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Health benefit for the child and promotion of the common good were the two most important reasons for participation in the FinIP vaccine trial

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ABSTRACT

Background and aims: The Finnish Invasive Pneumococcal disease (FinIP) vaccine trial was a nationwide cluster-randomised double-blind trial designed to demonstrate the effectiveness of pneumococcal conjugate vaccine in vaccinated children and indirect effects in unvaccinated populations. Together with the parallel carriage/AOM trial, over 47,000 children were enrolled, 52% of the initial target. We conducted a questionnaire study to find out which factors affected parents' decision on their child's study participation.
Methods: A questionnaire designed to evaluate parents' attitudes to vaccine trial participation in general and the FinIP trial in particular was mailed after the trial enrolment period had ended to parents of randomly selected children: 1484 who participated in the trial and 1485 who did not participate.
Results: Altogether 1438 parents (48%) responded to the questionnaire. The response rate was higher among FinIP participants (65%, 965/1484) than among FinIP non-participants (32%, 473/1485). The two most important reasons for giving consent to the FinIP trial were the potential benefit of immunisation against pneumococcal diseases (75% of consenters) and the promotion of the common good and public health (11%). The reasons reported as most important for declining consent were suspicions of vaccine safety (36%) and the double-blind trial design (12%). Up to 65% of the non-consenters declared that drug and vaccine trials should not be conducted in children at all.
Conclusions: The expected health benefit for the child was by far the most important reason for consenting to the vaccine trial. Safety concern was the main reason for decline. Importance and necessity of clinical drug and vaccine trials among children and the rationale of the blinded studies should be thoroughly explained to the public. This may increase participation in future vaccine trials.

1. Introduction

All clinical research is dependent upon the acceptance and consent of the study participants or their legal representatives. Enrolment of children in vaccine trials is especially challenging due to the involvement of healthy individuals with a low parental tolerance for any adverse effects, perceived low individual risk of acquiring the disease being prevented by vaccination and the need for a large sample size especially in phase III–IV trials.

The Finnish Invasive Pneumococcal disease (FinIP) trial (NCT00861380) was a nationwide field trial designed to demonstrate the effectiveness of a new pneumococcal conjugate vaccine [1]. Since FinIP trial was a cluster-randomized trial aiming to evaluate also indirect effects of the pneumococcal vaccine, the number of participants needed was especially high to reach high vaccination coverage in the study clusters. Together with the parallel acute otitis media trial (AOM trial, NCT00839254) more than 47,000 children were enrolled, 52% of the initial target defined in the protocol. The percentage of families who accepted the invitation to the trial was lower than anticipated, even though the study participation was planned to be as easy as possible. The FinIP trial was conducted at local well-baby clinics during routine health check-up and vaccination visits. Furthermore, no laboratory samples or active monitoring of possible symptoms were required, as national health registers were used for the follow-up of outcomes.

Abbreviations: AOM, acute otitis media; FinIP, The Finnish Invasive Pneumococcal disease; THL, National Institute for Health and Welfare.

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We conducted a questionnaire study to assess the perceptions and attitudes of the parents of the children invited to the trial to discover the reasons to consent or not to consent to the child's participation in the study. The purpose was to identify success factors and barriers in research information and study conduct that might be taken into consideration in future vaccine trials.

2. Methods

The FinIP trial was a nationwide phase III/IV cluster-randomised double-blind field trial conducted by the National Institute for Health and Welfare (THL). The enrolment period extended from February 2009 to October 2010. The aim of the trial was to investigate the direct and indirect effects of pneumococcal conjugate vaccine PHiD-CV10 (Synflorix™, GSK Vaccines) against pneumococcal diseases (invasive, pneumonia and otitis media). The trial design has been previously described [1]. Briefly, all children aged <19 months residing in the study area covering most of Finland were eligible if they had not received and were not expected to receive any of the study vaccines. The children were administered two to four doses of either the pneumococcal vaccine or a control vaccine (hepatitis A, Havrix™, or hepatitis B, Engerix-B™, GSK Vaccines). The control vaccine and the number of doses depended on child's age at enrolment. All study vaccines were licensed in Finland before the trial began but they were not included in the national vaccination programme at the time of enrolment, except for specified risk groups.

All age-eligible children living in the study areas were identified using data from the Population Register Centre. THL sent invitations to parents and/or guardians by mail ($N \sim 125{,}000$). The mailed information package included the invitation (1 page) and a consent document (available as Supplement 1) with the full information sheet (6 pages) and a consent form filled with dummy details (1 page). Additionally, an open website (www.finip.fi) including all the information material was developed, and leaflets and posters were displayed at well-baby clinics and maternity hospitals. Furthermore, THL phone and e-mail services were available to parents.

The trial was conducted at well-baby clinics ($N = 651$) at municipal health centres by public health nurses ($N \sim 2000$) who are in charge of routine child health follow-up [2], including the vaccinations according to the national vaccination programme. Well-baby clinic services are free of charge, and nearly all families with under school-age children use them as scheduled [3]. Well-baby clinic nurses, and physicians when needed, provided verbal information during the scheduled visits and obtained the written informed consent from a parent willing to have the child enrolled in the trial. Nurses administered the study vaccines. THL study personnel educated the personnel of the well-baby clinics to conduct the trial according to good clinical practice, conducted repeated follow-up visits at the WBCs and, if needed, provided instant advice to well-baby clinic nurses via telephone and/or e-mail. Furthermore, a secure website was developed with full study information and regular newsletters were sent by email as reminders of any topical issues.

In addition to enrolment through well-baby clinics, the Tampere University Vaccine Research Centre conducted a parallel trial (AOM trial) with the same design for acute otitis media and nasopharyngeal carriage. Its participants were also followed for the outcomes of the FinIP trial [4]. These subjects were enrolled at 15 dedicated study clinics located in the biggest cities in Finland. Additional differences in the practical conduct included sampling of nasopharyngeal swab specimens, and active follow-up for acute otitis media and safety.

A questionnaire was designed to evaluate parents' attitudes to drug trials in general and to the FinIP trial in particular. The questionnaire was based on questionnaires used in other similar studies [5–7]. It was tested and finalised according to feedback from study personnel, well-baby clinic nurses and families with age-eligible children. The questionnaire translated into English is available as Supplement 2.

Respondents were first asked whether their child had participated in the vaccine trial or not. If the child did not participate, we asked whether their child had an exclusion criterion or whether the parents were reluctant to consent to the child's participation. The responses from parents whose child had an exclusion criterion were excluded from analysis.

In the primary question, respondents were asked to rank one to three most important reasons for giving or declining consent to vaccine trial. In other sections of the questionnaire, parents were asked how the characteristics of the trial had influenced their decision, the characteristics of the information sources, parental attitudes towards clinical drug and vaccine trials, persons influencing parents' decision, the parents' feelings about the decision-making process, and background data (Supplement 2).

Responses to most questions were scored using a seven-step Likert-type scale (steps from extremely important reason for participation to extremely important reason for refusing participation, Fig. 2). For some questions, we used five-step and three-step scales. The questions were designed to be analysed separately.

According to the sample size calculation 440 responses were needed from both participants and non-participants to achieve adequate power to show the possible differences between the groups. In previous questionnaire studies, the response rate among non-participants had been 30% to 50% [6–8]. Based on this we decided to select 1500 non-participants and an equal number of participants as the target group of this study. After checking the addresses of the randomly selected subjects, the questionnaire was mailed to parents of 2969 children invited to the FinIP trial. The first mailing took place in January 2011, four months after the enrolment of the vaccine trial had ended. Altogether 1484 families with enrolled children received the questionnaire. Of them, 135 were enrolled in the AOM trial which enabled evaluation of potential differences of participants in this trial with a different enrolment and data collection methods. The questionnaire was re-mailed once to families who did not respond within one month after the first mailing.

Families were invited to respond to the questionnaire either by mail or online, using their personal answering code. The questionnaire did not include any personal identification data and the answering code was used only for linking the FinIP vaccine trial consent date to the questionnaire data. Respondents were offered cinema tickets, lottery scratch cards or a donation to charity (~12€) as a compensation for responding.

A positive statement after ethical review was obtained from the institutional review board of the National Institute for Health and Welfare.

3. Statistical methods

The responses are presented in two main groups: families participating in the FinIP or AOM trial (consenters) and families who refused to participate in the trial (non-consenters). For questions concerning the FinIP trial methods and consent document, the responses of AOM trial consenters were excluded from the analysis.

The differences between consenters and non-consenters were compared with chi^2-test and t-test. The responses to the Likert-type questions were plotted graphically, and differences between the groups were analysed with Mann–Whitney U test. All analyses were conducted using IBM SPSS Statistics 21. p-Value < 0.05 was considered statistically significant. No corrections for multiple testing were performed.