MICHEL GARENNE vs. PETER AABY

(2) **Report from the appointed ad hoc sub-committee**

February 1994

Michel Garenne (MG), Associate Professor of Demography at the Harvard School of Public Health, has in a letter to the **Danish Committee on Scientific Dishonesty (DCSD)** of May 27, 1993 raised charges against **Peter Aaby (PAa),** mag. scient., dr. med., Epidemiology Research Unit, Statens Seruminstitut, Copenhagen, for: **1.** recommending a certain strategy of measles vaccination in Senegal in spite of his knowledge that this strategy involved severe risks, **2.** inappropriate data collection and analysis and **3.** Publication of data belonging to MG. The letter also contained **(4.)** a number of additional charges.

DCSD decided, August 25, 1993, according to usual practice to appoint an **ad hoc sub committee (AHSC)** to investigate the case:

Member from DCSD:	Professor Daniel Andersen, Copenhagen (chairman)
Member from DCSD:	Professor Povl Riis, Copenhagen (substituting Daniel Andersen from January 4, 1994)
External expert member:	Professor Morten Harboe, Oslo
External expert member:	Professor P. Helena Mäkelä, Helsinki

MG (letter of November 4, 1993) and PAa (letter of October 27, 1993) had no objections to the membership of the AHSC.

Material used

This report from AHSC is based on MG's letter of May 27, 1993, PAa's response of August 24, 1993, MG's response of November 4, 1993, PAa's responses of November 16 and 22, 1993, on several papers and letters contained in the two basic documents from MG and PAa, and on material requested by AHSC from PAa, from professor Paul Fine, London School of Hygiene and Tropical Medicine, University of London, from dr. Francois Simondon, the French research organisation ORSTOM, and from the Danish statistician Kim Mark Knudsen.

A list of the documents used is found on the pages 24-32. The first 5 items are MG's and PAa's letters. Thereafter follow all other documents in the order of the date of their origin. A short summary of the content of each document is presented, and sometimes comments are added. The documents will be identified in the report by their number in the list.

Background.

Measles vaccines of the standard Schwarz (SW) type are given to children at 12-15 months of age in European countries. In Africa, and many other areas of the world, there is a need for earlier vaccination because of the much higher risk of infection already after 4-6 months of age. Maternal antibodies may decrease the efficacy of vaccination when the vaccine is based on a live attenuated microbe, this is known to be the case for the current measles vaccines. It has, therefore, been a major goal to develop new types of measles vaccines, which can be effective in spite of maternal antibodies. SW has been used from the age of 9 months, and conveys a satisfactory protection, but it still leaves an interval from 4 to 9 months with a high infective risk and a high mortality.

Evidence has been found for a satisfactory immunization already at the age of 4-5 months using Edmonston-Zagreb vaccine at a high titer (EZ-HT), and strategies consequently have been developed for the use of this vaccine in areas like Africa, with a high incidence of measles.

PAa et al. published a paper in 1988 (7) based on a study from Guinea Bissau performed in 1985-87. It supported the view, that EZ-HT afforded significant protection from the age of 4 months, while SW, given at 9 months, was "not satisfactory" since a number of cases of measles developed among those children following this scheme of immunization.

In December 1986 agreement was reached about a collaborative project in Niakhar, Senegal, studying efficacy, safety and immunogenicity of two high titer measles vaccines (EZ-HT and high titer Schwarz vaccine (SW-HT)) and one standard vaccine, SW (6). The study was funded by the Task Force for Child Survival, Atlanta, GA, USA (TFCS), by ORSTOM-UR Population et Santé, Paris and by the British Medical Research Council, The Gambia. The study was based on a pre-existing demographic and epidemiologic surveillance system of a rural population of about 25.000 people. A Data Monitoring and Safety Committee (DMSC) with representatives from the Ministry of Public Health, Senegal, TFCS and ORSTOM followed the progress of the study and made decisions about the performance of the study.

MG was Project Director from the start of the project and until June 1990 when PAa became Principal Investigator for a continuation of the study 1990-94 (protocol see (11) and (12)).

In the study starting 1986 a total of 24 monthly birth cohorts were randomized to vaccination with a HT-vaccine at age 5 months or SW at age 10 months. The first 16 cohorts (vaccinated August 1987 - October 1988) were randomized to either EZ-HT, SW-HT or SW, while the last 8 cohorts (vaccinated November 1988 - June 1989) were randomized only to EZ-HT or SW, since the SW-HT had given inferior serological response. This change was decided by DMSC in October 1988 (9).

The results from the study have been published by MG et al. in a final report (30), issued by ORSTOM in June 1991, and in an article (31) which is especially relevant for the actual case (Lancet October 12, 1991). These publications indicated an increased long-term mortality in children vaccinated with high-titer vaccines (EZ-HT and SW-HT) as compared to children receiving the standard Schwarz vaccine (SW). The excess mortality became evident about the age of 18 months and, therefore was detected with some delay.

EZ-HT was recommended by WHO/EPI (Expanded Programme of Immunization) in October 1989 for infants at 6 months of age, but the recommendation was withdrawn in November 1992 (40).

Investigation carried out by AHSC

In the following sections AHSC will analyse the two main charges: 1. irresponsible vaccination strategy and 2. inappropriate data handling, separately. The 3rd charge concerning ownership of data and 4th, additional charges, will be commented on. In every sub-section of the analyses statements from the persons involved and the contents of relevant papers and letters will be presented followed by comments and conclusions from AHSC.

1. MG's charges concerning the strategy of measles vaccination recommended by PAa.

In his letter of May 27, 1993 (1), p. 1 and 2 MG writes about some earlier work of PAa: "Here again, Mr. Aaby's findings were based on inappropriate data collection and inappropriate analysis. Fortunately, this case did not have much importance....." "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."

On p. 4 MG states, that PAa, assisted by his co-worker F. Simondon in the summer 1990 decided to carry out an unauthorized mass vaccination in Senegal, although "he was among the few people to know that the vaccine was seriously increasing the risk of death of children." MG also states on p.4, that PAa and F. Simondon in November 1990 "refused to present the data to the representative of the Ministry of Health in Senegal and decided to continue the vaccine." MG maintains that his intervention in November 1990 brought a stop to the mass vaccination.

The charges of MG can, according to the above mentioned statements, be summarized as follows: PAa recommended and carried out an EZ-HT vaccine strategy during the summer 1990 in spite of prior knowledge of severe problems in respect to long-term mortality, and he tried to suppress information about these problems.

Review of events.

Spring 1989

MG (1): PAa warned MG that he had found a clustering of child deaths among female recipients of EZ-HT in Guinea Bissau (p.3). The results were statistically non-significant. MG's results from Senegal did not reveal any excess mortality at that time.

PAa (2): Warned MG about possible problems with a higher morbidity, especially diarrhoea, after EZ-HT than after SW already in 1987 or 1988 (p.10). Gave also warnings about excess mortality in 1987 or 1988 ($p=0.10$) (37). He had noted this higher mortality during a second study in Bissau 1986-88. He had discussed it with Hilton Whittle (senior researcher, Medical Research Council). Analyzing the unexpected findings, they decided to use $p<0.01$ as the appropriate level of significance when considering to bring the trial to a stop.

MG (3) Reproaches PAa (p.3) for not having warned about increased diarrhoea in the Lancet paper of October 8, 1988 (7).

Comments from AHSC:

It appears from these statements that there exists a certain disagreement about the time and the nature of PAa's warnings. This matter seems not, however, to be very important. PAa had at the latest in the spring 1989, and perhaps earlier, discussed an observed excess mortality after EZ-HT in Bissau with MG. MG had in a progress report on the 1986-89 Niakhar study from October 1988 expressed the view, that EZ-HT seemed to be safe (8) and a report in June 1989 to DMSC did not find any excess mortality for EZ-HT (10). MG and PAa were, therefore, not ready to take any consequences, since the findings were uncertain, and statistically non-significant at conventional levels.

PAa's paper (7) concerned the first study in Bissau (1984-86), while the comments on increased diarrhoea and mortality concerned the second study in Bissau (1986-88). MG, therefore, could not expect PAa to comment on the diarrhoea problem in this paper.

The use of a low p-value in case of unexpected findings at interim checks is usually considered a wise precaution.

AHSC considers the disagreements between MG and PAa about the events in the spring 1989 to be unimportant. Suspicions about excess mortality after EZ-HT were raised on the basis of data from Bissau, but it was in the opinion of both investigators too early for consequences to be taken.

AHSC finds no support for any dishonesty in PAa's actions in the spring 1989.

Spring 1990

MG (1): MG and PAa compared their data in Boston in April 1990 (p.3). There was now a trend towards an excess mortality in Senegal as well as in Bissau for children vaccinated with EZ-HT. When pooled the results were statistically significant. WHO was informed by PAa on behalf of both investigators.

PAa (2): PAa had already in January 1990 informed WHO/EPI about a possible negative effect of EZ-HT in Bissau (p.2), especially in girls. At the meeting in Boston in April 1990 (p.10) there was no trend towards a higher mortality in the data from Senegal, when they were considered as a

whole, only a difference of two deaths (EZ-HT 41, SW 39). But there was the same skewed sex ratio in mortality as found in Bissau with an excess mortality in girls. Even when pooled, the two studies did not show any statistical significance. The warning of WHO/EPI (see above) took place in January 1990, and it was not on behalf of MG and PAa, but only PAa.

MG (3): Maintains (p.6) that the combined results were statistically significant in April 1990. On p.1 MG states, that the Ministry of Health, Senegal should have been informed as early as June 1990 when the combined results from the Bissau and Senegal were statistically significant ($P<0.05$). He claims (p.3) similarities with the situation, when donor blood was not screened for HIV when testing kits became available.

Comments from AHSC:

MG and PAa disagreed in the spring 1990 about the statistical significance of the data and the consequences to be taken on them. Both investigators were, however, aware of observed excess mortalities among recipients of EZ-HT. PAa stressed a sex difference, which MG found less important.

PAa had in January 1990 (13) informed WHO/EPI about an excess mortality in girls after EZ-HT in his study from Bissau, but Dr. Clements, EPI, indicated the need to await further information before any steps were taken. AHSC, thus, finds that PAa had informed adequately on the basis of the data he had.

MG finds, that the combined and statistically significant results from Bissau and Niakhar as discussed at a meeting in Boston in April 1990 gave reason for a warning of the Ministry of Health, Senegal in June 1990. PAa denies this in (2). In his letter to MG in May 1990 (15) he did express the view, that a non-significant trend for a higher mortality existed in girls in the Niakhar study, but he found further observation necessary, and in (2) he maintains that the combined studies did not give a significant result.

MG and PAa agreed, that the single studies gave statistically non-significant results (1,2,3). As to the combination of studies, carried out according to different protocols and without any prior planned combination, AHSC finds that much doubt exists about the justification of any such procedure. It is different from well organized multicenter studies and meta- analyses. AHSC, therefore, finds it of minor importance whether a combination of the results produced a so-called significant p-value. The important matter for a continuation of the Niakhar study must be the results from this study. In respect to this MG did not as late as June 1990 (16) and August 1990 (22) find any significant excess mortality for EZ-HT. MG later (3) denies the value of these data

(from 22), since they were incomplete. They were, however, what he had, and they were the basis for his conclusions at that time. In August 1990 (21) MG, furthermore, declares that a potential relationship between EZ-HT and an increased mortality is a preliminary hypothesis to be investigated. It follows from these quotations, that a warning to the Ministry of Health in June 1990 could not have received the support of MG, and it seems unreasonable for him to demand such an act from PAa.

AHSC finds it incorrect when MG in (1) and (3) and in the final report (30) indicates that a statistically significant excess mortality after EZ-HT was found as early as April 1990. Instead, the data suggested a possible, unexpected adverse effect of one vaccination strategy compared to another. In this situation it was very important to carefully collect and analyze as much information as possible to obtain a decisive result. This was especially important because of the far-reaching consequences of the result on the world-wide vaccination-programmes recommended by WHO/EPI: If measles vaccination at 5 months were possible, a large number of potentially fatal cases of measles could be prevented; on the other hand, if the early vaccination itself increased the risk of death, it would not be recommended, and the benefits could not be obtained. It is a matter of judgement to decide when results of this type of study are so alarming and so definite as to require a major change in the protocol. Much harm could be done by a sudden change in a vaccination programme, since it might be interpreted by the community as a negative signal, warning against vaccinations in general. It is obvious that these effects were very carefully considered by PAa and his collaborators, when deciding not to report, in June 1990, on the at that time very uncertain findings to the Ministry of Health, Senegal, and again when deciding to stop the use of the EZ-HT vaccine and to inform the ministry in November the same year.

The observed late mortality after EZ-HT was unexplained and poorly understood, because the deaths had no specific cause, which could be explained from known biological effects of the immunization. This might have added to the uncertainty about the reality of the phenomenon, which was shared by others than PAa (cf. the letter from Paul Fine (47)).

AHSC can not find any support for allegations about dishonesty or irresponsibility in PAa's actions in the spring 1990.

Summer 1990

MG (1): WH0 resolves to let PAa replace MG as Principal Investigator in the vaccine-project in Senegal. PAa decides with F. Simondon to carry out a mass vaccination with EZ-HT during the summer 1990 (p.4) although he knew the risk and had warned WHO about it.

PAa (2): In June 1990 DMSC had a meeting in Dakar. PAa was elected Principal Investigator for the Long Term Follow Up project in Niakhar, Senegal for the period 1990-94). EPI in Senegal wanted more effort done to get children from the first trial cohorts vaccinated if they had not received the planned immunization during the first year of life. PAa believes (p.10) that the mass vaccination mentioned by MG must be the immunization of the un-immunized children from the first cohorts. This immunization involved 136 children, all more than 10 months old.

MG (3): Mentions again a mass vaccination campaign during the summer 1990, initiated by F. Simondon (p.2 and p.6). States that it was not approved by the Ministry of Health. Finds that a letter from PAa to EPI (23) proves that PAa concealed the facts to the Ministry. MG informed ORSTOM, Director General, who did not want to interfere.

Comments from AHSC:

It follows from these quotations and from (17,18,36,38,41,42,44) that PAa took over after MG in June 1990 as Principal Investigator.

Disagreement exists about a vaccination campaign in the summer 1990. MG mentions (1,3) a mass vaccination but is not very specific about it. In (21) he mentions some "weird vaccinations" done by F. Simondon in May 1990. It seems at least partly to have been re-vaccinations, and MG expresses concern that they will reduce exposure to measles and impair the trial. PAa maintains that he did not start any mass vaccination at that time.

The vaccinations mentioned in the various papers are:

1. EZ-HT vaccination as part of the 1986-89 Niakhar study (6)

2. PAa explains (2) that he after request from EPI completed on a limited scale (136 children) the trial already started by immunizing un-vaccinated children (non-attenders). MG offers no comments on this in (3). The follow-up vaccination was planned as part of the protocol for the Long Term Follow Up of the 1986-89 Niakhar project (11) and (12), which was approved by the Gambia Ethical Committee (29). In the protocol is mentioned a number of 636 children. At the DMSC-meeting in June 1990 (17) immunization of un-vaccinated children was mentioned as one of the tasks to be done by PAa, and he planned to do so (19).

3. PAa also explains that EZ-HT was used as part of a trial of pertussis vaccination (39) under the responsibility of F. Simondon. This is also described in the protocol for the follow-up of the 1986-89 Niakhar study (11) and (12). MG did not object to this part of the follow-up study (21). It was planned to use EZ-HT, with the first vaccinations starting in April 1990 (49). In November the plan was, however, revised and EZ-HT was replaced by SW (39).

4. F. Simondon explains (49) that besides the vaccinations taking place as part of protocols (6,39,12), children born between February 1989 and October 1989 were vaccinated with EZ-HT without a protocol.

5. F. Simondon, furthermore, explains (49) that a vaccination campaign in May 1990 was nation-wide and was initiated by the Regional Medical Officer on behalf of the Ministry of Health (51). SW and not EZ-HT was used.

The vaccinations mentioned as items 1, 2 and 3 were initiated by others than PAa and were carried out under the full understanding of his superiors. The vaccination mentioned under 4 was a routine immunization taking place after the completion of the 1986-89 trial, and EZ-HT was used according to the recommendation of WHO, valid at the time (40). PAa was not in charge until June 1990. The vaccination mentioned under 5 was carried out by F. Simondon. MG states that EZ-HT was used, F. Simondon that SW was used. Even if EZ-HT had been used the vaccination would have been in accordance with the recommendations of WHO. F. Simondon specifically mentions that the national health authorities ordered the campaign. This is corroborated by letters exchanged between F. Simondon and a representative from the Ministry of Health (51). MG is very vague about the nature of the alleged mass vaccination, both in (1) and in his response (3) to PAa's statement (2).

AHSC concludes, that the campaign MG alludes to is the vaccination mentioned under 5. It was performed under the initiative and approval of the national authorities and it was decided on before PAa took charge. He had given warning in January 1990 about suspicions of an increased mortality after EZ-HT. ORSTOM was informed by MG about the alleged mass vaccination (3, p. 6), but did not interfere. AHSC, therefore, finds, that any vaccination which might have taken place was known by and approved by PAa's superiors and that it was in accordance with the prevailing WHO-recommendation (40).

AHSC can not find any evidence for dishonest or irresponsible behaviour of PAa during the summer 1990.

November 1990 to March 1991

MG (1): Just before a meeting in the DMSC in November 1990 MG informed the Committee, by fax of November 5 (24), about an at this point significant excess mortality in the Senegal trial in the EZ-HT group. He asked the Committee to stop the use of EZ-HT and inform the Ministry of Health. When they refused, MG informed the Ministry, and the use of EZ-HT in Senegal was stopped.

After this the WHO called a meeting in Geneva in March 1991. MG did not succeed in convincing the investigators, and, therefore, published his results (Lancet October 12, 1991 (31)).

PAa (2): The meeting in November 1990 was not a DMSC meeting, but a meeting with representatives from EPI, intended as an internal discussion, and no representative of the Ministry was present. The group did not refuse to inform the Ministry and actually did so by a letter of November 11, 1990. It was stated, that the group had decided to suspend the use of EZ-HT until further information was available. It was not a decision of the Ministry.

The meeting in Geneva was in February 1991 (not in March 1991) and was held on PAa's initiative.

MG(3): Maintains (p.2), that the meeting in November 1990 was in DMSC. PAa tried to suppress the information about excess mortality among EZ-HT vaccinated children. When they eventually informed the Ministry it happened after MG's intervention.

Comments from AHSC:

There is some disagreement between MG and PAa in respect to the nature of the meeting in Dakar, November 7-9, 1990. MG maintains that it was a meeting in DMSC with representatives from the Ministry of Health. PAa indicates, that it was a meeting arranged to discuss the project with representatives from EPI, but that it was not a meeting in DMSC, and that no representative from the Ministry was present. F. Simondon reports in his letter of November 13 (25) to the Ministry about the meeting, and he gives the names of those present. It, thus, becomes clear, that it was a meeting between some of the investigators in the project, representatives from ORSTOM and Dr. L. Markowitz, consultant for WHO/EPI. It was not a meeting in DMSC, and no representative from the Ministry was present. This corroborates PAa's statement. Furthermore MG gives a list of DMSC-meetings in his final report (30). According to that list no meeting took place in DMSC in November 1990.

When this is made clear, it also becomes clear, that it is without any reality, that PAa should have tried to hide the facts from the Ministry at the meeting. PAa had informed EPI about an excess mortality in the first 16 cohorts of the Niakhar study in a letter of September 26, 1990 (23) which is the same message as MG presented for the meeting by his fax of November 5, 1990 (24). MG, thus, had no new information, which was not known to PAa beforehand and which he had not passed on to his superiors. PAa wanted according to (23) to postpone information of the Ministry until the data had been discussed at the meeting in November 1990. After this meeting had taken place, the Ministry was informed (25).

MG wanted to stop EZ-HT immediately (24). PAa was not that determined (23), but found it advisable to follow MG and recommend suspension of immunization with EZ-HT in order to avoid anxiety in the population, until more information was available (5). This decision about suspension of EZ-HT was a result of the meeting (25), and the Ministry had not, as maintained by MG, taken any initiatives to that effect at that time. Later, however, on November 27 (28) it was decided by the Ministry to follow up on the November meeting and make an official stop of the use of EZ-HT. WHO (26,27) and ORSTOM (28) found the decision premature and wanted to uphold the recommendation from WHO of the use of EZ-HT.

AHSC finds that PAa is correct when he states that he and his co-workers took the decision to suspend the use of EZ-HT, and that MG is wrong when he states that it was a decision taken by the Ministry after his intervention. The Ministry took decision about 3 weeks later and it was against the advise of WHO and ORSTOM.

These quotations demonstrate, that disagreement existed between MG and PAa in respect to the consequences to be taken from the available data. PAa felt inclined to wait and see in order to get further information, as recommended by WHO/EPI, while MG wanted to act immediately. In the end PAa did suspend the use of EZ-HT and he did with his co-workers inform the Ministry about the problems.

It seems, therefore, that PAa and co-workers have taken adequate steps to inform the Ministry in Senegal and to have suspended the immunization programme with EZ-HT and in accordance with the wishes of MG, although they were not convinced about the necessity of doing so.

At a consultative meeting in Geneva in February 1991 (40) arranged by WHO/EPI, on the initiative of PAa (50) it was decided to uphold the recommendation of EZ-HT after the guidelines from 1989. MG, PAa and co-workers seem, therefore, to have been even more cautious than the responsible authorities found necessary.

AHSC's conclusion about the charges raised concerning the continuation of a vaccination strategy in spite of knowledge about increased risk, and concerning withholding of information:

From the available evidence it can be concluded, that PAa has consulted the relevant authorities and given warning as soon as his and MG's information was sufficiently reliable to give grounds for changes in the immunization policy. PAa and his collaborators stopped the use of EZ-HT by their own decision in November 1990 at the same time as MG requested it.

There is no evidence for the view that PAa should have started new mass vaccinations during the summer 1990. F. Simondon has explained about the campaigns, and PAa was not responsible for any of them, and he did not take the initiative to do them.

Confronted with PAa's denial in (2), MG has not given any further evidence to support these allegations (3).

AHSC furthermore points out that the allegation that "the strategy recommended (of use of EZ-HT (1, p. 2)) could have caused the death of many millions of children..." is misleading and has not been supported by any calculations of the adverse effects in relation to the benefits of protection from measles between the ages of 6 and 9 months in areas of high measles incidence, i.e. areas to which the WHO/EPI recommendation pertain.

AHSC will on this basis draw the conclusion, that PAa is to be cleared for these allegations.

2. MG's charges concerning inappropriate data collection and analysis.

Charges concerning PAa's work in Guinea-Bissau.

MG (1) On p.6 MG criticizes a paper written by PAa and co-workers in The Lancet, October 8, 1988 (7). The paper describes a study from Guinea-Bissau, where a trial of measles vaccination was carried out in 1985-87. The children were randomized to either EZ-HT at age 4 months or SW at age 9 months. MG quotes the authors for stating, that SW was hardly efficacious, and that EZ-HT was almost perfect. He criticizes the study on several points: The children were not vaccinated at the same age and many in the EZ-HT group were vaccinated beyond the age of 9 months. There were no serological confirmation of measles cases. The number of vaccine failures was small making conclusions impossible and confidence intervals were not computed. Survival analysis was not presented.

PAa (2): The study was designed to compare two different vaccination strategies, EZ-HT starting at 4 months, and SW starting at 9 months. It was not intended to carry out the vaccinations at the exact ages of 4 and 9 months.

Comments from AHSC:

AHSC has asked professor Paul Fine, London, as an independent expert, and the statistician, Kim Mark Knudsen, Copenhagen, a co-author on the paper, about their views on the statistics used in the paper.

Paul Fine (47) considers MG's criticism to be unjustified: PAa did not use the expression, that the SW was "hardly efficacious", but stated that it was "not satisfactory". This was justified, given the observed failures. It was unavoidable to vaccinate at different ages in the comparison of two strategies. AHSC points out that these in fact were the only realistic alternatives for measles vaccination. At least 11 cases of measles were serologically evaluated. The comments about absence of confidence limits and survival analysis were not important.

Kim Mark Knudsen (48) points out, that the log rank test used is standard procedure, but exact tests were also used for comparison. Since the results were almost identical, only the log rank test was stated.

AHSC finds MG's criticism a little hard to understand. The paper explicitly states that survival analysis was done with Kaplan-Meier estimates and that log rank test was used. The results were presented albeit without a graph.

AHSC will from the statement from Paul Fine and the elaboration from Kim Mark Knudsen conclude, that the Lancet-paper from 1988 (7) describes a reasonable research plan and presents a satisfactory data management without any indication of impropriety.

Charges concerning PAa's analysis and interpretation of data from the Senegal study.

MG (1): At a WHO-meeting in Geneva in March 1991 MG presented data indicating an excess mortality for EZ-HT as compared to SW. His views were not generally accepted by the other delegates at the meeting. MG published the results in The Lancet, October 12, 1991 (31). Following this PAa tried to manipulate the data in order to reduce the statistical significance (32). He did not use life table analysis, and he used a sex difference for arguing to continue using the vaccine. After the publication, WHO decided to have an independent expert review, which was carried out by prof. Paul Fine, London. After that, WHO decided to stop the vaccination with EZ-HT.

PAa (32): Explains in a letter to the editor of The Lancet, December 14, 1991 (32): MG did only publish 16 of 24 cohorts of vaccinated children. In the 16 cohorts there was found an excess mortality for girls vaccinated by EZ-HT as compared to SW, but not for boys. The remaining 8 cohorts showed the opposite trend with a reduced mortality in the EZ-HT group. PAa points out that vaccination has been suspended, and that there is reason for concern about the safety of EZ-HT.

MG (33) Replies in The Lancet, December 14, 1991: PAa did not use life table analysis. When this is done the excess mortalities for EZ-HT in cohorts 1-16 and 1-24 are seen more clearly. MG does not consider the sex difference important and finds it unacceptable to justify continued use of EZ-HT with the argument, that an excess mortality is only found in women.

Kim Mark Knudsen

(48): The results (in 32) were, as stated in the paper, evaluated by life-table analysis, using a Cox regression model, as well as by crude estimates. It is, therefore, not correct when MG critizises a lack of life table analysis. In the analysis all 24 cohorts should be used, and the last 8 cohorts ought not to be left out as MG did.

MG (3): The analysis was based on the first 16 monthly cohorts because the scheme of randomization was changed thereafter (p.7). In the 16 cohorts the children were randomized to EZ-HT, SW-HT or SW. In the last 8 cohorts only EZ-HT and SW were used. By using the first 16 cohorts the effect of titer could be made visible. MG also emphasizes that the observation period for the last 8 cohorts was too short. PAa ought to have published his data from Bissau instead of trying to reduce the statistical significance of MG's data from Senegal in his Lancet-letter of December 14, 1991.

Paul Fine

(47): It creates a problem that long term mortality and sex differences were not formulated as criteria for evaluation prior to the trial. Sub-group analysis of survival based on cohorts or sex, therefore, involves risks for unjustified conclusions. PAa was correct in (32) to caution against being too conclusive on the basis of MG's interim analysis or on the basis of gender sub-group analysis (31). The claim, that PAa manipulated the data seems not justified.

The question of excess risk by using EZ-HT is not conclusively decided. P. Fine could in 1992 only conclude about an overall effect, including both sexes, that: "The probability of such a combined result occurring by chance, even if there were no true increase in mortality risk associated with these vaccines is in the order of 1 in 20. In this sense the results cannot be considered conclusive".

Comments from AHSC:

The data from Senegal presented in several tables in (22,23,24,31,32,33,34,43) and in the final report (30) consistently show an excess mortality after HT-vaccines. Girls consistently have an especially high excess mortality after EZ-HT and SW-HT as compared to SW. The sex difference was most pronounced for EZ-HT. All the differences were of relatively low statistical significance.

In spite of this general consistency MG and PAa disagree about the facts from the study:

The absolute numbers of deaths vary between the tables depending on the observation periods and the care taken in securing all deaths, but the message is the same.

The statistical significance varies depending on the methods used, and the sex difference becomes more or less marked according to the method of calculation: whether comparison takes place within vaccination groups (MG) or between HT-groups and SW (PAa). The excess mortality after HT-vaccines and a sex difference do, however, come forward whatever method is used.

AHSC can not find any indication of dishonesty behind these professional differences of opinion about methods, when the substance in the results stands undisputed. Much disagreement probably would have been avoided, if the statistical calculations had been planned and agreed upon beforehand.

AHSC agrees with the point made by Paul Fine (47) and Kim Mark Knudsen (48), that it is a dangerous practice to base conclusions on reports comprising only a part of the material in the study (16 cohorts instead of 24 in the Lancet paper (31)).

MG and PAa do also disagree about the weight to put on the sex difference:

MG feels that PAa stresses the sex difference and the small differences in results for boys between different vaccine groups in order to cast doubt about the reality of the excess mortality after HT-vaccines.

AHSC finds it proper that PAa draws attention to the sex difference since this gender phenomenon has been found in 3 of 4 major studies (40), which supports the reality of the difference. PAa has indicated concern for the safety of HT-vaccines at several occasions, also in (32), and AHSC, therefore, can not accept that his interpretation of the results should serve other purposes than elucidation of the problems involved in HT-vaccines.

AHSC finds no indication to the effect that dishonesty should have played any role in the professional difference in interpretation of data.

AHSC finds it proper, as Paul Fine did (47), that PAa in (32) makes it clear, that sub-group analysis and short observation periods harbour risks for erroneous conclusions.

Since the correspondence was a reaction upon MG's Senegal data, it seems unreasonable to claim, that PAa ought to have presented his Bissau data at that occasion.

AHSC also points out that the incidence of measles during the study, especially pertaining to the first 16 cohorts, as described in (31) was low.

This was a situation in which the expected benefits of measles vaccination became impossible to evaluate, specifically the expected benefit of immunizing at 5 rather than 10 months of age. The basic reason for recommending early measles vaccination is to obtain a protective effect in areas of high measles incidence (as explicitly stated in the WHO/EPI recommendation); such an effect would not be seen in periods of low incidence. Therefore, only the possible adverse effects of the vaccines would be seen, instead of the benefits.

AHSC's conclusions about the charges raised concerning PAa's treatment and presentation of data.

Having considered the charges from MG against PAa for his handling of data from the Bissau and Senegal studies, AHSC must conclude that it has found nothing but understandable professional disagreements about statistical methods and interpretation of data with low statistical significance, and differences in opinion about the time and way in which to react upon the findings. The data and methods have been clearly described by PAa and have been open for discussion and critics. No indication of dishonesty has been found.

3. MG's charges against PAa for using data belonging to MG.

MG and PAa have successively been principal investigators in the same study area. Both participated as investigators in both projects (6,12). MG was the director for the Niakhar measles project from 1986-June 1990. At a Working Group meeting (17) in Dakar in June 13-15 1990 PAa was appointed Principal Investigator for a Long Term Follow Up Study, which was approved by the Ministry of Health.

The protocol for the Follow-Up study (12) specifies analysis of the cumulative mortality until the end of 1994 as one of the tasks of the program.

In letters from ORSTOM to PAa and to Statens Seruminstitut, Copenhagen of March 11, 1992 (36) PAa is appointed scientifically responsible for the follow-up programme. The programme had till then been carried out by ORSTOM in collaboration with PAa. The Co-ordination Committee for the program now wanted to make PAa's responsibility the subject of a formal contract.

In a letter of June 29, 1992 TFCS and ORSTOM made an agreement (38) to the effect that PAa became Director for all matters relating to data collected under the former contract (terminated December 1991) on the 1986-89 Niakhar study. He also became co-ordinator for all following studies relating to the vaccine trial. PAa should give his approval prior to any publication of results under this agreement.

In letters from ORSTOM to TFCS (44) and to PAa (45) of May 17, 1993 information is given about a new Bureau permanent, which will take over the management and publication of data from the 1986-89 Niakhar study. The contract of June 29, 1992 (38), therefore, is terminated. This does not affect the contract of March 11, 1992 relating to the Follow-Up study (36).

March 8, 1993 a subcontract was signed between ORSTOM and Statens Seruminstitut, Copenhagen. It was a subcontract under a contract between Statens Seruminstitut and EEC on research in developing countries. The subcontract relates to the Long Term Follow Up Study of the measles program. It became effective from January 1, 1992. No data before January 1, 1992 can be utilized as a result of the present program.

From these letters and contracts emerge a rather complex situation in respect to the right to the use of data from the project.

Until June 1990 no doubt exists about the right of MG to the data. After that time PAa was Principal Investigator for a Follow-Up project. One of his assigned tasks in that project was to analyze cumulative mortality for several years. This must of course imply a right to the use of data from 1986-89 necessary for this analysis.

In principle no problems should exist in a sharing of the right between MG and PAa. PAa actually indicates his interest in such a co-operation with MG in a letter of July 21, 1990 (20).

Soon personal problems, however, between MG on one side and F. Simondon and PAa on the other side made this solution difficult to handle.

There is no doubt about PAa's right to the follow-up data 1990-93 (12,17,36,44,45).

Quite a new situation was created by the contract of June 29, 1992, which was effective until May 17, 1993. This contract gave PAa all rights to the data from 1986 until 1993, and it abolished any right MG might have preserved.

MG declares (3) that a "Lettre de mission" for PAa states that he can not utilize data collected after January 1, 1992. Actually it is the subcontract already mentioned(41) and not a Lettre de mission. What the exact meaning is, stands not quite clear. The subcontract does not specify who has the right to data from June 1990 to January 1992, and it probably can not erase the contracts for the Long Term study ascribing the right to data after June 1990 to PAa. The subcontract may not be the only source of economic support. It can, therefore, hardly determine every aspect of the project. In all circumstances the subcontract does not specify any exclusive right for MG to the data from June 1990 to January 1992. From May 1993 neither MG nor PAa have any rights to data from the 1986-89 study (44,45).

In summary:

Until June 1992 both MG and PAa seem to have some right to use the data from the 1986-89 study. PAa at least to the extent that he could perform cumulative mortality analysis.

From June 1992 - May 1993 PAa alone had the right to the data from the 1986-89 study.

From May 1993 neither MG nor PAa have any right to the data from the 1986-89 study.

PAa has the right to the follow-up data.

There exists, thus, a complex and not at all clear situation concerning the right to use the data from different periods. This matter, however, has to be decided in co-operation with the funding and supervising authorities.

AHSC finds no indication of improper utilization of data by PAa.

4. Additional charges

A. In the initial letter to DCSD (1) MG states: "Therefore, I was extremely disappointed by his very controversially political attitude during the case of the Edmonston-Zagreb." (On page 2.) On page 7 it is further stated: "Mr. Aaby is an excellent politician. In fact, his background was in political anthropology. But, is this going to make him a "good scientist"?".

These statements have no further specification and are not substantiated. AHSC considers these statements immaterial for the case and out of place.

B. On page 7 in (1) MG states: "Recently, in December 1992, Mr. Aaby has been excluded from ORSTOM, after many requests from the Scientific Commission and from the Researchers Union".

A statement from ORSTOM (46) however, specifies that PAa continues to be responsible for the follow up study (36), and a new contract concerning a continuation of the follow up study was made in May 1993 (41).

AHSC , therefore, finds MG's statement to be untrue.

C. In his reply to PAa and colloquies of November 1993 (3) MG claims: "By hiding the facts and by organizing a mass-vaccination campaign in Senegal in the Summer 1990, Mr. Aaby new that he was putting many children at excess risk of death. This situation has some similarities with that when people refused to screen the blood bank for presence of the AIDS virus when testing kits became available".

AHSC finds this comparison misleading. With regard to the measles vaccination, the observed late mortality after EZ-HT was uncertain and unexplained. By contrast, the appropriate and serious criticism of lack of HIV testing of blood products relates to a situation, when appropriate test kits had been developed and the consequences of the use of HIV contaminated blood products had been established.

AHSC finds this additional charge against PAa in a late document irrelevant.

D. MG accuses PAa of not informing the families of children vaccinated with the EZ-HT vaccine in the study, and of not arranging for appropriate care and financial compensation to these children.

The increased risk of death, if indeed true, became known only late during the follow-up. At the time the study children were already beyond the age of high risk of death, and no further action could have given additional benefit. All the children in the study had access to medical care, very likely better than would have been the case if there had been no study going on. It would not have been possible to prevent the deaths observed in the study because of their very unspecific nature. Thus no benefit would have accrued to the children from such information, which, on the other hand, might have caused much anxiety in the community, and adversely affected the trust of the people in the health care as a whole.

In conclusion, AHSC finds all the charges under point 4 unfounded. This observation should be considered in relation to the evaluation of MG's credibility in the other charges against PAa.

5. THE AD HOC SUB-COMMITTEE'S SUMMARIZED CONCLUSION:

1. MG's charges concerning the strategy of measles vaccination recommended by PAa

In accordance with the AHSC comments and evidence related to these charges, Peter Aaby should be relieved of all accusations of dishonesty in handling and presenting the measles studies in Bissau and Senegal. This also holds true for his relations to the involved authorities.

2. MG's charges concerning inappropriate data collection and analysis

Peter Aaby has not performed any dishonest actions in his administration or presentation of data in respect to the measles studies in Bissau and Senegal, and he has not in any way been dishonest in his relations to his superior authorities. AHSC finds Michel Garenne's accusations to be unfounded.

3. MG's charges against PAa for using data belonging to MG

AHSC finds the conditions established in the various contracts concerning right to publish data from the vaccinations programmes to be complex. Some are probably even mutually incompatible. This is difficult to avoid in programmes with several investigators and different organisations serving as employers. In a situation of this kind no individual investigator can have an exclusive right of using data from an extended period during the work. This especially holds true, when the data are of great public importance, as in this case. PAa should be relieved of MG's charge of improper use of data belonging to MG.

Mechanisms have to be sought for making proper publication of data from these extensive vaccination programmes possible. AHSC does not find this problem a part of its concern or mandate, considering it a matter and primary responsibility of the funding and supervising authorities.

4. MG's additional charges

AHSC finds all the additional charges unfounded.

As an overall comment, AHSC has noted in particular the statement of Paul Fine (point 8 in 47): "A sad irony in this affair is the fact that the conflict between these two scientists has meant an inordinate delay in publication of results from the Senegal trial. This has in turn slowed the research on a subject of importance to the health of children throughout the world, and has allowed critics of vaccination to accuse the scientific establishment of withholding data." AHSC also finds this type of delay unacceptable.

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List of documents

1. May 27, 1993: Letter from Michel Garenne to DCSD.
Charges against Peter Aaby for: **a.** Having performed together with Francois Simondon a mass vaccination against measles with EZ-HT in Senegal during the summer 1990 in spite of their knowledge, that this would endanger a great number of children. Use of EZ-HT was stopped through intervention from MG in November 1990. **b.** Having manipulated data in order to reduce the statistical significance of results proving the risks involved in immunization with EZ-HT. **c.** Having published data belonging to MG.

2. August 24, 1993: Letter from Peter Aaby to DCSD.
a. Has no knowledge of any mass vaccination during the summer 1990.
Only 136 children were vaccinated because they for various reasons had been left un-vaccinated during the former trial, running from August 1987 to October 1990. The use of EZ-HT was stopped in November 1990 through a decision initiated by PAa. **b.** Admits no wrongdoing with respect to the statistical treatment of data. **c.** Finds the accusations concerning publication of data belonging to MG untrue.

3. November 4, 1993: Letter from Michel Garenne to DCSD.
Maintains that a new vaccination campaign was started during the summer 1990, and that it had nothing to do with the original protocol for the vaccine trial 1987-1990. Repeats charges concerning the use of statistical methods and publication of MG's data.

4. November 16, 1993: Letter from Peter Aaby to DCSD.
Measles vaccination with EZ-HT took place from May 1990 as part of a trial on pertussis vaccination under the responsibility of F. Simondon. Furthermore some un-vaccinated children from the former trial were vaccinated during the summer 1990 with EZ-HT. A vaccination campaign was as far as PAa remembers started in May 1990 by the district health authorities as part of a national campaign using standard SW.

5. November 22, 1993: Letter from Peter Aaby to DCSD.
In November 1990 there was no evidence for a statistically significant excess mortality after EZ-HT. The Ministry of Health was, however, informed of the potential problems. Maintains that there has been no inappropriate use of data belonging to MG.

6. November 1986: Protocol for an efficacy trial of EZ-HT and SW-HT in 5-10 months old infants in Senegal (English (a) and French edition (b)) (encl. from F. Simondon).
The main hypothesis of the trial is: Are children who receive EZ-HT or SW-HT at age 5 months better protected against measles between 5 and 10 months than non-vaccinees ?
Response variables are: measles incidence between 5 and 10 months, morbidity within 3 months after vaccination and sero-conversion. The impact of the vaccination on child mortality, morbidity and nutritional status will also be observed. The main hypothesis will be

evaluated with risks of type 1 error of 0.05, and type 2 error of 0.90. Twenty eight monthly cohorts of 109 infants will be randomized to EZ-HT or SW-HT at 5 months of age, or to SW at 10 months of age.

The study will include children born August 1, 1986 to December 31, 1988. They will be vaccinated during the period January 1987 to June 1989.

MG is among the participants. PAa will participate at the epidemiological validation of clinical measles.

A Data Monitoring and Safety Committee (DMSC) composed by representatives from the Ministry of Health, Senegal, ORSTOM, MRC and the Task Force for Child Survival (TFCS) will follow he study.

7. October 8, 1988: Paper in The Lancet by PAa et al. (enclosure 11 from MG with (1)). Describes results from a trial on measles vaccination in Guinea-Bissau 1984-87. EZ-HT was found to offer a better protection than SW, and it was effective from the age of 4 months.

8. October 27, 1988: Progress report no. 2 from the Niakhar Measles study, written by MG (delivered by MG).

Mortality calculations between 5 and 12 months from the first 7 cohorts (18 deaths among 613 children) showed no difference between EZ-HT and other groups. It is concluded, that EZ-HT seems to be perfectly safe. The immunological response was inferior for SW-HT as compared to EZ-HT.

9. October 25, 1988: Report on a meeting held in the Ministry of Health in Dakar in the Safety and Monitoring Committee (delivered by MG).

MG vas present, PAa was absent. It was decided to stop the use of SW-HT in the trial.

10. June 28-30, 1989: Report from a meeting in Dakar in DMSC.

MG and PAa present. The report presents results from the vaccine trial 1986-89, comprising 16+8 cohorts. Table 2-2 shows mortality for the first 16 cohorts. SW-HT is followed by a statistically significant higher mortality than EZ-HT ($p=0.0566$) at age 5-15 months. EZ-HT is not followed by a significant excess mortality when compared with all groups of children not vaccinated at 5 months.

The statistical calculations in the paper are identical with the statistical calculations in table 4-2 in the report of June 8, 1990 (16) although the raw data are different.

The calculation of mortality for the first 5 months of life (table 2-1) must contain a major error. A total of 233 children are indicated as dead, while the total number in the final report (30, table 4-1) is only 131. The numbers for 0-5 months in (30) are very similar to the numbers for 28 days-5 months in table 2-1. The conclusion, that the different vaccination groups have very similar mortalities before age 5 months, is not changed by the error.

11. July 31, 1989: Draft Protocol for Long Term Follow Up of the Efficacy and Immunogenicity of High Titer Measles Vaccine in Senegal (Niakhar) 1990-93 (revised August 24, 1990). PAa is Principal Investigator. MG is indicated as co-investigator among others. One objective is to follow-up the children vaccinated during the period 1986-89. Another objective is to follow children vaccinated against measles with EZ-HT as part of a new pertussis vaccination study, directed by F. Simondon. The new study with EZ-HT shall start in the summer 1990 with children born January 1, 1990 to June 1993. Furthermore an effort will be done to vaccinate 636 children, who for various reasons were left un-vaccinated in the 1986-89 trial. It is an observational study especially designed for the evaluation of failure rate for EZ-HT. The impact of EZ-HT on mortality for children born after January 1990 will be examined through a case control study. Cumulative mortality for children in the 1986-89 trial will be analyzed until January 1994.
It is stated, that data from the draft report for the 1986-90 trial showed an excess mortality for SW-HT. Suspicions about an excess mortality after EZ-HT are not mentioned.

12. July 31, 1989: Protocol for the Long Term Follow Up of the Efficacy and Immunogenicity of High Titer Measles Vaccines in Senegal (Niakhar) 1990-93 (revised August 24, 1990), (encl. 4 from PAa (4)).
It seems to be the final protocol while (11) must be an earlier draft. Both of them are dated July 31, 1989 with revision August 24, 1990.
The plans for: **1.** Follow-up of children from the 1986-89 trial, for **2.** The children vaccinated with EZ-HT starting in the summer 1990 as part of a new pertussis trial 1990-93, and **3.** Vaccination of 636 un-vaccinated children from the 1986-90 trial are identical with the plans in the draft protocol except for minor changes and addition of some numbers for calculation of sample size.
In this edition suspicions are mentioned about an excess mortality after EZ-HT as well as after SW-HT.

13. January 22, 1990: Letter from PAa and Hilton Whittle to dr. Ralph Henderson, EPI (encl. A from PAa with (2)).
Reports "worrying results" from a second trial in Guinea-Bissau with children born between May 1, 1986 and April 30, 1987. There was observed an excess mortality among girls who had received EZ-HT at the age of 4-5 months.

14. February 8, 1990: Letter from dr. C.J. Clements, EPI to PAa (delivered by PAa).
Recognizes PAa's letter of January 22, 1990. Will await further information.

15. May 1990: Letter from PAa to MG (delivered by PAa).
Recapitulates data from Niakhar, discussed at a recent meeting between PAa and MG in Boston. Data based on survival status until December 31, 1989. Although not significant, a tendency is suggested similar to the Bissau-study: Higher mortality after HT-vaccines and higher mortality for girls. No consequences, since vaccination has stopped. Suggests further control of survival data.

16. June 8, 1990: Fax from MG to dr. J. Bennett, TFCS (encl. 3 from PAa, with (4)).
Presents draft tables for the final report. They represent an update of the tables from the DMSC-meeting June 28-30, 1989 (10). Data are presented for age 5-15 months. Again SW-HT is followed by an excess mortality as compared to EZ-HT (table 4-2). EZ-HT is followed by a non-significant lower mortality than all children who were un-vaccinated at 5 months.
The raw data in table 4-2 are, as it could be expected, different from the raw data in table 2.2 in (10). Some of the data are, however, quite out of context with the figures in (10) and in the final report (30) and must be erroneous. The statistical calculations of z and p-values are, however, identical for the two tables. MG is the author of both these reports.

17. June 13-15, 1990: Minute from a meeting in Dakar in a working group with representatives from WHO, MRC Gambia and ORSTOM (encl. 1 from PAa with (4)).
PAa present, MG absent. PAa is appointed Principal Investigator for a Follow-Up study, which is approved by ORSTOM and MG. The decision was submitted to the Ministry of Health on June 15, 1990 and was approved.

18. June 14, 1990: Fax from F. Simondon to dr. A. Fontana, ORSTOM, Paris (encl. 2 from PAa, with (4)).
PAa is Principal Investigator for the Follow-Up study in Niakhar.

19. June 20, 1990: Plan of work for B. Samb during the fall 1990 (encl. 5 from PAa with (4)).
Shall control survival and nutritional status of children with measles, and he shall vaccinate un-vaccinated children.

20. July 21, 1990: Letter from PAa to MG (encl. 6 from PAa with (4)).
Wants to assure MG's continued access to the data from the 1986-90 trial. F. Simondon and PAa do not want to limit MG's possibility of publishing the data. Discusses authorship. B. Samb and MG should be first authors of papers from the 1986-90 study. Discusses the conflict between MG and F. Simondon. Advises MG to stop fighting F. Simondon. Regrets that no written agreement exists about the continuation of the programme after MG left Senegal and F. Simondon took over.

21. August 2, 1990: Letter from MG to PAa (encl. 7 from PAa with (4)).
Thinks that the continuation of EZ-HT vaccination should be discontinued, since we are not sure of the long term safety (high mortality).
Has many objections to the work plan for dr. B. Samb. Accuses F. Simondon for doing "weird vaccinations" in May 1990. At least some of these seem to be re-vaccinations. It seems clear, that he does not, and could not, blame PAa for these vaccinations, which took place before PAa became the principal investigator. MG's main concern seems to be, that re-vaccination could reduce the exposure to measles infection and impair the trial.

MG has also many objections to the protocol for the follow-up study. Agrees to include the possible relationship between EZ-HT and survival as an objective, but there is no need for a case control study.
Objects to the word "impact" of EZ-HT on mortality. It is a "potential relationship" and is a preliminary hypothesis to be investigated.
Mentions no objection to the use of EZ-HT in the pertussis trial in spite of his general view that EZ-HT should be stopped.

22. August 24, 1990: Letter from MG to PAa (encl. B from PAa, with (2)).
Concludes from data in an early draft to the report on the measles vaccine trial in Niakhar, that a clustering of deaths especially among girls was observed after SW-HT and EZ-HT. "But firm conclusions could not be drawn at this point....".

23. September 26, 1990: Letter from PAa to dr. John Clements, EPI (encl. C from PAa with (2)). (There is no date on the paper, but PAa indicates in (2), that the date is September 26, 1990).
Reports excess mortality in the first 16 cohorts in the Niakhar study after EZ-HT and SW-HT as compared to SW. Confined to girls as in Bissau. The last 8 cohorts have different results with a lower mortality after EZ-HT than after SW. At the moment little evidence that early vaccination is beneficial. Recommends confidentiality, so that the Ministries of Health in Bissau and Senegal will not receive the information until the researchers themselves can present it for them.

24. November 5, 1990: Fax from MG to PAa (encl. E from PAa with (2)).
Calculations from October 1, 1990 show, that for the first 16 cohorts HT-vaccines have excess mortality. For all 24 cohorts no significant difference as compared to SW. Feels that it is necessary to stop all vaccination with EZ-HT, until more information is available.

25. November 13, 1990: Letter from F. Simondon to the Ministry of Health, Senegal (encl. D from PAa with (2)).
It was decided at a meeting November 9, 1990 to suspend the use of EZ-HT, until final conclusions can be drawn.

26. November 27, 1990: Fax from dr. C.J. Clements, EPI to dr. Agbessi, WR Senegal (encl. from F. Simondon).
Asks dr. Agbessi to try to persuade the Ministry to avoid an official stop for the use of EZ-HT, since it would be a premature decision. Some months will be needed to get more information. Since the immunization as part of the trial has run out anyway no harm is done to the trial. The general recommendation of WHO regarding the use of EZ-HT at six months remains.

27. November 28, 1990: Letter from WHO (Dr. Nguete-Kikhela), representation for Senegal, to Ministry of Health, Senegal (encl. from F. Simondon).
The decision to stop EZ-HT occurs to WHO to be premature.

28. January 22, 1991: Letter from F. Simondon to the Ministry of Health, Senegal (encl. from F. Simondon).
Maintains that the decision to stop EZ-HT taken at a meeting in the Ministry on November 27 was premature. He quotes dr. Clements' views from November 27, 1990 (26).

29. June 19, 1991: Minutes from a meeting in The Gambia MRC Ethical Committee (delivered by Hilton Whittle (MRC).
A project concerning immunosuppression and persistence of measles virus infection after measles vaccination (follow-up study from Niakhar) was approved.

30. June 1991: Final Report by MG et al. on efficacy, safety, and immunogenicity of two high titer measles vaccine. A study in Niakhar, Senegal.
Mortality data were entered until October 1990. An excess mortality was found after EZ-HT and SW-HT as compared to SW. When survival analysis starts at age 5 months, EZ-HT was found to have the highest mortality. It was significantly different from SW for cohorts 1-16, but not for 1-24. The difference between the survival curves for EZ-HT and SW became evident at about age 18 months. The difference was detected as statistically significant in April 1990 (p.64 and p.108). Since excess mortality was concentrated at older ages the analysis concentrates on cohorts 1-16.
No significant sex difference in mortality was found in any of the vaccination groups, but most of the excess mortality between HT and standard vaccines was found among females. The differences between male groups were not significant. Random fluctuations in the sex ratio might be responsible (p. 61).
As mentioned under (10) a discrepancy exists between table 4-1 in the final report and table 2-1 in (10).

31. October 12, 1991: Paper in the Lancet by MG et al. (encl. 19 from MG, with (1)).
Describes the trial in Niakhar, Senegal, 1986-89. It presents the results from the final report (30), and therefore the data collection ended in October 1990.

32. December 14, 1991: Letter in The Lancet by PAa et al. (encl. 24 from MG, with (1)).
Stresses the necessity of including all 24 monthly cohorts, and not only the first 16, since the difference between EZ-HT and SW then becomes less prominent. The excess mortality occurred among females.

33. December 14, 1991: Letter in the Lancet by MG et al. (encl. 25 from MG, with (1)).
It is necessary to use life-table method. Finds the sex difference complex. Although not statistically significant there was also found an excess mortality among boys.

34. February 12, 1992: Letter from PAa to the editor of The Lancet (Encl. from PAa, with (2)).
The letter was not published. Is an answer to (33) (letter from MG of December 14, 1991).

35. February 17, 1992: Letter from dr. H. Whittle to MG (with letter from H. Whittle to AHSC)
Rejects co-authorship in the final report from the Niakhar study.

36. March 11, 1992: Letters from Gèrard Winter, Director General, ORSTOM to PAa and to Statens Seruminstitut(encl. K from PAa, with (2)).
Recognizes in a formal contract PAa as scientifically responsible for a long term follow up of efficacy and immunogenicity after HT-vaccination until the end of 1993.

37. June 6, 1992: PAa's account of his relations with MG (encl. L from PAa, with (2)).

38. June 29, 1992: Letter of agreement between TFCS and ORSTOM (encl. M from PAa, with (2)).
The contract for the trial in Senegal 1986-89 has terminated with the submittal of MG's final report December 22, 1991. PAa shall be project director for the evaluation and exploitation of data from the Niakhar study 1968-89 and co-ordinator for all following studies relating to the vaccine trial.

39. September 1992: Revised Protocol for the ORSTOM study of pertussis vaccination (encl. from F. Simondon).
The study comprises children born between February 1, 1990 and November 30, 1994. In the original plan EZ-HT should be given as part of the trial at 6 months of age. The first children, thus, should receive EZ-HT in August 1990. The plan was, however, changed and EZ-HT was discontinued in November 1990. After that time SW was used at 9 months of age.

40. November 27, 1992: Statement in Weekly Epidemiological Record from EPI (encl. 26 from MG, with (1)).
Announces a withdrawal of the recommendation of October 1989 to use EZ-HT from 6 months of age. SW is recommended.

41. March 8, 1993: Subcontract between Statens Seruminstitut and ORSTOM.
The subcontract concerning the long term study of the measles trial is valid for 3 years from January 1, 1992. No data before January 1, 1992 can be utilized as a result of the present programme.

42. March 10, 1993: Letter from ORSTOM to WHO (encl. I from PAa, with (2)).
Recognizes PAa as Principal Investigator for the long term follow up of children vaccinated against measles.

43. May 1993: Report from PAa et al. to the Ministry of Health, Senegal and to EPI (encl. G from PAa, with (2)).
Reports that there persists an excess mortality after EZ-HT as compared with SW, but the problem is not increasing with the years. No explanation has been found.

44. May 18, 1993: Letter from dr. B. Philippon, ORSTOM to dr. J. Bennett, TFCS (provided by PAa).
The agreement of June 29, 1992 between ORSTOM and TFCS (38) concerning management and publication of data from the vaccination program in Niakhar 1986-1989 with PAa as director is terminated, because a Bureau permanent has been created and will be in charge. PAa is still in charge of the long term study of efficiency and immunogenicity after HT.

45. May 18, 1993: Letter from dr. B. Philippon, ORSTOM to PAa (provided by PAa).
Same content as (44).

46. August 30, 1993: Letter from dr. B. Philippon, ORSTOM, to PAa (provided by PAa).
ORSTOM decided in December 1992 to terminate from September 1993 the agreement of June 29, 1992 between TFCS and ORSTOM (38) assigning PAa the role as project director for all data collected November 1986 to October 1989 and for follow up studies regarding the vaccination trials. PAa is not excluded from ORSTOM, and the contract of March 11, 1992 (concerning long term study of the efficiency and immunogenicity of HT, see (36)) is not affected.

47. October 28, 1993: Letter from Prof. Paul Fine, London, to AHSC.
Was asked late in 1991 by WHO/EPI to carry out an independent review of data relating to the safety of HT measles vaccines. In co-operation with a statistician, Dr. Jonathan Sterne, a report was prepared for a meeting in Atlanta in June 1992.
Knows nothing about any recommendation to continue vaccination with EZ-HT in Senegal during the summer 1990. MG's criticisms of PAa's Lancet paper from October 8, 1988 on the Bissau study are not justified. Questions the propriety of MG's analysis of sub-group results like the first 16 cohorts in the Niakhar study. Does not believe that PAa has manipulated the data. Regrets that the conflict between MG and PAa has meant an inordinate delay in publication of results from the Senegal trial.

48. November 15, 1993: Letter from statistician Kim Mark Knudsen to AHSC.
Had taken precautions before using the log-rank test in (7). Maintains the rationale for using crude estimates in (32). Also here precautions had been taken.
In two figures is demonstrated the same as was found by MG in (30): EZ-HT has a significantly higher mortality than SW for cohorts 1-16 when the calculation is started at age 10 months, while the difference is non-significant for cohorts 1-24. There is a discrepancy between the p-values in the text and in the figures. What was stated above referred to the p-values in fig. 1 and 2.

49. November 16, 1993: Letter from F. Simondon to AHSC.
Comments to the charges of MG in (1) and enclosure of a number of protocols and other documents.
Summarizes the vaccination programs in Niakhar, using EZ-HT: **1.** The 1986-89 trial (6). **2.** Children born February 1, 1989 to October 1989 vaccinated with EZ-HT without a protocol.

3. Children born November 1, 1989 to May 1, 1990 under the pertussis protocol (39). **4.** Immunization of un-vaccinated children (non-attenders) from the 1986-89 trial.
5. A vaccination campaign May 1990 was nation-wide and was initiated by the Regional Medical Officer on behalf of the Ministry of Health to increase vaccine coverage. SW standard was used, not EZ-HT.

50. November 23, 1993: Letter (fax) from dr. Hilton Whittle to AHSC.
The follow-up study was approved by the Gambia Government/MRC Ethical Committee (cf. 3, p.3) (29). Whittle did not want to be co-author of the final report (cf. p.8 L in (3)). PAa in many ways initiated the meeting in Geneva in 1991. Has consulted properly with superiors.

51. December 28, 1993: Letter (fax) from dr. F. Simondon to AHSC, with two enclosed letters.
1. Letter of June 17,1990, from the Ministry of Health to several local medical leaders in the area, signed by dr. I. Diallo, head of "Region de Medicale Fatick". This letter presents results from the vaccination campaign in May 1990 and it expresses the satisfaction of the Ministry with the result obtained and indicates that the Ministry wants the programme "opération ratissage", to be continued.
2. Letter of May 14, 1990, from F. Simondon to dr. Diallo. It is a response to a letter of May 11, 1990, from dr. Diallo, and F. Simondon accepts in his letter to take part in "opération ratissage", about which the letter of May 11 informed him of the necessary operational details. From these letters it is evident, that the initiative to the vaccinations in May 1990 came from the Ministry and that all planning was taken care of by the Ministry.