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The Senegal Pertussis Trial: Safety and Surveillance of Adverse Reactions

M.-P. Preziosi[1], M. Ndiaye[1], A. Coll-Seck[2], F. Simondon[1]

[1] Unité de recherche sur les maladies infectieuses et parasitaires, Orstom, Institut Français de Recherche Scientifique pour le Développement en Coopération, Dakar, Senegal

[2] Infectious Diseases Unit, Fann Hospital, Cheikh Anta Diop University, Dakar, Senegal

Abstract: In the Senegal pertussis trial, common adverse reactions were actively monitored during the pilot phase II study, while the frequency of severe adverse reactions was monitored as a secondary objective within the phase III efficacy trial. Since the trial was conducted in Niakhar, an area in rural West Africa under intensive surveillance, the safety monitoring during the study was incorporated within the general surveillance system. This was a two-step procedure : detection of a potential reaction by a field worker, followed by confirmation report by a physician. The frequency of severe reactions was low among both pertussis vaccine groups, receiving either the two-component acellular vaccine or the whole-cell vaccine currently used in the Senegal Expanded Programme on Immunisation. Among severe reactions, only persistent crying was found to be at a significantly higher rate in the whole-cell group. Common adverse reactions were more frequent in the whole-cell group.

INTRODUCTION

Safety was one of the secondary objectives of the Senegal clinical trial, stated as follows *«to monitor the frequency of serious systemic events after the injection of a two component acellular pertussis vaccine and the currently used whole-cell vaccine»*. Due to the context of the study, active monitoring of common, non-severe, adverse reactions was not feasible. In particular, measurement of body temperature in vaccinees is not routinely possible in this setting during a large field trial. Common reactions following DTP vaccination were monitored in this population in the pilot phase II study.

Organisation of the Safety Monitoring

The trial took place in rural West Africa within a study area where long-term observation of the population was implemented more than 10 years ago. The monitoring of adverse reactions following vaccination could not be organised by using conventional methods, such as parents daily diaries or telephone calls. Instead, surveillance was concluded within the general demographic and epidemiological surveillance system carried out in this area for 12 years. In this part of Senegal, families are living in compounds, that is, residential units of one or more households. In the study area, each compound is visited every week by a field worker for data collection purposes. We used this systematic surveillance system to detect severe systemic adverse reactions. The monitoring of severe adverse reactions was a two-step procedure:

(i) detection of the potential event by the field worker during the weekly visit (one to 14 days after vaccination);

(ii) a physical examination by a physician of all children detected as having a potential adverse reaction.

The first step consisted of a systematic screening for adverse reactions by field workers, applied to all children included in the pertussis vaccine trial. During the two weekly visits following each vaccine dose, field workers enquired about adverse reactions using a simple standardised questionnaire with «trigger» questions including «Did or does your child present with severe sleepiness or seizures?».

Two other trigger questions seeking to detect irritability and fever, also used at the beginning of the trial, were considered not specific enough and were dropped after one year of the study. Whenever the answer to one of these questions was positive – or whenever the child presented with any major illness – the field worker was required to report promptly to a physician.

Shortly after this report, the compound was visited by a physician who interviewed the parents, performed a physical examination of the child, organised hospitalisation if needed, and filled out an adverse reaction report form. All case reports were reviewed on a monthly basis by the Technical Committee which decided whether the child should be excluded from subsequent vaccination, according to the protocol. All children presenting with a severe adverse reaction were followed up by a physician at least at one month and one year after the occurrence of the event.

Results of the Safety Monitoring

From May 1990 to June 1995, 4,821 children were included in the study, equally distributed between the two vaccine groups, representing a total of 13,724 doses. Out of these children, 12% were missed in the follow-up during the first week after vaccination and 14% were missed during the second week. When considering either week of follow-up, however, adverse reaction surveillance could be completed in 97% of the children after a given dose.

Among the 13,256 doses with surveillance, 2.7% (355) events per dose were confirmed by a physician. They mainly concerned fever 2.2% (296), irritability was only 0.3% (33), severe sleepiness 0.1% (15) and seizures 0.08% (11) per dose. More than 75% of these events occurred within the first 48 hours after inoculation.

Severe reactions

As shown in Table 1, among severe adverse reactions systematically monitored during the study, only persistent crying of three or more hours was found to be at a significantly higher frequency in the whole-cell group compared to the acellular group. No Hypotonic-Hyporesponsivness Episodes (HHE), collapse, nor cyanosis reactions were reported. No fever above 40°C was reported, probably because of the time lapse between the immunisation and the physician's visit, and mothers not having thermometers. Other adverse reactions were equally distributed between the two groups.

Hospitalisations within 15 days post-vaccination

Every child presenting with seizures or any major illness upon the physician's visit was hospitalised if parents agreed. Table 2 shows that five children were hospitalised within 15 days after a vaccine dose, all of them because of febrile seizures. Thirteen days after vaccination, one child in the acellular group who presented with febrile seizures followed by loss of consciousness, was diagnosed as having encephalitis (cerebral malaria could neither be confirmed, nor ruled out) and died four days later, despite anti-malarial therapy. Three children, one in the whole-cell group and two in the acellular group, had febrile seizures within 24 hours after a dose; they all recovered promptly. One child in the whole-cell group presented with febrile seizures upon day eight after vaccination; he was diagnosed as having cerebral malaria and recovered after treatment.

Deaths within two months post-vaccination

Table 3 shows that 72 deaths occurred within two months of immunisation, 38 in the whole-cell group and 34 in the acellular group. These numbers have to be interpreted knowing that, in the study area, the usual infant mortality is about 85 per thousand infants. No deaths occurred within 48 hours after vaccination.

Table 1: Severe adverse events within 48 hours of immunisation.

Number of doses	Vaccine				
	Whole-cell 6595		Acellular 6661		Chi^2
Reactions*	N	%	N	%	p-value
Persistent crying ≥ 3 hours	8	0.12	0	0	0.004 (Fisher)
HHE/collapse or generalized cyanosis	0	0	0	0	–
Seizure (no afebrile seizure)	2	0.03	2	0.03	NS

* Physician assessment or mother's report.

Table 2: Hospitalisations within 15 days post-vaccination.

	Vaccine		Diagnosis	Outcome
	Whole-cell	Acellular		
Reactions	Time since vaccination	Time since vaccination		
Febrile seizure		13 days	encephalitis	death on day 17
Febrile seizure	1 day		–	recovered
Febrile seizure		1 day	–	recovered
Febrile seizure		1 day	–	recovered
Febrile seizure	8 days		Cerebral malaria	recovered

Table 3: Deaths within two months of immunisation by vaccine group*

	Vaccine					
	Whole-cell			Acellular		
	Vaccinated children	Deaths		Vaccinated children	Deaths	
Dose	N	N	%	N	N	%
Dose 1	2379	14	0.59	2396	10	0.42
Dose 2	2245	11	0.49	2284	10	0.44
Dose 3	2115	13	0.61	2174	14	0.64
Total	2379	38	1.60	2396	34	1.42

* No death occurred within 48 hours after vaccination.

The main causes of deaths were diarrhoea (39%), pneumonia (21%) and malaria (11%). They were equally distributed among both groups (Fig. 1).

Common adverse reactions

Common adverse reactions reported during the study are shown in Table 4. Irritability was not systematically sought by the field workers, but was monitored by the physician whenever he visited the child for another detected symptom. Similarly, since temperatures are not taken by family members after vaccination, measurements were taken by the physician when indicated, upon a visit being made. Sleepiness, fever, fretfulness were additional signs systematically sought during the medical visit. We considered startled reactions to be a sign of fretfulness. Of these reactions, fever and fretfulness were found to be at significantly higher rates in the whole-cell group compared to the acellular group. Other adverse reactions were equally distributed between the two groups.

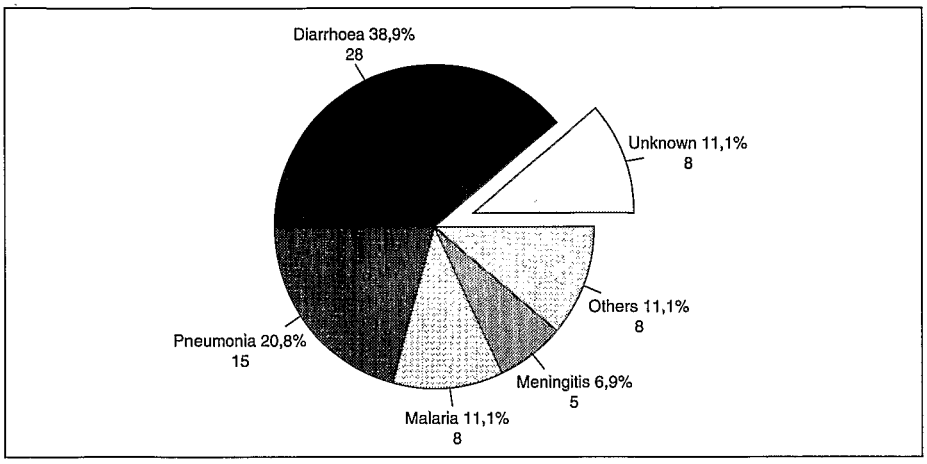

Fig. 1: Main causes of deaths among both groups within two months post-vaccination.

In Table 5 the results are presented of the surveillance of common adverse reactions, i.e. redness, swelling, local pain, crying, fever ≥ 38°C during the Senegal phase II study. These parameters have been described to be the minimum data set needed to discriminate between DTaP and DTP vaccines with respect to the common adverse reactions [1]. They were all found to be more frequent with high significance in the whole-cell group. The frequency rates for fever given here are somewhat lower than expected, this again being due to the interval of 48 hours between the immunisation and the physician's visit, and mothers not having thermometers.

CONCLUSIONS

Both vaccines were found to have a good safety profile; no HHE were observed in either vaccine group. However, the evaluated acellular vaccine was associated

Table 4: Common adverse reactions reported within 48 hours of immunisation.

Number of doses	Vaccine				
	Whole-cell 6595		Acellular 6661		Chi^2
Reactions	**N**	**%**	**N**	**%**	**p-value**
Sleepiness*	7	0.11	7	0.11	NS
Fever > 38°C**	146	2.21	83	1.25	0.00002
Fretfulness «Startled reaction»*	22	0.33	9	0.14	0.02

* Mother's report.

** Physician's assessment (no fever ≥ 40.5°C reported).

Table 5: Senegal phase II study: common adverse reactions within 48 hours of immunisation.

Number of doses	Vaccine					
	Whole-cell 285		Acellular 306		Relative Risk WC vs AC	Chi^2
Reactions	**N**	**%**	**N**	**%**	**RR [IC 95%]**	**p-value**
Rednes* ≥ 3 cm	10	3.51	2	0.65	5.37 [1.19-24.29]	0.01
Swelling* ≥ 3cm	71	24.91	22	7.19	3.47 [2.21-5.44]	$< 10^{-7}$
Local pain**	40	14.04	17	5.56	2.53 [1.47-4.35]	0.0004
Crying**	111	38.95	56	18.30	2.13 [1.61-2.81]	$< 10^{-7}$
Fever > 38°C*	10	3.51	0	0	–	0.0006 (Fisher)

* Physician's assessment.
** Physician's assessment or mother's report.

with a lower frequency rate of a severe adverse reaction such as persistent crying and markedly lower rates of common reactions such as fever, fretfulness and local reactions compared to a whole-cell vaccine widely used in the Expanded Programme on Immunisation.

The role of reactogenicity as a cause of drop-out for the second and third doses remains an issue for vaccine policy as it may be a factor in poor compliance with repeated immunisation and lead to a failure to promote acceptance of a full course of immunisation. These results are consistent with those found in other studies conducted with the same vaccines in other parts of the world [3, 4].

With respect to the other recent pertussis vaccine trials, the observed frequencies of severe adverse reactions for the acellular vaccine used in this study are comparable with those found with other acellular vaccines; the exception is for high fever which, as mentioned before, was not systematically measured within 48 hours. For the whole-cell vaccine studied, except for seizures within 48 hours of vaccination, rates are always lower than those found with the whole-cell vaccines included in the other studies. This might be in accordance with the suggestion that DTP products available throughout the world are not consistent in reactogenicity characteristics [5], or related to differences in safety data collection, or both.

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Dr. M.-P. Preziosi, Projet Niakhar, Orstom, B.P. 1386, Dakar, Sénégal.