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Occasional Notes

PRACTICAL EXPERIENCES IN OBTAINING INFORMED CONSENT FOR A VACCINE TRIAL IN RURAL AFRICA

THE Helsinki Declaration outlines clear ethical principles, including the basic concepts of informed consent, for physicians conducting biomedical research. There are guidelines for applying those principles specifically in research conducted in developing countries.¹⁻⁴ One guideline allows a community-based approach to enrollment, according to which the decision whether or not to participate can be elicited through an intermediary, such as a trusted community leader, who helps convey information about the research to the people in the community.¹

There is considerable debate about the appropriateness of obtaining individual informed consent in non-Western cultures.⁵⁻⁸ In the process of conducting a study of a new pertussis vaccine in a rural community in Senegal, we sought to evaluate the incorporation of clear procedures for obtaining individual informed consent from parents. In this part of Senegal, consent for all previous research with human subjects had been obtained from community leaders on behalf of all eligible members of the community. Individuals could subsequently decline to participate.

METHODS

Since 1983, the Institut Français de Recherche Scientifique pour le Développement en Coopération (ORSTOM) had conducted a longitudinal follow-up of Niakhar, a farming area in Senegal that had 26,045 residents in January 1992. Extended families live grouped in 1800 compounds, each under the authority of an elder. Compounds are grouped in 30 villages, led by elected chiefs. In this stable and ethnically homogenous Sereer (a Senegalese ethnic group) community, composed almost exclusively of millet and peanut farmers and their families, responsibility for the health of children is generally delegated to the mothers. The average per capita annual income is equivalent to \$100. The literacy rates are 30 percent for men and 10 percent for women. The fertility rate is 7.8 children per woman 15 to 45 years of age; infant mortality is 80 per 1000.

When the Expanded Programme of Immunization (EPI) was launched in Senegal in 1987, ORSTOM began a clinical trial of measles vaccine in Niakhar that lasted until 1989.⁹ Since 1987, ORSTOM, on behalf of EPI, has held a vaccination session each month in three community clinics. Field workers visit all compounds in advance to request that all children eligible for a given vaccine dose attend. Transportation to the clinics is provided.

Pertussis is highly endemic in Niakhar. Questions about the safety and efficacy of the whole-cell pertussis vaccines that are currently used led us to evaluate a safer, acellular, vaccine in Niakhar. From May 1990 through September 1995, we conducted a randomized, double-blind controlled trial of the relative efficacy of a diphtheria-tetanus-acellular-pertussis vaccine (glutaraldehyde-detoxified pertussis toxin and native filamentous hemagglutinin)

and a whole-cell diphtheria-tetanus-pertussis (DTP) vaccine after studying the safety and immunogenicity of both vaccines.¹⁰ Infants were randomly assigned to receive three doses of one of the vaccines at two, four, and six months of age. The study showed that both vaccines were highly efficacious. The whole-cell vaccine was more efficacious (96 percent) than the acellular vaccine (86 percent), but the acellular vaccine was safer.¹¹ The collaborative study was reviewed initially and then annually by the Human Subjects Institutional Review Board of the Centers for Disease Control and Prevention; such boards did not exist in Senegal and France in 1990. Before the trial began, village chiefs were informed of the study by a field physician. In 1992, an information campaign was launched and individual consent procedures initiated, after a reconsideration of the issue based on the recommendations of the institutional review board, an increase in staff, and debate on this topic in the medical literature.

Between April and September 1992, meetings were held by the field staff and physicians in each village to provide information and obtain consensus. All residents were invited. Presentations were given simultaneously in Sereer and in French translated to Sereer; the Sereer text had previously been verified by back-translation. Each presentation included a review of the activities of ORSTOM in the study area, information about vaccination, and a description of the study, as required by French law.^{12,13} To illustrate the principle of randomization and the possibility that one of the vaccines might fail, the presenters used a familiar agricultural example: the evaluation of fertilizers or of seed varieties on randomized plots, a procedure familiar to farmers in the area.

In August 1992, we began to inform the mothers further and to give them a distinct opportunity to refuse to participate. During one vaccination session, a pilot evaluation of the feasibility of obtaining individual oral informed consent was conducted. Subsequently, a physician fluent in Sereer routinely presented the information at each monthly vaccination session and recorded the mothers' answers as witnessed by the vaccination nurse. From that point until the last vaccination in the study, the mother of each child eligible for inclusion in the vaccine study was asked whether she had been informed about it and if so how. If she had not, the study was explained to her fully as described above. The mother then decided whether or not to participate. Throughout the study, whole-cell DTP-poliovirus vaccine was available for the infants of mothers who declined to be included in the study or to have subsequent doses administered. The interventions were evaluated through August 1994 to determine the feasibility and validity of seeking individual informed consent.

RESULTS

Group Meetings

Of 13,555 residents 15 years of age or older, 2607 (19.2 percent) attended at least 1 of the 30 meetings (Table 1). Of the 1800 compounds in which the residents lived, 1053 (58.5 percent) were represented. Participation was lowest in three of the largest villages (those with more than 600 residents). At the meetings, both male and female attendees emphasized the need for research to bring about changes and made comparisons with the evolution of agriculture. They discussed the lack of such consensus meetings before the study began. The residents' questions indicated their difficulty in understanding the concept of a double-blind study: participants wanted to choose one of the vaccines for their children or at least to know which vaccine was given in order to be able to make their own judgments about both vaccines.

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TABLE 1. NUMBERS OF RESIDENTS 15 YEARS OF AGE OR OLDER WHO ATTENDED VILLAGE MEETINGS ABOUT A VACCINE STUDY IN NIAKHAR, SENEGAL, 1992.

	WOMEN	MEN	TOTAL	COMPOUNDS
Total no.	7091	6464	13,555	1800
No. attending	1480	1127	2,607	1053
Proportion (%)				
Mean	20.9	17.4	19.2	58.5
Range among villages	4.7-69.2	4.4-64.0	5.0-60.0	23.7-100

TABLE 2. KNOWLEDGE ABOUT THE VACCINE STUDY AMONG MOTHERS BRINGING THEIR CHILDREN FOR VACCINATION IN NIAKHAR, SENEGAL, AUGUST 1992 THROUGH AUGUST 1994.

MOTHERS	TOTAL	INFORMED AT A GROUP MEETING	INFORMED BY A THIRD PERSON	NOT PREVIOUSLY INFORMED
		number (percent)		
In the study	2071*	479 (23.1)	191 (9.2)	1401 (67.6)
Agreeing to participate	2040	471 (23.1)	188 (9.2)	1381 (67.7)†
Declining to participate	31	8 (25.8)	3 (9.7)	20 (64.5)
Monthly proportion (range)		10.9-32.6%	0-27.0%	48.0-82.4%

*The 2071 mothers included 22 who were offered a choice more than once — 12 with twins and 10 with a second child who was born during the time period of the study.

†Two mothers deferred consent until they had obtained the father's opinion.

Summary comments reflected agreement in principle to vaccination and to the participation of children in the study. Community members reiterated their trust in the research team; several noted that refusals to participate would always occur. In one village, attendees unsuccessfully offered to participate in exchange for milk and butter.

Individual Informed Consent

During the pilot test of obtaining individual informed consent for their children's participation, some women said they were confused by being asked to give their consent, which they believed they had already done during the meeting. Many mothers asked which pertussis vaccine their children were to receive and why the study was blinded. Of 55 women in the pilot session, 50 consented to the inclusion of their children in the study, stating as primary reasons that they trusted the research team or wished to do as others did; 4 women declined to have their children included, and 1 woman waited to see whether her husband would give his consent (he did).

After informed-consent procedures became routine, no further concern was voiced about the indi-

vidual requests for consent. The majority of the mothers who attended the monthly vaccination sessions indicated that they did not know the details of the study (Table 2). The predominant reason for not participating remained the same — a preference that children receive the routine whole-cell DTP vaccine. In general, the mothers expressed more concern about the overall side effects of the study vaccines than about their efficacy. They noted that pertussis, when it occurs, has been less severe since the initiation of DTP vaccination; it now appears as a "prolonged cold" with shorter paroxysms of coughing and is rarely associated with vomiting.

Participation in the vaccination study before the implementation of individual informed consent (May 1990 to July 1992) was compared with that in the period after the policy change (August 1992 to August 1994). In the former period, when 2343 mothers were approached, refusal of vaccination, which consisted of not taking one's child to the clinic for vaccination, averaged 7.4 percent (46 of 620 eligible children) during 1990 (monthly range, 3.8 to 10.9 percent) and 4.5 percent (78 of 1723) thereafter (monthly range, 1.0 to 8.2 percent). In the period after routine individual informed consent was introduced, 2163 mothers were approached and the overall rate of refusal of the first vaccine dose was 4.9 percent (107 of 2163 eligible children; monthly range, 1.0 to 10.7 percent); 3.5 percent (76 of 2163) were "no-shows." Among the mothers of children attending the clinic sessions, the rate of refusal was 1.5 percent (31 of 2071). Of the 2071 mothers, 85 (4.1 percent) were under the age of 18 years; their consent was considered valid on behalf of their children. In each village, there were mothers who brought their children to the clinics but declined enrollment in the study. However, a high frequency of "no-shows" was limited to a few specific villages. Of the children whose mothers declined participation in the study, 93.5 percent (29 of 31) were subsequently fully vaccinated with EPI vaccines, as compared with 6.0 percent of the "no-shows" (12 of 200) since the beginning of the study.

Among the mothers who gave their consent, there were no instances of later refusal to continue participation in the study. However, there was a stable rate of "no-shows" for the second and third doses of any DTP vaccine — an average of 1.3 percent of the eligible children (56 of 4276). Most such children lived in the same villages as those who did not appear for the first DTP dose. Only 28.6 percent of these children (16 of 56) received a DTP dose elsewhere afterward, and fewer than half completed their immunizations.

DISCUSSION

Is it appropriate to obtain informed consent individually from mothers of children eligible for studies

in cultures where such choices are uncommon? Some members of our study team who are native residents of rural and urban Senegal were resistant to the idea; our discussions echoed the divergent conclusions reached in the medical literature.^{5,6}

Our experiences indicate that the parents understood the study sufficiently to make informed choices. During the meetings, comments by community residents emphasized their understanding of the principles of the vaccine study after these principles were illustrated with better-known examples drawn from agriculture. Informed refusals occurred at both the group consensus meetings and during the individual-consent process. Mothers often declined to include their children because they had "chosen" the well-known EPI vaccines. An "informed refusal" has been considered a sign of full understanding that there is a choice.¹⁴ At the community level, refusal to attend the clinics for immunization was partly replaced, after the group meetings, by refusal to be included in the study. This increased acceptance of vaccination overall suggests an effect of the informational sessions, which included observation by parents of the reduced frequency and severity of clinical pertussis in children who have been vaccinated.

Communicating information about a choice and its implications can be difficult and time-consuming, but it allows valid, informed decisions.⁵ We found that widespread illiteracy is not a barrier to comprehension, especially since informed consent is more an interactive process than one that depends on reading.⁶ Nonetheless, understanding abstract scientific concepts, such as double-blinding, can be difficult.

Mothers knew of deaths among children due to measles or pertussis, and people in general saw vaccination as providing a benefit that was much greater than the associated risk. The perception of the risk associated with the disease might offset the perception of the risk associated with a new vaccine.¹⁵ Further sociological studies as performed in other settings could allow a better evaluation of the information received and its use in decision making.¹⁶⁻¹⁹

Information about a study should be provided before individual consent is sought.²⁰ Within the Niakhar community, general information circulated widely after the consensus meetings and allowed the study to be described more easily to individual mothers, despite the low percentage of well-informed mothers at the time of the first vaccination. Such communication allows decision making to take place over time.²¹ In addition, the meetings provided each mother an opportunity to make an individual choice for her child within the context of community consensus, which is consistent with the social organization in Niakhar. Furthermore, the community discussions indicated a common concern about health problems and a perception of research as an element

of progress and of social benefit that people wished to have access to. Similar sentiments have been expressed in other settings.²²

Of necessity, our protocol was reviewed by only one ethics committee, located outside the country. A local ethical review by persons not associated with the study is still necessary.^{7,23} Biomedical research in developing countries is best served by a system of ethical review that is shared by both local and sponsoring committees.²² Subsequent research in Niakhar has been conducted after review of the protocols by locally constituted ad hoc committees.

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