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: 1,484 who participated in the trial and 1,485 who did not participate.
Results: Altogether 1,438 parents (48%) responded to the questionnaire. The response rate was higher among FinIP participants (65%, 965/1,484) than among FinIP non-participants (32%, 473/1,485). 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.

Keywords:

Questionnaire, consent, vaccine trial, clinical trial

Abbreviations:

AOM acute otitis media

FinIP The Finnish Invasive Pneumococcal disease

THL National Institute for Health and Welfare

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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.

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.

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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~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~2,000) 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 email. 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, Figure 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 1,500 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 2,969 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 1,484 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.

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.

The questions which respondents had left unanswered were omitted from statistical testing, but their percentages are shown in the figures. For the primary question, i.e. ranking of reasons, responses with more than one reason marked as the most important were excluded from analysis.

Results

A response to the questionnaire was returned by 1,438 families (48%). The response rate was higher among FinIP participants (65%, 965/1,484) than among FinIP non-participants (32%, 473/1,485, p<0.001). The FinIP non-participants included 356 children whose parents had declined consent (non-consenters) and 117 who had an exclusion criterion preventing participation (Supplement 3).

The background information on the respondents is shown in Table 1. Over 90% of them were mothers. The average number of children per family was two. According to the questionnaire, single parents declined consent more often than families with two parents. The mother's level of education affected participation. Both the lowest and highest educational attainment were more common among non-consenters than consenters (Table 1). The families who declined consent were more likely to belong to groups with lowest annual income than participating families (p<0.01). The majority of families (67%) reported that none of the family members had participated in any medical trial before the FinIP.

The AOM trial consenters were more likely to live in a city or municipal centre than the FinIP consenters, as only children living near study clinics were invited to the AOM trial. None of the AOM trial consenters who responded to the questionnaire were single parents. In other respects, the AOM consenters did not differ from the FinIP consenters.

The consenters trusted their well-baby-clinic nurse more than non-consenters. "I trust my own well-baby clinic nurse in matters related to my child's health" was agreed or strongly agreed by 81% (771/956) of consenters and 68% (242/356) of the non-consenters (p<0.001). According to the responses the consenters'

children had received the vaccines offered by the well-baby clinic more often than the non-consenters, 97% vs 86%, p<0.001.

The most common reason declared as the most important for consenting was the potential benefit of immunisation against pneumococcal diseases (75%, 681/905), followed by the promotion of the common good (11%, 100/905). The main reasons for refusing consent were suspicion of vaccine safety (35%, 111/321), and the double-blind trial setting (12%, 38/321, Figure 1).

The same reasons to consent or decline participation were also seen in the Likert-type questions (Figure 2): 77% (742/965) of the consenters reported that promoting the common good and public health had a positive impact on participation; 16% (121/742) of them thought that it was an extremely important reason to consent. Most non-consenters (68%, 241/356) reported that promoting the common good and public health was among reasons with no impact on the decision.

The majority of non-consenters (66%, 235/356) responded that they would not agree to their own child participating in any research. A similar number of non-consenters (65%, 232/356) responded that drug or vaccine trials should not be conducted in children (Figure 2).

More detailed results about the reasons affecting the willingness to consent to the FinIP trial, are given in Figure 2 and Supplement 4. In line with earlier responses the expected health benefit was seen as the most important reason to participate. The importance of participation being easy was apparent in the responses. The use of licensed vaccines and study conduct during routine well-baby clinic appointments were both at least positively impacting causes; also among non-consenters (Figure 2).

Both consenters and non-consenters were satisfied with the study information received (Figure 3). The most important information sources for parents were the verbal information given by well-baby clinic nurse and the consent document. The consenters gave a positive assessment of the well-baby clinic nurses' ability to describe the trial (Figure 3). Among non-consenters, the percentage of respondents who considered that the

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well-baby clinic nurse had given them sufficient information about the trial and that the given information was clear was lower than among consenters, 42% vs. 90% and 46% vs. 90%, respectively (p<0.001, Figure 3).

Both parents had input in the participation decision. The well-baby clinic nurse conducting the trial affected the parents' decision. Anti-vaccine movement, social media discussions and other information sources had only a minor influence on the decision. Their influence was stronger among non-consenters: about 15% to 20% of the non-consenters were somewhat influenced by the social media or anti-vaccine movement, whereas among consenters the percentage was around 10% (Figure 4).

Discussion

The potential personal health benefit for child was the main reason to consent participation in the FinIP trial. The finding was evident and in line with previous studies [9,10]. Promotion of the common good and public health was the second most important reason to participate. It can be interpreted as a form of altruism, which in previous studies has been discovered to be an important reason to participate in clinical trials [9,11-13].

The possible risks of trials have commonly been reported to be the dominating cause for declining consent [5,6,9,12,14]. For the present questionnaire, the safety concerns may have been even further inflated due to the special media attention on the association between pandemic flu vaccine and narcolepsy [15] at the time of the questionnaire study. Unexpected and often serious disease cases accused to be caused by vaccinations are eagerly brought up by the media. These suspicions, even if not evidence-based, affect the perceptions of the population. Therefore, steps to cope with these unpredictable potential media alerts should be planned proactively.

A finding of serious concern was that over half of non-consenters were reluctant to accept drug or vaccine trials involving children. Provided that the non-consenters responding to questionnaire were a representative sample of all non-participants in the population there would have been almost 58 000 families (75% of the 77 000 non-participants, supplement 3) that did not want to participate in FinIP vaccine trial. Of those 22% (figure 2), ~13 000 families, would think that opinion "drug and vaccine trials should not be conducted in

children" was an extremely important reason to decline consent. Furthermore, 16% (~9 000) of non-participating families would say this opinion was an important reason to decline and even more families (27% ~16 000) would assess the opinion to have a negative impact on consenting. Thus, considering that there were ~125 000 families with age eligible children in Finland at the time of the trial, these figures reveal that every third Finnish family with young children think that clinical trials in children are at least somewhat repellent. This should prompt scientists and health care professionals to inform the public about the importance of trials among children.

Another significant observation was that blinded vaccine administration allocated in random was considered to have impacted participation negatively in nearly 40% of the consenters and in up to 60% of the non-consenters. Randomisation and blinding of the study vaccine or drug are usually crucial in trials, their importance and practical meaning need to be clearly explained in the consent document and other information sources. Offering possibility for cross-over vaccination after the trial follow-up, when feasible, might alleviate some of the concerns related to random allocation and blinding.

In several studies, the consenters' understanding of the aims and methods of clinical trial have been better than the non-consenters' [5,11,16]. The only way to increase understanding is adequate and clear information. The most important information source was the verbal information given by the well-baby clinic nurses. This was considered even more important than the written information accepted by ethical review board. Consenters thought that the nurses were able to describe the trial clearly and understandably. Most non-consenters skipped this question. As the FinIP trial was kind of extra work on top of the routine work in well-baby clinics the nurses' motivation to conduct trial varied by site. Most probably well-motivated nurses informed the parents better and thus recruited more children. In earlier questionnaire studies, the professionalism, motivation and other characteristics of personnel have been associated with the willingness to participate [11,17,18]. Likewise, the importance of the clearness of knowledge and attitudes of the health care personnel administering vaccines has been shown to affect vaccine coverage [19]. It was also seen in our study that consenters trusted the well-baby clinic nurses and adhered to the national vaccination program more than non-consenters. Thus, in trials and in preventive health care, the motivation of the employees is one of the most important issues affecting the success.

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The consent document was the second most important information channel for parents. According to most respondents the consent document was easy to understand and included adequate information. About 40% thought the document was too long, and a similar percentage considered its length appropriate. The obligatory information specified in Declaration of Helsinki [20] and by national regulatory and ethics bodies often extends the consent documents and may lead to situation in which the consent becomes difficult to fully understand [21]. The challenge that is likely to continue at least in the near future is to balance the legal and regulatory requirements with the understandable length and content of the consents in a manner that would secure the rights of the eligible study participants.

In the vast majority of cases both parents had influenced on the participation decision as expected. However, only one of them was requested to sign the consent form, which is compatible with the Finnish legislation. In practice, it may be difficult to get both parents to attend a vaccine trial appointment for the informed consent process, especially in large post-licensure studies. Our study showed that providing timely and adequate information for the decision-making is adequate to guarantee both parents' opinions.

Even though the social media has been seen as an important information source and opinion former, responses indicated that the FinIP participation decisions were not affected by it as much as anticipated. The influence of anti-vaccine movement was also quite low. However, the influence was higher among parents who declined consent. Thus, it is important that the facts of the trial can be found online to counter the possibly misrepresented study information published by organisations and/or persons against vaccines or trials. It might be beneficial to add peer experiences of participating persons or families to the web pages. This kind of informal information would at least increase the probability of finding positive information about studies and vaccines. So far the power of stories, often more effective than the scientific facts [22], have been used almost solely by anti-vaccine persons and movements [23-25]. Recently, also pro-vaccine parents have established websites and appeared in to the social media discussions [26,27].

Low income and low educational attainment decreased consenting. This may be associated with the low number of single parent families among the consenters, since most of the families with lowest incomes were

single parent families, and the single mothers had lower educational attainment than mothers living with a spouse. However, 10% of toddlers live with one parent in Finland [28], and thus single parents were under-represented among questionnaire respondents. Therefore, it is possible that these families responded less often if they were consenters rather than consented less often. The higher number of non-consenters among highly educated mothers has been reported previously [5,11,14]. However, it has been suggested that highly educated parents may answer questionnaires more eagerly and feel that they have to explain their refusal [11].

The questionnaire was conducted months after the enrolment of the vaccine trial had ended. The time gap between the enrolment and the questionnaire may have affected the responses, as respondents may have not remembered in detail the reasons affecting their decision and what kind of information material they had received.

An unavoidable bias in questionnaire studies is the lack of completeness in the response. In this study, we sent out nearly 3,000 questionnaires and received responses from half of recipients. This is roughly the percentage usually seen in similar studies [6-8,11]. Another important bias in questionnaire studies is the skewed distribution of the responses: the consenters respond significantly more often than non-consenters [6-8].

Conclusion

Common good and public health were important reasons to participate in the trial. However, study showed that achieving high recruitment proportion will be possible only by trial design that guarantees some personal benefit for every study subject. Safety concern was the main reason for decline.
The study showed lack of information among the public on importance and necessity of clinical drug and vaccine trials in children. The rationale of the blinded study approach should be explained to the public, i.e. potential participants, in an understandable manner. The opportunity for such informing is not only when a new study is starting but also in the phase where research results are published to the general population. This might increase the willingness to participate in future clinical trials.

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Conflict of interest

All authors are employees of the Department of Health Protection at the National Institute for Health and Welfare, which has received research funding from GlaxoSmithKline. TP was an employee of GlaxoSmithKline Vaccines during the study until August 2012. AAP has had travel paid for and honoraria from GlaxoSmithKline to attend expert group meetings, has had travel paid by Merck to attend expert group meetings and has received a travel grant from SanofiPasteur MSD but none since 2011.

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Legends of the table and figures

Table 1. Background information on the respondents to the questionnaire among FinIP trial consenters and non-consenters

Figure 1. The most important reasons to consent or to decline consent in the FinIP trial.

Figure 2. Influence of the general and vaccine-related reasons and the methods of the trial on the decision whether to consent or not. The responses of consenters and non-consenters differed significantly (Mann-Whitney U test, $p<0.001$) for every question. AOM trial consenters were excluded from the analysis of the methods, their responses are available in supplement 4.

Figure 3. Parents' opinions on the various information sources used in the FinIP trial. Statistical significance tested with Mann-Whitney U test, p-values marked in the figure, NS = not significant.

Figure 4. Parents' responses on whose opinions had influence on their decision concerning the child's participation in the trial. Statistical significance tested with Mann-Whitney U test, p-values marked in the figure, NS = not significant.

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	Consenters		Non-consenters		
Respondent					
Mother	500	52%	177	50%	
Father	22	2%	8	2%	
Both	15	2%	2	1%	
No answer*	428	44%	169	47%	
Mean (range) age of respondents, years	31,6	(19-48)	31,4	(20-44)	
Mean (range) number of children in the family	2,1	(1-12)	2,2	(1-14)	
Single parents	26	3%	18	5%	p<0.05
Previous participation in medical trials					
No	642	67%	282	79%	p<0.001
Yes, at least one parent	171	18%	38	11%	p<0.01
Yes, at least one children	177	18%	41	12%	p<0.01
Level of education, mother					
Comprehensive school	33	3%	22	6%	p<0.01
Secondary level qualification	408	42%	143	40%	
Lower university degree	321	33%	98	28%	
University degree	196	20%	92	26%	p<0.05
Not known/ no answer	7	1%	1	0%	
Level of education, father					
Comprehensive school	65	7%	20	6%	
Secondary level qualification	504	52%	191	54%	
Lower university degree	214	22%	76	21%	
University degree	169	18%	64	18%	
Not known/ no answer	13	1%	5	1%	
Employment situation, mother					
Student	54	6%	27	8%	
Employee or entrepreneur	646	67%	220	62%	
Unemployed or retired	33	3%	11	3%	
Stay at home mother	160	17%	80	22%	
No answer / multiple choices	72	7%	18	5%	
Employment situation, father					
Student	28	3%	11	3%	
Employee or entrepreneur	837	87%	310	87%	
Unemployed or retired	41	4%	17	5%	
Stay at home father	12	1%	5	1%	
No answer / multiple choices	47	5%	13	4%	
Family's total annual gross income at the moment, EUR					
< 20,000	69	7%	42	12%	p<0.01
20,000 – 40,000	283	29%	112	31%	
40,000 – 60,000	339	35%	104	29%	
60,000 – 80,000	158	16%	48	13%	
>80,000	92	10%	31	9%	
No answer	24	2%	19	5%	
Residence					
City centre	93	10%	45	13%	
Suburb	442	46%	156	44%	
Municipal centre	212	22%	71	20%	
Sparsely populated area	205	21%	77	22%	
Other / no answer	13	1%	7	2%	

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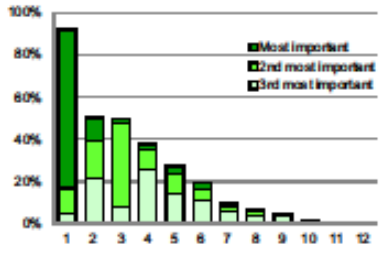
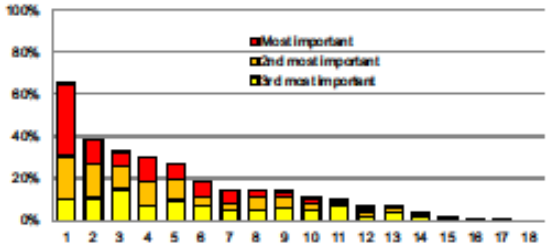
Most important reasons to consent

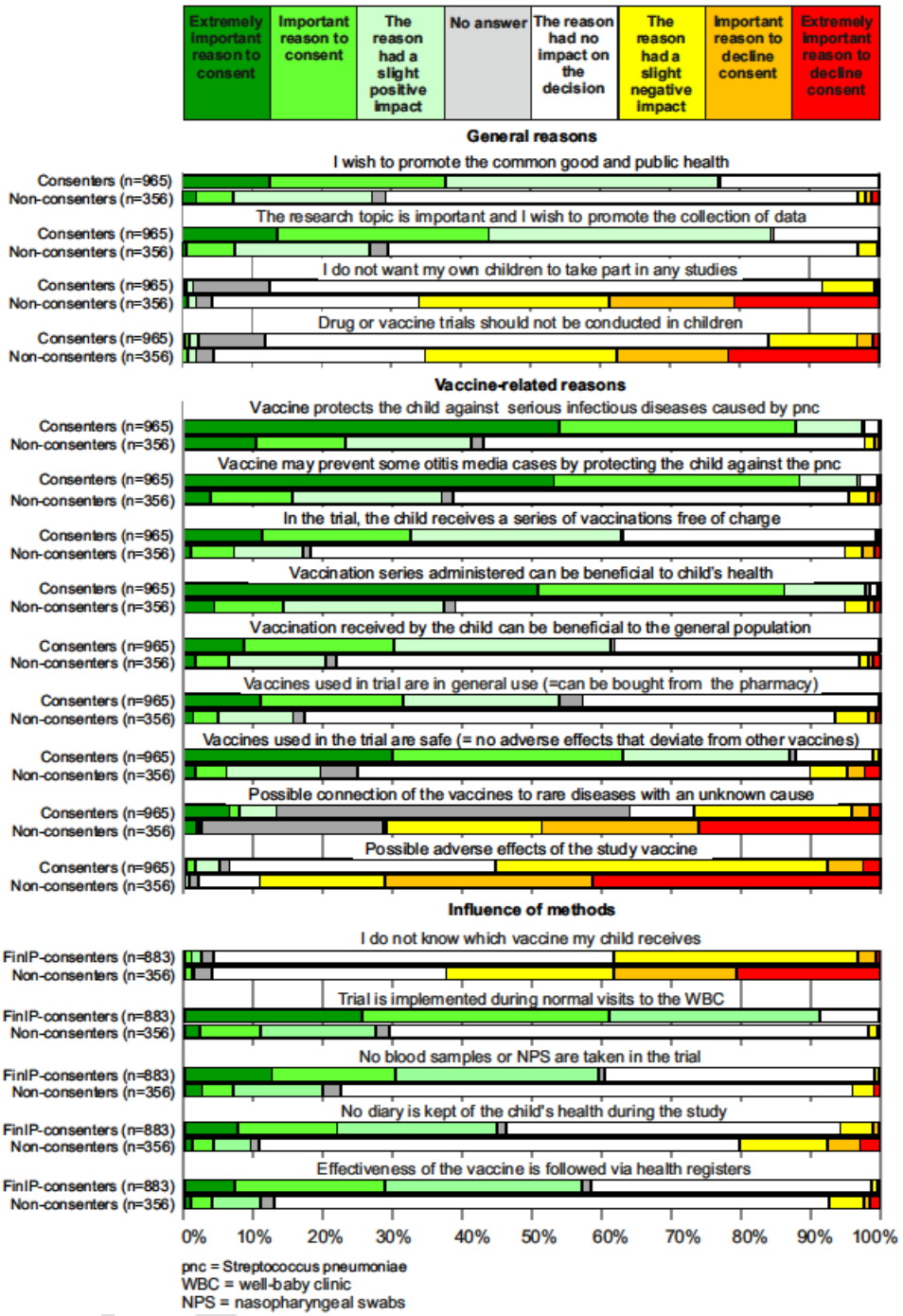


1 Immunisation against pneumococcal diseases
2 Common good, area of research is important
3 Immunisation against hepatitis
4 Trial was conducted at well-baby clinics during normal visits
5 Vaccines used in the trial are in common use, and their safety have been studied
6 Vaccinations given free of charge
7 Well-baby clinic nurse recommended participation
8 No blood samples or nasopharyngeal swabs were taken
9 Outcomes were monitored using national health registeries, and no follow-up visits were required
10 Friend/acquaintance recommended participation
11 Physician recommended participation
12 Other reasons

Most important reasons to decline consent



1 I was suspicious of the safety of the vaccines
2 I would not have known which vaccine my child received during the course of the trial
3 I would not allow trials among children
4 I don't want my child to participate in any trials
5 Study vaccines would have been administered in addition to the vaccines in the national vaccination programme and I did not want my child to receive several vaccinations at the same time
6 I wanted to avoid the extra pain caused by vaccination
7 Other reasons
8 My child would have received several vaccination doses in the study
9 I wanted to avoid the extra discomfort caused by the trial
10 I do not think pneumococcal diseases are a notable threat to my child's health
11 I was unable to make a decision on the matter
12 I did not understand the information regarding the trial to an adequate extent
13 The trial is sponsored by the vaccine manufacturer to whom the data gathered in the study will be handed over (without personal identification details)
14 My child was going to participate but the matter slipped my mind
15 I was not aware of the trial
16 I bought pneumococcal or hepatitis vaccine for my child
17 The study involved monitoring of the vaccine effects via national health registers using personal identity code
18 The child received the pneumococcal or hepatitis vaccine as a part of the national vaccination programme (belongs in a risk group)



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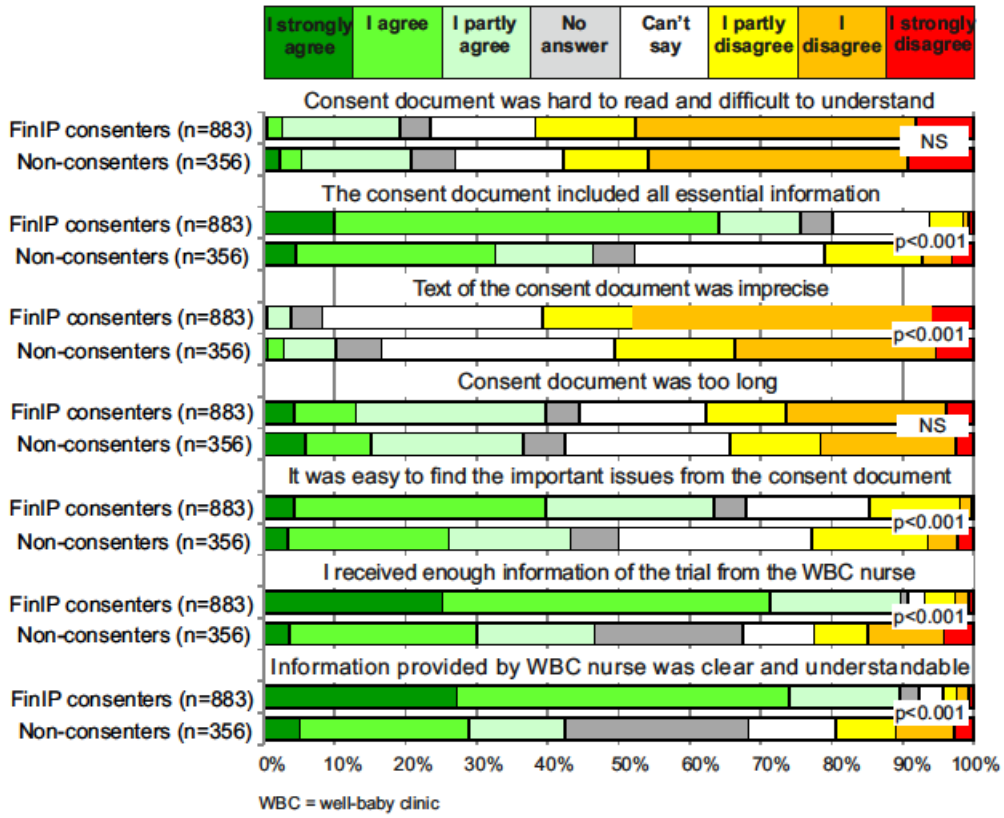

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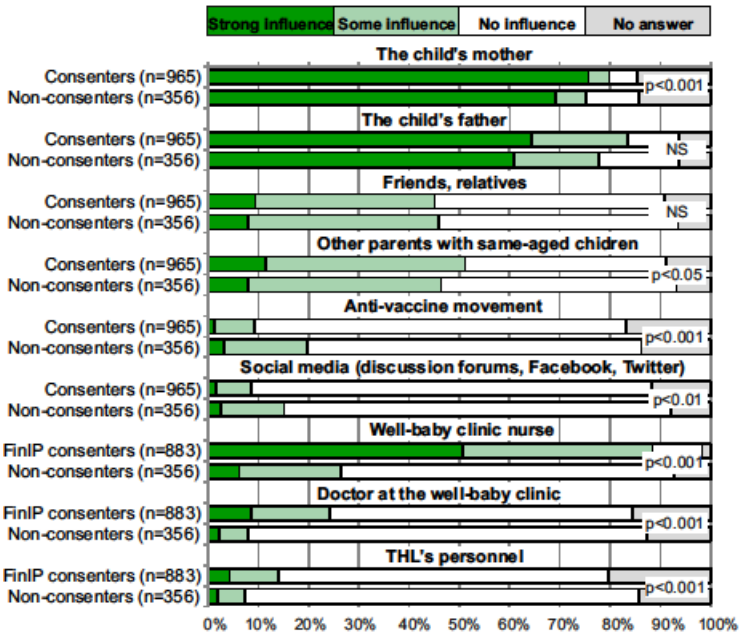
This manuscript does not include the supplementary material referred in the text.



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