une réunion consultative tenue à Genève les 21 et 22 février 1991. Après avoir examiné les données et en avoir discuté, les participants à la réunion ont estimé que les informations n'étaient pas suffisamment convaincantes pour les amener à recommander une modification de la politique vaccinale du PEV. Ils ont recommandé au PEV/OMS de continuer à appliquer sa politique d'encouragement à l'utilisation du vaccin EZ de titre élevé conformément aux grandes orientations formulées en 1989 lors de la réunion de Tokyo du Groupe consultatif mondial du PEV. Le PEV/OMS était également invité à continuer de contrôler la survie des enfants ayant reçu un vaccin antirougeoleux de titre élevé.

Au départ, des difficultés d'approvisionnement n'ont pas permis de donner effet à la recommandation de vacciner à 6 mois. Par la suite, d'autres difficultés sont apparues, notamment la constatation que le vaccin de titre élevé est plus coûteux que prévu, le manque d'uniformité dans la définition du titre du vaccin, des résultats d'études qui ne confirmaient pas la forte immunogénicité constatée dans des essais précédents et, enfin, des préoccupations suscitées par un petit nombre d'effets indésirables.

En octobre 1991, le Groupe R&D du PEV a recommandé de réunir de nouveau le groupe ad hoc pour qu'il réexamine toutes les observations concernant l'innocuité, l'immunogénicité et l'efficacité des vaccins antirougeoleux de titre élevé chez les nourrissons de moins de 9 mois. Le Secrétariat a été invité à élargir le groupe en lui adjoignant des immunologistes, des virologistes, des statisticiens et un représentant du groupe spécial pour la rougeole du programme OMS pour la mise au point des vaccins. La réunion a eu lieu à Atlanta les 16 et 17 juin 1992.

Résumé des observations

Les chercheurs principaux de toutes les études sur les vaccins de titre élevé ont présenté leurs résultats, et notamment des données qui n'étaient pas encore disponibles en février et en octobre 199[illegible]. De plus, les données fournies par chacune des études ont fait l'ob

[1] Par définition, un vaccin EZ de titre élevé devait correspondre au minimum, en 19[illegible] à 5,0 $\log_{10}$, chiffre ramené en 1990 à un minimum de 4,7 $\log_{10}$ par dose.

lysed by an investigator at the London School of Hygiene and Tropical Medicine who presented his analysis and results. Thus, all survival data were analysed by a single investigator.

Immunological studies on vaccine recipients were discussed and immunogenicity and efficacy studies using high titre vaccines summarized. A modelling exercise was presented which took into account the benefits of early measles immunization with high titre vaccine and the impact of decreased survival as a result of the vaccines in comparison with standard titre vaccines.

The principal conclusions were as follows:

• *The studies*. The controlled trials allowed for conclusions to be drawn about survival, despite the fact that survival, as an outcome, was not specifically included in the initial design of these studies.

• *Association with decreased survival*. In each of the 4 studies with *high background infant mortality*, an association between administration of high titre measles vaccine and decreased survival was consistent when compared with survival of children administered standard titre vaccine at 9 months of age. The combined analysis suggested a relative risk of mortality of approximately 1.25 associated with receipt of high titre vaccine ($p = 0.05$).

Trials with *low background infant mortality* did not show evidence of decreased survival among recipients of high titre vaccine. This suggested that the reduced survival effect associated with the vaccine was multiplicative, and not additive — that is, the effect was to multiply the background death rate by some factor, approximately 1.25, rather than to add a constant absolute risk to recipients.

• *Gender*. The reduced survival effect differed between the sexes in all the major studies, being greater in females in 3 out of 4 studies using high titre vaccines. The interaction with gender was statistically significant after exclusion of the hypothesis-generating data set ($p<0.02$).

• *Dose*. In the 4 studies with high background levels of infant mortality, the dose of the vaccine appeared to be a major factor associated with reduced survival. The risk of adverse events diminished if lower titres of vaccine were used, but the lower limit below which the increased risk disappeared could not be defined precisely.

Based on a large body of safety data, there was no reason for concern regarding the administration of the currently recommended doses of EPI antigens, except for high titre measles vaccine.

Measles virus is known to be associated with transient immunosuppression; however, long experience has shown that immunosuppression is not of concern following the administration of standard titre measles vaccines. Immunosuppression has not been noted following administration of other EPI vaccines at currently recommended doses.

• *Age*. The available data from several studies indicated no consistent relationship between age at immunization and decreased survival. Immunization at 6 months of age with standard titre vaccines appears safe and continues to be endorsed by EPI under appropriate epidemiological circumstances.

• *Causes of death*. The causes of death identified from verbal autopsies revealed no unusual pattern of disease in children who received high titre measles vaccines as compared with children who had received standard titre vaccines.

• *Strain*. While minor strain differences were observed in some studies, the risk of decreased survival was not associated with a single strain.

• *Biological explanation*. No definitive biological explanation has been found for the differences in survival among

d'une analyse indépendante par un chercheur de la *London School of Hygiene and Tropical Medicine*, qui a présenté son analyse et ses résultats. Ainsi, toutes les données relatives à la survie ont été analysées par le même chercheur.

Les études immunologiques sur les sujets vaccinés ont fait l'objet de débats, et les études sur l'immunogénicité et l'efficacité des vaccins de titre élevé ont été résumées. Les participants se sont vu présenter un modèle qui prend en compte les avantages d'une vaccination antirougeoleuse précoce avec un vaccin de titre élevé et l'impact d'une diminution de la survie après l'administration du vaccin, par comparaison avec des vaccins de titre standard.

Les principales conclusions ont été les suivantes:

• *Les études*. Les essais contrôlés ont permis de tirer des conclusions au sujet de la survie, bien que l'étude de celle-ci n'ait pas été expressément prévue au moment de la conception initiale de ces études.

• *Association avec une diminution de la survie*. Dans chacune des 4 études effectuées dans des *populations où la mortalité infantile générale est élevée*, on retrouve régulièrement une association entre l'administration de vaccins antirougeoleux de titre élevé et une diminution de la survie par rapport à celle des enfants qui ont reçu un vaccin de titre standard à 9 mois. L'analyse combinée donne à penser qu'il existe un risque relatif de mortalité d'environ 1,25 associé à l'administration d'un vaccin de titre élevé ($p = 0,05$).

Les essais effectués parmi des *populations où la mortalité infantile générale est faible* n'ont apporté aucun signe de diminution de la survie chez ceux qui avaient reçu un vaccin de titre élevé, ce qui donne à penser que le vaccin, en termes de diminution de survie, a un effet multiplicatif et non additif — c'est-à-dire que l'effet a été de multiplier le taux de mortalité existant par un facteur donné, 1,25 environ, plutôt que de faire courir au sujet vacciné un risque supplémentaire constant et absolu.

• *Sexe*. Dans toutes les grandes études, l'effet de diminution de la survie différait selon le sexe, et il était plus marqué chez les sujets de sexe féminin dans 3 des 4 études concernant les vaccins de titre élevé. L'influence du sexe était statistiquement significative, une fois exclues les autres hypothèses évoquées par les données ($p<0,02$).

• *Dose*. Dans les 4 études réalisées dans des populations où la mortalité infantile est élevée, la dose de vaccin semblait être l'un des principaux facteurs associés à la baisse de survie. Le risque d'effets indésirables diminuait avec le titre du vaccin, mais il n'a pas été possible de définir avec précision le seuil en dessous duquel il n'y avait plus d'accroissement de risque.

Compte tenu de la multitude des données relatives à l'innocuité, il n'y a aucune raison de s'inquiéter au sujet de l'administration des doses d'antigènes du PEV actuellement recommandées, sauf pour ce qui concerne le vaccin antirougeoleux de titre élevé.

L'on sait que le virus de la rougeole est associé à une immunodépression temporaire; cependant, de longues années de pratique ont montré qu'il n'y a pas lieu de s'inquiéter de l'immunodépression consécutive à l'administration de vaccins antirougeoleux de titre standard. On n'a pas noté d'immunodépression après l'administration d'autres vaccins du PEV aux doses actuellement recommandées.

• *Age*. Les données fournies par plusieurs études n'ont fait apparaître aucune relation systématique entre l'âge au moment de la vaccination et la diminution de la survie. La vaccination à 6 mois avec des vaccins de titre standard ne présente, semble-t-il, aucun danger et reste recommandée par le PEV dans des situations épidémiologiques appropriées.

• *Causes de mortalité*. Les causes de mortalité déterminées à partir d'interrogatoires n'ont révélé aucune évolution pathologique inhabituelle chez les enfants qui ont reçu des vaccins antirougeoleux de titre élevé par rapport à ceux qui ont reçu des vaccins de titre standard.

• *Souches*. Des différences mineures entre souches ont été observées dans certaines études, mais le risque de diminution de la survie n'a été associé à aucune souche particulière.

• *Explication biologique*. Aucune explication biologique définitive n'a été trouvée pour les différences de survie chez les sujets vaccinés.

• *Immunogenicity.* A comprehensive review of seroconversion rates after EZ vaccine confirmed that EZ vaccine was more immunogenic than Schwarz vaccine at ages 4-6 months, especially in the presence of maternal antibodies. However, the public health implications of such an observation are not clear at this time.

• *Vaccine efficacy.* Studies evaluating the impact of high titre measles vaccine at 6 months were dependent on the extent of wild measles virus circulation in the 6- to 9-month age group. An Asian study showed a four-fold reduction in measles cases in infants immunized at 6 months when compared with a control group immunized at 9 months. This study was done during a measles epidemic. On the other hand, vaccine efficacy studies from Western Africa, in places where there was little measles transmission, showed no benefit for cohorts immunized at 6 months with high titre vaccine when compared with those immunized with standard Schwarz vaccine at 9 months.

• *Mathematical model.* A mathematical model was examined based on the published estimates of decreased survival after high titre measles vaccine in study sites with high background levels of measles. The model suggested that, even in communities with severe measles-associated mortality, infants under 9 months would derive, at best, only marginal benefit from the use of a high titre vaccine (when compared with those given standard titre vaccine at 9 months and at equivalent levels of coverage). It was noted that modelling such as this had limitations when generalizing to actual field situations.

Recommendations

1. *For immunization programmes*

High titre (equal to or greater than 4.7 $\log_{10}$ per human dose as expressed in relation to the International Reference Reagent for measles vaccine) measles vaccine derived from the original Edmonston measles virus isolate should no longer be recommended for use in immunization programmes.

The evidence examined at this meeting supported the continued use of standard measles vaccines for all infants in immunization programmes. Standard measles vaccines have been shown to be safe and highly effective and have resulted in significant reductions in morbidity and mortality in numerous countries throughout the world. Measles immunization is generally considered the most cost-effective public health intervention available.

2. *Research initiatives*

2.1 Additional field trials of high titre measles vaccine derived from the original Edmonston measles virus isolate are not recommended unless evidence of a biological explanation of reduced survival which would change this recommendation becomes available.

2.2 Insofar as possible, samples of all vaccines used in studies of high titre measles vaccine should be sent to a single reference laboratory (coordinated by WHO) for titration and analysis; vaccine potency should be expressed in relation to the International Reference Reagent for measles vaccine.

2.3 Newly licensed measles vaccines should have post-licensure long-term follow up for a minimum time period of 3 years after immunization. The monitoring system should be capable of identifying decreased survival by gender. (Note: the EPI R&D Group made an additional comment on this recommendation. It suggested that before introduction of new measles vaccines prior to 9 months of age in routine immunization programmes, attention be given to the need for randomized trials with sufficient power to detect gender-specific decreased survival over a 3-year period when compared with a standard measles vaccine.)

• *Immunogénicité.* Une étude exhaustive des taux de séroconversion après administration du vaccin EZ a confirmé que ce vaccin était plus immunogène que le vaccin Schwarz lorsque le nourrisson est âgé de 4 à 6 mois, en particulier en présence d'anticorps maternels. Cependant, on ne voit pas encore très bien quelles sont les incidences d'une telle observation sur la santé publique.

• *Efficacité vaccinale.* Les évaluations de l'impact de l'administration du vaccin antirougeoleux de titre élevé à 6 mois dépendaient de l'étendue de la circulation du virus rougeoleux sauvage dans le groupe d'âge des 6-9 mois. Une étude réalisée en Asie a fait apparaître que le nombre de cas de rougeole chez les nourrissons vaccinés à 6 mois était 4 fois moins élevé que dans le groupe témoin vacciné à 9 mois. Cette étude a été réalisée pendant une épidémie de rougeole. Par contre, les études sur l'efficacité du vaccin réalisées dans des zones d'Afrique occidentale où la transmission du virus rougeoleux était peu importante n'ont fait apparaître aucune amélioration dans les cohortes vaccinées à 6 mois avec un vaccin de titre élevé par comparaison avec celles vaccinées à 9 mois avec un vaccin Schwarz standard.

• *Modèle mathématique.* On a étudié un modèle mathématique établi à partir des estimations publiées sur une diminution de survie après administration d'un vaccin antirougeoleux de titre élevé dans des sites d'étude où les cas de rougeole sont fréquents. Ce modèle a donné à penser que, même dans les communautés où l'on observe une importante mortalité liée à la rougeole, l'administration d'un vaccin de titre élevé ne bénéficierait au mieux que marginalement aux nourrissons de moins de 9 mois (par comparaison avec ceux qui reçoivent un vaccin de titre standard à 9 mois et à des niveaux de couverture équivalents). Il a été relevé que des modèles de ce type sont difficilement généralisables à des situations réelles sur le terrain.

Recommandations

1. *Pour les programmes de vaccination*

Le vaccin antirougeoleux de titre élevé (c'est-à-dire égal ou supérieur à 4,7 $\log_{10}$ par dose lorsque le titre a été mesuré par rapport au réactif international de référence pour le vaccin antirougeoleux) fabriqué à partir de la souche originale Edmonston ne doit plus être recommandé aux fins d'utilisation dans les programmes de vaccination.

Les données examinées pendant cette réunion sont en faveur de l'utilisation continue, dans les programmes de vaccination, du vaccin antirougeoleux standard pour tous les nourrissons. Il a été démontré que ce vaccin est sans danger et très efficace et qu'il a entraîné un abaissement sensible de la morbidité et de la mortalité dans de nombreux pays du monde. La vaccination antirougeoleuse est généralement considérée comme l'intervention de santé publique la plus rentable.

2. *Initiatives au niveau de la recherche*

2.1 Il n'est pas recommandé de procéder à de nouveaux essais sur le terrain du vaccin antirougeoleux de titre élevé tiré de la souche originale Edmonston, à moins que l'on ne puisse disposer d'éléments d'explication biologique à la diminution de la survie.

2.2 Dans toute la mesure du possible, les échantillons de tous les vaccins utilisés dans les études du vaccin antirougeoleux de titre élevé devront être envoyés à un seul laboratoire de référence (coordonné par l'OMS) pour titrage et analyse; l'activité vaccinale devra être exprimée par rapport à celle du réactif international de référence pour le vaccin antirougeoleux.

2.3 Les vaccins antirougeoleux récemment mis sur le marché doivent faire l'objet, pendant au minimum 3 ans après la vaccination, d'une pharmacovigilance attentive qui doit permettre de repérer une diminution de la survie selon le sexe. (Note: Le groupe R&D du PEV a formulé une observation supplémentaire au sujet de cette recommandation. Avant d'adopter, dans des programmes de vaccination systématique, de nouveaux vaccins antirougeoleux à administrer avant 9 mois, il a été suggéré de procéder à des essais randomisés suffisamment puissants pour faire apparaître une différence de diminution de survie selon le sexe sur une période de plus de 3 ans en utilisant, aux fins de comparaison, un vaccin antirougeoleux standard.)

2.4 Biological and virological response after receipt of measles vaccine should be studied with special emphasis on the possibility of gender differences. Similar studies should be undertaken in past recipients of high titre vaccine and their controls. Studies in non-human primates are also encouraged.

2.5 Community studies with data on measles-related morbidity and mortality should be re-analysed for differential effect by gender.

2.6 Principal investigators should alert health authorities or other responsible parties to the possibility of decreased survival in recipients of high titre measles vaccine.

2.4 Il faudra étudier la réaction biologique et virologique provoquée par l'administration d'un vaccin antirougeoleux en accordant une place particulière à l'éventualité d'une différence selon le sexe. Il faudra entreprendre des études similaires chez les sujets qui ont reçu par le passé un vaccin de titre élevé et chez leurs témoins. Il conviendra également de procéder à des études sur des primates.

2.5 Il faudra procéder à une nouvelle analyse des études communautaires comportant des données sur la morbidité et la mortalité associées à la rougeole pour déceler une différence d'effet selon le sexe.

2.6 Les chercheurs principaux devront alerter les autorités ou autres responsables de la santé au sujet de l'éventualité d'une diminution de survie chez les sujets à qui il a été administré un vaccin antirougeoleux de titre élevé.

Rabies

Two cases of imported rabies in France

Mexico

During a visit to Mexico, a 28-year-old man and his female companion were both bitten by a stray dog that was found injured by the roadside on 20 December 1990. No rabies prevention treatment was administered. On 5 February 1991 (47 days after being bitten), the man complained of fever and diarrhoea which were relieved by symptomatic treatment. On 12 February, the young woman noticed that her companion was behaving strangely, with alternating periods of apathy and agitation, accompanied by abnormal movements of the arms. Over the next few days he developed insomnia, anorexia and hydrophobia. On his return to France on 17 February, the patient was admitted to hospital, where he refused to drink in spite of dehydration, and presented pharyngeal spasms and hypersalivation. He died soon afterwards.

The diagnosis of rabies was confirmed by direct immunofluorescence and isolation of the virus from cerebral biopsy. The patient's companion was given serum and full vaccine regimen as soon as rabies was diagnosed and has presented no abnormal symptoms in spite of the long delay before treatment. She had certainly not been infected.

Algeria

On 23 April 1992, a child aged 3 and a half years living in Algeria was transferred from a hospital in Batna to the intensive care unit at the Necker Children's Hospital in Paris with viral encephalitis of undetermined origin. The first symptoms, which included hydrophobia and aerophobia, had appeared on 15 April and led to the child's admission to hospital in Batna on 19 April. The boy died on 9 May, 25 days after the onset of symptoms and 17 days after hospitalization in Paris.

No specific antibodies were detected in the serum and cerebrospinal fluid (CSF) on 24 April, but antibodies were detectable in the serum as from 5 May. The skin biopsies and corneal impressions taken on 5 and 9 May were negative when tested by immunofluorescence. No virus was isolated from the CSF samples taken on 24 and 27 April and 5 and 9 May. Saliva samples were taken between 5 and 9 May, but rabies antigen was found only in the samples taken on 7 and on 9 May.

The diagnosis of rabies was confirmed by indirect immunofluorescence tests in a sample of nerve tissue obtained post mortem by retro-orbital puncture, isolation in cells and in mice, and antigen detection.

Postexposure antirabies treatment was administered to 143 subjects (hospital workers and members of the family living in Paris). This high figure is accounted for by the lengthy period of hospitalization before the diagnosis of rabies, during which biological samples were handled without special precautions by the laboratory personnel.

The boy had been chased and knocked down by a dog on 17 March in his village (Khenchela). Although he had

Rage

Deux cas de rage importés en France

Mexique

Lors d'un séjour touristique au Mexique, un homme de 28 ans et sa compagne ont tous deux été mordus par un chien errant, trouvé blessé au bord de la route le 20 décembre 1990. Aucune mesure thérapeutique préventive vis-à-vis de la rage n'a été pratiquée. Le 5 février 1991 (47 jours après la morsure), l'homme se plaint de fièvre et de diarrhées calmées par un traitement symptomatique. Le 12 février, la jeune femme remarque chez son compagnon des troubles du comportement avec des alternances de périodes d'apathie et d'agitation, accompagnés de mouvements anormaux des membres supérieurs. En quelques jours apparaissent insomnies, anorexie et hydrophobie. A son retour en France, le 17 février, et à son admission à l'hôpital, malgré sa déshydratation, le patient refuse toute boisson et présente des spasmes pharyngés et une hypersialorrhée. Le malade décède rapidement.

Le diagnostic de rage a été confirmé par immunofluorescence directe et isolement du virus à partir d'une biopsie cérébrale. La compagne du patient a reçu une séro-vaccination dès que le diagnostic de rage a été porté et n'a présenté aucun symptôme anormal malgré ce traitement très tardif. Elle n'avait certainement pas été contaminée.

Algérie

Le 23 avril 1992, un enfant de 3 ans et demi vivant en Algérie est transféré d'un hôpital de Batna à l'unité de soins intensifs de l'hôpital Necker-Enfants-Malades (Paris) pour une encéphalite virale d'étiologie indéterminée. Les premiers symptômes, parmi lesquels hydrophobie et aérophobie, sont apparus le 15 avril et ont conduit à l'hospitalisation à Batna le 19 avril. Le jeune garçon est mort le 9 mai, 25 jours après le début des symptômes et 17 jours après son hospitalisation à Paris.

La détection d'anticorps spécifiques dans le sérum et le liquide céphalorachidien (LCR) était négative le 24 avril mais, à partir du 5 mai, des anticorps étaient décelables dans le sérum. Les biopsies de peau et calques cornéens pratiqués les 5 et 9 mai sont restés négatifs par l'épreuve d'immunofluorescence. Aucun virus n'a pu être isolé des échantillons de LCR prélevés les 24 et 27 avril, 5 et 9 mai. Des prélèvements de salive ont été effectués quotidiennement entre le 5 et le 9 mai. De l'antigène rabique n'a été détecté que sur les prélèvements des 7 et 9 mai.

Un échantillon de substance nerveuse obtenu par ponction rétro-orbitaire postmortem a permis de confirmer le diagnostic de rage par les épreuves d'immunofluorescence indirecte, isolement sur cellules et souris, et détection d'antigène.

Parmi le personnel hospitalier et les membres de la famille résidant à Paris, 143 traitements antirabiques après exposition ont été pratiqués. Ce nombre important est lié à la longue durée de l'hospitalisation avant que le diagnostic de rage n'ait été porté et à la manipulation sans précautions de prélèvements biologiques par le personnel de laboratoire.

L'enfant avait été poursuivi et renversé par un chien le 17 mars dans son village (Khenchela). Il présentait une plaie au front, mais

The occurrence of measles in older children should not divert attention or resources from the need to increase coverage in young children. Countries are urged to immunize children as soon as they become eligible and to improve health information systems so that groups with low coverage can be identified and immunized.

In many countries, immunization programmes have reduced measles incidence to such an extent that health workers and the public expect measles outbreaks *not* to occur, and outbreaks thus generate strong political and social pressure for response that cannot be ignored. Countries which have reached moderately high coverage levels should be aware that future outbreaks in older children may occur. These should be notified promptly. Plans for their control should be developed which do not jeopardize routine immunization of younger children.

Neonatal tetanus elimination

In May 1989, the World Health Assembly adopted a resolution to eliminate neonatal tetanus (NNT) from the world by 1995 (WHA42.32). The goal of elimination of neonatal tetanus will be pursued in ways which strengthen EPI as a whole, fostering the development of maternal and child health programmes and primary health care.

The Group endorses the revised Plan of Action for Global Elimination of Neonatal Tetanus by the Year 1995.

Recognizing the 784 000 infants deaths due to neonatal tetanus still occurring in 1989 and the need to rapidly increase tetanus toxoid immunization coverage and the proportion of deliveries respecting the "3 cleans" (clean hands, clean delivery surface and clean cutting and care of the umbilical cord), the Group recommends the following additional actions:

- organizing integrated training planning workshops at national and district level;
- adopting a "risk approach" to designate high priority geographical or socioeconomic areas for elimination activities;
- administering a protective course of tetanus toxoid to all women of childbearing age as early as possible and ideally before school-leaving and the first pregnancy;
- reducing/eliminating the number of "missed opportunities" by offering tetanus toxoid to mothers when children are immunized;
- providing a life-long immunization card (record) for all tetanus toxoid recipients;
- reporting of neonatal tetanus cases by month and by district jointly with other EPI target diseases;
- making greater use of all antenatal visits, including those during the first trimester of pregnancy, to:
  - administer tetanus toxoid,
  - identify women at risk for complications from delivery, and
  - deliver a cord care kit to those women who will not deliver at a health facility;
- simplifying recommendations concerning the tetanus toxoid immunization schedule and indicators for monitoring progress, including those relating to the coverage among target groups and the proportion of births protected from tetanus;
- encouraging the use by maternal and child health programmes of tetanus toxoid coverage of pregnant women as an indicator of adequacy of service; and
- encouraging the adoption of the neonatal tetanus incidence rate as a health indicator supplemental to the infant and maternal mortality rates.

L'apparition de cas de rougeole chez des enfants plus âgés ne devrait pas détourner l'attention ou les ressources de la nécessité d'accroître la couverture chez les jeunes enfants. Les pays sont instamment invités à vacciner les enfants dès qu'ils peuvent l'être et à améliorer les systèmes d'information sanitaire afin que les groupes mal couverts puissent être répertoriés et vaccinés.

Dans de nombreux pays, les programmes de vaccination ont réduit l'incidence de la rougeole à un point que les agents de santé et le public ne s'attendent *pas* à ce que des flambées de rougeole puissent se produire, ce qui fait que les poussées épidémiques suscitent de fortes réactions politiques et sociales que l'on ne saurait ignorer. Les pays qui ont atteint des taux de couverture moyennement élevés devraient être conscients du fait que des épidémies pourront se produire chez des enfants plus âgés. Elles doivent être notifiées au plus vite. Des plans de lutte qui ne compromettent pas la vaccination systématique des jeunes enfants doivent être élaborés.

Élimination du tétanos néonatal

En mai 1989, l'Assemblée mondiale de la Santé a adopté une résolution visant à éliminer le tétanos néonatal dans le monde d'ici 1995 (WHA42.32). Le but de l'élimination du tétanos néonatal sera poursuivi de façon à renforcer le PEV dans son ensemble, en favorisant le développement des programmes de santé maternelle et infantile et celui des soins de santé primaires.

Le Groupe approuve le plan d'action révisé pour l'élimination mondiale du tétanos néonatal d'ici 1995.

Reconnaissant que 784 000 décès de nourrissons dus au tétanos néonatal sont encore survenus en 1989, et la nécessité d'accroître rapidement la couverture vaccinale par l'anatoxine tétanique, ainsi que la proportion d'accouchements pratiqués en respectant les 3 règles d'hygiène fondamentales (avoir les mains propres, pratiquer l'accouchement sur une surface propre, couper proprement le cordon ombilical et prodiguer ensuite les soins nécessaires), le Groupe recommande les mesures supplémentaires ci-après:

- organiser des ateliers de formation/planification intégrée au niveau national ou au niveau des districts;
- adopter une approche fondée sur la notion de risque pour recenser les zones géographiques ou socio-économiques hautement prioritaires pour les activités d'élimination;
- assurer le plus tôt possible la protection par l'anatoxine tétanique de toutes les femmes en âge de procréer, et de préférence avant la fin de la scolarité et la première grossesse;
- réduire le nombre d'« occasions manquées » ou les éliminer en proposant l'anatoxine tétanique aux mères venues faire vacciner leur enfant;
- délivrer un carnet (dossier) de vaccination qu'elles conserveront toute leur vie à toutes les personnes à qui l'on administre de l'anatoxine tétanique;
- signaler le nombre de cas de tétanos néonatal survenus par mois et par district en même temps que les cas de maladies cibles du PEV;
- mettre davantage à profit toutes les visites prénatales, y compris pendant le premier trimestre de la grossesse, pour:
  - administrer l'anatoxine tétanique,
  - repérer les femmes à risque de complications pendant l'accouchement, et
  - remettre aux femmes qui n'accoucheront pas dans un centre de santé un nécessaire pour soigner la plaie ombilicale;
- simplifier les recommandations concernant les schémas de vaccination par l'anatoxine tétanique et les indicateurs pour la surveillance des progrès, y compris ceux qui ont trait à la couverture des groupes cibles et à la proportion de naissances protégées du tétanos;
- encourager l'utilisation par les programmes de santé maternelle et infantile du taux de couverture par l'anatoxine tétanique des femmes enceintes comme indicateur de l'adéquation des services; et
- encourager l'adoption du taux d'incidence du tétanos néonatal comme indicateur sanitaire complémentaire au taux de mortalité maternelle et infantile.

Measles Battle Loses Potent Weapon

Use of an experimental vaccine that showed promise in tackling the disease in the Third World has been halted because it has been associated with excess mortality in some countries

In a disheartening finale to a decade of promising clinical trials, the World Health Organization (WHO) this month suspended all use of the most effective measles vaccine ever developed. The difficult decision followed a review of studies that reached a baffling conclusion: Children in some Third World countries inoculated with the potent formulation—called the high-titer Edmonston-Zagreb vaccine—remain well protected from measles but have an increased risk of dying from a variety of other diseases in the years following vaccination. And, to add to the mystery, girls who had been given the vaccine seem to be more at risk than boys.

The vaccine's loss constitutes a significant setback for developing countries, where measles remains the number one infectious killer. The disease strikes about 44 million children a year and kills 1.5 million of them. Public health officials had been hoping that the new vaccine would make a dent in those horrifying statistics in the 1990s. Its key advantage compared to the standard vaccine is that it can be used much earlier in infancy, a time when millions of children in developing countries contract the disease.

The impact will be less immediate in countries like the United States, where measles tends to strike later in childhood. But that doesn't mean domestic officials are unconcerned. Researchers are at a loss to explain the excess mortality linked to the new vaccine, although they suspect it may be a result of immune suppression. And that lack of knowledge points up a key problem: Measles research has lagged badly in recent years. Moreover, large-scale measles outbreaks have appeared in 3 out of the past 4 years in the United States, with as many as one-third of the cases in some cities occurring in children already vaccinated with the standard vaccine. Still reeling from the reemergence of tuberculosis, experts are concerned that the country could be caught off guard by another highly infectious slumbering giant (see box).

"Much of the work on measles was done between 1954 and 1966, and everything went wonderfully," says Duke University pediatrician Samuel Katz, chairman of the Centers for Disease Control's (CDC) Advisory Committee on Immunization Practices. Indeed, measles research may have been a victim of its own success. The first vaccine was approved in 1963, and within 5 years, Katz notes, the U.S. incidence of measles dropped by an incredible 95%. "The attractiveness of the field declined and funding became skimpy," Katz says. "Today, you can count on one hand, almost, the number of people who are doing basic research with the measles virus."

But while interest and money waned, the measles problem had hardly been solved, especially in developing countries. Aside from the difficulty of reaching enough people in poor countries with any vaccine program,

HANS GEL DEBIL OMNISTAL'S UNLIMITED

Black box. Little is known about the inner workings of the measles virus.

the standard vaccine, made from live attenuated viruses, has a serious drawback: It is generally ineffective in the presence of maternal antibodies, which remain in the blood for about the first 9 months of life. In developing countries, where measles is often "hyperendemic," as many as one in three infants catch the disease within their first 9 months. (In developed countries, where the disease is less common, young infants run little risk of exposure to the virus and vaccination can be postponed until 12 or even 15 months of age.)

Hopes for a better vaccine rose in 1983 when a preparation made from a nonstandard measles strain, called Edmonston-Zagreb, proved immunogenic in Mexican infants 4 to 6 months old when given in doses 10 to 100 times the usual concentration. Studies in Guinea-Bissau and Haiti confirmed the vaccine's effectiveness in this critical age group, and in 1990 WHO recommended that the high-titer Edmonston-Zagreb vaccine be used in areas where measles in younger infants was a major health problem.

It wasn't long before the bubble burst, however. By late that same year, researchers in Guinea-Bissau reported that children who had been inoculated with the high-titer vaccine were dying at higher than expected rates from a spectrum of ailments already common to the region, including pneumonia, diarrhea, and parasitic diseases. In February 1991 Senegal reported the same problem. In one key study, children who received the high-titer formulation had a mortality rate in the first few years after inoculation that was 80% higher than that of their counterparts who received the standard inoculum. But these studies were preliminary and WHO allowed trials to continue while gathering more data.

By June of this year, however, when a WHO task force met in Atlanta to discuss the vaccine, similar data were coming in from Haiti; the link seemed irrefutable, with an average increased risk of mortality of about 20%. After the meeting, WHO recommended that use of the vaccine be halted temporarily pending further review. Last week, at a meeting held in Indonesia, the Global Advisory Board of WHO's Expanded Programme on Immunization officially ratified that suspension, effectively killing further trials of the formulation. (Standard doses of the Edmonston-Zagreb strain have been used safely for years in some parts of the world and are still allowed, however.) The agency is expected to publish its findings and recommendations in its weekly report within the next few weeks.

Although immunologists and virologists are mystified by the high-dose vaccine's ill effects, they are focusing on the possibility of immune suppression. Indeed, the measles virus itself is known for its ability to cause a transient, generalized immune suppression even as it triggers long-lasting specific immunity. "It's well known that infection with the wild-type measles virus can suppress the immune system, as evidenced by a weakened delayed hypersensitivity response to tuberculin skin tests," says Johns Hopkins virologist Diane Griffin. "A high-dose vaccine may just mimic, in an amplified way, what happens with natural measles."

Unfortunately, Griffin says, scientists

U.S. Epidemics: The Price of Neglect?

It was science at its best: In the 5 years following the introduction of a measles vaccine in 1963, the number of domestic measles cases dropped dramatically from 458,000 to 22,000; by 1983 the number had fallen to an all-time low of fewer than 1500. But incidence has increased annually since then. More than 18,000 cases occurred during the epidemic of 1989, and epidemics recurred in 1990 and 1991.

Public health officials blame most of the recent U.S. upswing on parents' growing failure to vaccinate their children. A recent survey of eight major U.S. cities by the Centers for Disease Control found vaccination rates ranging from 52% to 71%. But beyond the problem of coverage, it has also become clear that up to 5% of those who do get vaccinated fail to develop antibodies, and an even greater percentage may lose their protection years later. To remedy the situation, U.S. officials began recommending a two-dose measles regimen in 1989, with the first dose to be given at 12 months followed by a booster several years later.

VOAY LEVY/PHOTOTAKE

Scattershot. Measles is making a comeback as vaccination lags.

Antibody development and persistence should increase with the new dose schedule, but some experts worry that compliance will be even worse than with the one-dose schedule. A better solution, they say, would be to develop a single-dose vaccine that could be given at a few months of age, when other vaccines are also being given. Public health officials had hoped that the high-titer Edmonston-Zagreb vaccine (see main story) might fill that role, but last week's permanent suspension of its use now has scientists going back to their drawing boards.

Unfortunately, the U.S. research establishment is hardly in a position to make up for the loss quickly. "We've had a relatively good vaccine for 25 or 30 years," says Kenneth Bart, director of the National Vaccine Program Office in Rockville, Maryland. "So research has virtually ground to a halt." Indeed, the National Institute of Allergy and Infectious Diseases currently funds only two projects relating to measles. It recently invited grant proposals in the area, but no new money has been allocated. That means that any new projects will have to cannibalize resources from the existing virology budget.

—R.W.

know very little about how the measles virus interacts with the immune system. "We know a lot more about viral immunology now than we did when measles vaccines were first developed," Griffin says. "There is hope for figuring it all out, but first we're going to have to understand what this immune suppression really is. If we could find out what causes it, we could figure out what not to do in a vaccine."

As equally baffling as the increased mortality itself is a mysterious gender bias. In several countries, like Guinea-Bissau and Senegal, girls were found to be much more likely to suffer from the vaccine-related delayed mortality. "Why on Earth should this vaccine effect be gender related?" asks John Clements, medical officer for WHO's vaccine program in Geneva. "It was totally unexpected." Some infectious diseases do cause higher mortality in one sex or the other, although no such bias has been recognized for naturally occurring measles. But in those cases, it's usually the girls who are better at fighting off pathogens. That has led at least one immunologist, E. Richard Stiehm at the University of California, Los Angeles, to propose that in fact girls do mount a superior immune response to the measles vaccine—and then go on to suffer from a generalized hypersensitivity that leaves them at an immunological disadvantage later on.

Some find the vaccine's gender correlation so counterintuitive they suspect it has sociological, rather than biological, roots. Kenneth Bart, director of the National Vaccine Program Office in Rockville, Maryland, suspects that equal numbers of boys and girls may get sick in the few years after vaccination, but that girls receive less adequate medical care and so die at higher rates. But Lauri Markowitz, a medical epidemiologist with CDC's Division of Immunization, counters that workers in West Africa have told her there is no evidence that boys in the trials were treated better than girls. "The whole thing is so strange," she says. "I don't think people really have a clue about what's going on." To shed light on the vaccine's mechanisms of immune suppression and gender bias, a research team headed by Markowitz plans to measure antibody levels and immune cell counts in 100 boys and girls in the Los Angeles area who received the high-titer Edmonston-Zagreb vaccine in clinical trials in the past 2 years.

One lingering worry is that any live virus measles vaccine potent enough to induce immunity in infants with maternal antibodies may cause long-term immunosuppression. "Given that possibility," asks Bart, "is it even ethical to continue tests of [measles] vaccines that are immunogenic in the presence of maternal antibodies, or should we be going back to animal models?" An advisory group to the National Vaccine Program will discuss ethical issues and other aspects of the high-titer vaccine at a conference on the National Institutes of Health campus next week.

One option sure to come under consideration is to move beyond live attenuated vaccines altogether. A killed measles virus vaccine was used for several years in the United States but was pulled from the market in 1967 when it was shown to increase the odds of getting a severe form of the disease called atypical measles. To this day nobody knows whether the problem is inherent to killed measles viruses or whether it might disappear if the vaccine were processed differently.

Virologists say that ideally they'd like to come up with an engineered vaccine containing protective viral elements and none of the components that cause immune suppression. But given the rather primitive state of knowledge about the measles genome, they concede, it will be years before such an effort has any hope of success.

"Meanwhile," says WHO's Clements, looking on the brighter side, "we still have a very good vaccine for children older than 9 months, and we need to increase coverage." More than 20% of the world's children remain beyond the reach of WHO's measles vaccination program, he says. And much could be gained by simply improving the distribution of the standard vaccine, which by itself has already reduced childhood mortality in Haiti, Guinea-Bissau, and other countries.

"That vaccine has saved millions of lives," Clements says. And in a comment unintentionally ironic for its combination of optimism and disappointment, he adds: "It will continue to be the pillar of measles control throughout the world."

—Rick Weiss

Rick Weiss is a staff writer at Health magazine in San Francisco.

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LETTERS

Business and Science

As the discoverer of *Thermus aquaticus* (*1*), the organism that is the source of Taq polymerase, I continue to be amazed at what has happened to our science as the result of the "biotechnology" revolution. I refer specifically to the 4 December News & Comment article by Peter Aldhous (p. 1572) stating that Hoffmann–La Roche is taking to court companies who produce and sell this enzyme for use in the polymerase chain reaction (PCR). As I understand it, Cetus took an organism that I freely deposited in the American Type Culture Collection, isolated an enzyme from this organism, and sold the patent to Roche, who [illegible] this enzyme for a particular laboratory procedure. I am not concerned about the money involved, but with how such practices (legitimate or not), stifle the development of scientific research. Where would biology and medicine be today if Walther and Fannie Hesse had patented the use of agar in the plate culture technique that Robert Koch developed in 1882? Agar is a natural product, like Taq polymerase, and the plate culture technique is a laboratory procedure, like PCR. The agar plate technique revolutionized medicine in a manner analogous to the PCR method.

Who do these business types who have sneaked into our scientific research community think they are?

Thomas D. Brock
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Measles Vaccine: Titre and Safety

The article "Measles battle loses potent weapon" by Rick Weiss (Research News, 23 Oct., p. 540) discusses the Edmonston-Zagreb (E-Z) measles vaccine, developed by the Institute of Immunology in Zagreb. I would like to comment on some points that may not have been clear. First, the E-Z high-titer vaccine (which contains 10 to 100 times the usual concentration of virus) has been successfully given to Mexican infants (*1*) with no reported death rate that was higher than expected. This contrasts with the puzzling observation that an unusually large percentage of infants given the high-titer E-Z vaccine in Guinea-Bissau died from diseases other than measles. Second, Weiss does not mention that another high-titer measles vaccine (Schwarz) has been used with delayed effects similar to those of the high-titer E-Z vaccine used in Guinea-Bissau; thus the problem may be with high titers, not with the E-Z vaccine itself.

Finally, it should be emphasized that the E-Z vaccine has been used in many countries in Europe, Asia, Africa, and Latin America. Millions of vaccinated children have been protected and have not shown side effects. The E-Z vaccine, given in a standard dose, has been approved by the World Health Organization. A recent consultation [illegible]

The evidence examined at this meeting supports the continued use of standard measles vaccines for all infants in immunization programmes. Standard measles vaccines have been shown to be safe and highly effective and have resulted in significant reduction in morbidity and mortality in numerous countries throughout the world. Measles immunization is generally considered the most cost-effective public health intervention available.

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My colleagues and I spent 4 years studying the Edmonston-Zagreb (E-Z) vaccine while doing field research in a rural area of Senegal. Our conclusions with respect to the safety, immunogenicity, and efficacy of this vaccine given at high titer early in life were different from the results of previous studies. In a clinical efficacy trial (*1*), we found a much higher rate of vaccine failure when the high-titer E-Z live measles vaccine was given to infants 4 to 6 months old than when the standard measles vaccine was given to infants 9 to 10 months old (which was the strategy recommended by the World Health Organization for Africa).

The rationale for the recommended use of the high-titer E-Z vaccine was the higher immunogenicity it provides when given to infants 4 to 6 months old and the hope that it would "pass the barrier of maternal antibodies." However, the study done in Mex-

ico (2) showed there was less seroconversion the higher the concentration of maternal antibodies at the time of vaccination. In our Senegal study (3), we also found no clear evidence of seroconversion among children with high concentrations of maternal antibodies. In fact, most of the clinical vaccine failures occurred in children with high concentrations of maternal antibodies at the time of vaccination. Most other studies did not provide an extensive tabulation of immunogenicity according to concentrations of maternal antibodies.

Scientists who have worked with the E-Z vaccine have observed that the virus infects cells in a different way from the Schwarz vaccine virus. This has complicated the definition of the titer of the vaccines, which is based on evidence of cell infection. There is still a wide variation in the estimates of vaccine titer between laboratories; these estimates span the threshold that distinguishes high-titer vaccines from medium-titer vaccines (4). The excess mortality associated with the high-titer E-Z vaccine was an unexpected development for investigators. there was early enthusiasm for it, and negative findings tended to be ignored.

To solve the problem of early measles mortality, more effort could be devoted to case management, which reduced the measles case-fatality rate by 73% in Senegal, a result similar to that produced by vaccination (1). Although more costly than vaccination, case management is an important complement to immunization.

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Research in Japan

The article "Japanese academics bemoan the cost of years of neglect" by Alun Anderson in the special issue devoted to science in Japan (23 Oct., p. 564) discusses the problem of practices in Japan that "are not exactly welcoming" to foreigners. I believe that the Japanese research community is making great efforts to overcome this problem. Over the past 2 years, as an American living in Japan, I have seen the Department of Public Health in the Faculty of Medicine at the University of Tokyo reach out to the international community. They hosted the Fourth International Symposium on Neurobehavioral Methods and Effects in Occupational and Environmental Health, sponsored by the World Health Organization and the International Commission on Occupational Health in 1991, and offered me and a visiting industrial health physician scholar from Belgium the opportunity to collaborate together on a public health study. In our case at least, there has been no lack of opportunity.

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The special issue on science in Japan did not mention one of Japan's most impressive recent accomplishments—a demonstration of the utility of fuzzy logic in industrial applications. Fuzzy controllers, for example, have been shown to be competitive in performance and cost. Their early use gave Japanese industries a technological advantage and impressive revenues. Moreover, fuzzy controllers have been designed for some control tasks that are beyond the capabilities of classical controllers: Michio Sugeno of the Tokyo Institute of Technology successfully tested one that controlled a pilotless helicopter by simple vocal commands (1). Other applications in knowledge engineering, robotics, medicine, and economics are opening ever greater opportunities for innovations in fuzzy logic.

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Brain Research in Europe

In the article "An uncertain start for a brain decade" by Peter Aldhous (News & Comment, 2 Oct., p. 23), it is stated that the ad hoc task force implemented by the Commission of the European Community (CEC) for preparing a "Plan of Action" for the European Decade of Brain Research is being dominated by neuropsychiatris that the scientific program is mainly f on clinical research and not enou basic neuroscience. As president of th force, I would like to clarify these First, the task force is composed of e from preclinical neuroscience, inc executive members from the Eur Neuroscience Association and other pean societies, and experts from cl neuroscience. The composition of th force is balanced. As reported in the a some parts of the scientific program a being developed. The task force is g by the principles of balance between and clinical neurosciences, interdiscip ry, and communication among all t scientists. The introduction of the sci program states

An understanding of the functions of th represents one of the greatest intellectu scientific challenges to mankind, and at th time will bring far-reaching practical appl which may contribute to solve the majo related medical and psychological problem ence has just reached the point where t ging technologies for this long-dreamt- have been developed: neuroscience has gone a major revolution in the last few ye the basis of the new capabilities created b lecular biology and genetics, by space-age mentation, and by information technology.

Encouraging collaboration with th dustry is important for both applied basic research. The final version of "Plan of Action" will have contribu from the relevant societies and the scie ic leaders from Europe representing basic and clinical neuroscience. It is es tial that this program be approved funded at an appropriate level without ther delay.

If these objectives are achieved, all roscientists in Europe will benefit.

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Fetal Transplant Update

I would like to clarify some of the infor tion in the article by Larry Thomp "Fetal transplants show promise" (New Comment, 14 Aug., p. 868). We have p performed transplants on 54 patients at University of Birmingham in the Uni Kingdom, 48 of which were reported (3 detail) at the Fourth International Sym sium on Neural Transplantation (held fr 12 to 16 July 1992 at the George Washi ton University School of Medicine Washington, D.C.). None of our pati has died as a result of the transplant o

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TRAINING

University of Pennsylvania (USA): M.A and Ph.D. in Demography (1982).

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ENSAE, Paris (France): M.A. in Statistics and Economics (1973).
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University of Paris VI (France): M.A. in Applied Mathematics (1972).
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University of Lyon (France): B.A. in mathematics (1970)
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Languages: French, English

TEACHING AND RESEARCH

1989-1994 : Associate Professor of Demography, Harvard School of Public Health. Boston.
Teaching a course on "Mortality Analysis".
Research focus: child survival, causes of death, measles, vaccines, and impact of health interventions.

1987-1989 : Senior Researcher at ORSTOM, Dakar (chargé de recherche 1ère classe). Head of Research Unit "Population and Health" (Population et Santé). Principal Investigator of an international efficacy trial of the Edmonston-Zagreb vaccine against measles in Senegal. Head of a research project on the diagnosis of pertussis.

1983-1986 : Junior Researcher at ORSTOM, Dakar (chargé de recherche 2ème classe). Head of a research project on the relationship between malnutrition and mortality among children 0-4 years of age in a rural area of Senegal (Niakhar). Head of a research project on causes and consequences of maternal mortality. Head of a research project on the assessment of causes of death through verbal autopsies.

1979-1982 : PhD candidate at the University of Pennsylvania (USA). Dissertation on age patterns of mortality in children in Senegal. Conducted two field studies in Senegal.

1978-1979 : Research Trainee at ORSTOM, Paris. Work on the determinants of fertility using WFS data.

1975-1977 : Statistician-Demographer at the Ministry of Planning in Algiers (Algeria). Work on the census, vital registration, longitudinal analysis. Factorial analysis of fertility determinants.

1973-1975 : Assistant Professor at Algiers University (Assistant-VSN). Teaching statistics for second year students in economics.

PROFESSIONAL AFFILIATION

Member of the IUSSP (International Union for the Scientific Study of Population).
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HONORS

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