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RESEARCH PAPER

Factors affecting willingness to participate in vaccine clinical trials in an underdeveloped country: perspective from Nepal

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ABSTRACT

Due to the inherent complex nature of clinical trials, individual's willingness to participate and hence, enrollment in a clinical trial maybe challenging. When it comes to vaccine clinical trial in children, informed consent needs to be secured from the parents or legally acceptable representatives (LARs). Some of the factors which contribute to hesitancy in taking part in clinical trials are based on the level of education, living standards, part of the world they live, associated burden of disease, fear of different procedures in clinical trial, side effects, limited understanding, limited time, and mistrust with Investigational product. This study included 201 parents/LARs, who approached Kanti Children Hospital site in Kathmandu with the interest to get their children enrolled in a vaccine clinical trial with objectives of describing the reasons for agreeing or disagreeing to participate in the vaccine clinical trial, factors affecting decision making, and finding the major concerns of parents/LARs. The acceptance for the study vaccine was 136 (67.7%) whereas denial was 65 (32.3%). This study showed that age, education level, family structure, advice from family and friends, and medical guidance play important roles in willingness of parents to get their child enrolled in the trial. If a proper counseling is done, fear of blood sampling is not a big factor which is contrary to the belief among clinical researchers. Safety of vaccine, frequency of injections, and cost of vaccine were the main concerns of the parents, which need to be addressed extensively while planning for any clinical trial in children.

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Introduction

Vaccine is one of the most cost-effective health tools ever invented[1] in medicine. It is estimated that vaccines prevent 6 million deaths annually from vaccine-preventable disease.[2] Vaccination has saved millions of lives and has potential to save millions more.[3] A study done in the United States estimated that every dollar spent on childhood vaccination could save US$3 from a tax-payer perspective and US$10 from a societal perspective, and this sets high standard from a 'return on investment' perspective for public health tools.[4] However, there is a huge disparity in the acceptance of vaccines globally (ranging between 39 and 88%). The coverage of routine vaccinations is higher in developed countries compared to low- and middle-income countries (LMICs).[5]

In developing countries, participation in new vaccine research is low as compared to that in developed countries,[6] though, recent trends show better participation.[7,8] Vaccine development is a lengthy process involving intense timelines, expertise, regulatory and ethical scrutiny, and financial commitments.[9] After initial animal studies, clinical trials are essential to generate evidence on safety and efficacy of candidate vaccines. Due to the inherent complex nature of clinical trials, willingness to participate from the community may be challenging and a concern.[10]

Clinical trials are generally conducted in age descending manner, starting with adults, followed by adolescent and children populations. This sequential approach helps to generate evidence in vulnerable and special population for which vaccine is generally intended for. When it comes to vaccine clinical trials in children, informed consent process needs to be secured from the parents or legally acceptable representatives (LARs). Sometimes parents are reluctant to have their child participate in vaccine clinical trials due to various reasons.

There is limited literature available highlighting the factors that drive the participants/LARs decision to agree or disagree to be part of any clinical trial. Factors contributing to participation in a clinical trial are based on the level of education, living standards, part of the world they reside and burden of disease, fear of different procedures in clinical trial, side effects, limited understanding, limited time, and mistrust with Investigational product.[11] If there is lesser burden of disease and access to treatment is easier and cheaper, then there will be less willingness to be part of any clinical trial. With regards to novel vaccine candidate clinical trials, potential participants are more concerned about the safety profile of the vaccine candidate which leads to difficulty in recruiting volunteers as shown in a few studies conducted for the Covid-19 vaccine candidate.[12]

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This paper summarizes the findings of the response of parents/LARs from a phase III typhoid conjugate vaccine clinical trial completed at a tertiary care children hospital in Kathmandu, Nepal. To our knowledge, very limited studies are available from LMICs in Asia focusing on factors associated with parents/LARs willingness to volunteer their children into vaccine clinical trials, therefore, findings from this study will help the vaccine manufacturers/clinical researchers to plan studies keeping in mind factors which matters to the parents/LARs before consenting for any vaccine clinical trial. The points addressed under this study were (i) Reasons for agreeing or disagreeing to participate in the vaccine clinical trial, (ii) factors affecting decision making, and (iii) major concerns of parents/LARs.

Material and methods

Study population

This study included responses from 201 parents/LARs having children aged from 9 to 15 months of age and visited Kanti children's hospital (KCH), Kathmandu at Vi-DT phase 3 clinical trial site with an interest for participation in the additional study group of IVI T003.[13] This is an ad hoc anlysis of the information gathered in additional study group.

Sample size calculation

Sample size was calculated by the following formula

$n_{o=}\frac{Z^2pq}{d^2}$

where p = .64, d = p × 5%

$$n_{o=}851$$

For finite correction:

$$n = \frac{n_o}{1+\frac{n_o}{N}}$$

N = Finite population i.e. 250

P = .64,[14]

n = 193, considering 5% error the number will be 203. We collected information from 201 participants purposely, 2 participants rejected to participate.

Participants enrolment

The study site, KCH, a government referral hospital for children in Nepal was part of a phase III, multicenter, observer-blinded, randomized, active controlled, immune non-inferiority and safety trial of typhoid conjugate vaccine.[15] All parents/LARs having children's 9–15 months of age and visited KCH with interest of participating in research were enrolled in this study.

Study team explained the parents/LARs about the study and test vaccine under trial including background, risk, benefits, rights, and responsibilities per the participants information sheet (PIS) provided by the study sponsor.

Before starting the informed consent signing process, we recorded the demographic information (age, address, educational status, and occupation) of the parents/LARs.As a part of the consenting process study team observed if they consulted others for further clarifications about the test/comparator vaccines or any other study related information. Study site recorded if they had expressed any concern during the information explanation process. As a part of the study procedures, the consented parents/LARs went ahead with the trial participation and those who did not consent were stopped for further processing. Details of trial procedures are outlined in the study protocol registered under ClinicalTrials.gov (NCT 03933098).[15] This study was conducted over a period of 4 months from September 2020 to December 2020 after securing all required regulatory & ethical approvals.

Staff training and data management

All study staff were trained on the informed consent process, good clinical practices (GCP), human subject protection policies, and study protocol. All study information was captured in electronic case report form (eCFR).

Study variables

The study questionnaire related to this paper contained socio-demographic characteristics of the parents/LARs, their major concerns during the consenting process and to seek other opinion/additional advice to reach the conclusion for participation in the trial. The outcome variable was the willingness to get their child participated in the proposed vaccine clinical trial (consented/not consented).

Statistical analysis

The study data was maintained in an excel sheet and analyzed using SPSS software version 16.0. Means with standard deviations and medians with interquartile range (IQR) were used to describe quantitative variables and proportions for categorical variables. The education was dichotomized, up to or more than 10 years of school education.The variables were selected manually (purposeful selection). Those variables which were associated with the outcome, odds ratio (ORs), 95% confidence intervals (CIs), and a p-value of <.05 was considered significant.

Ethics

The study was conducted according to The Code of Ethics of the World Medical Association (Declaration of Helsinki), International Conference on Harmonization-Good Clinical Practice (ICH-GCP) and Nepal Health Research Council (NHRC) guidelines.

Results

This study included 201 parents/LARs, who approached KCH site with the interest to get their children enrolled in the vaccine clinical trial. Trial participation and hence, acceptance for the study vaccine was 136 (67.7%) whereas denial was 65 (32.3%). Out of 201, 130 (64.6%) children were accompanied by both parents (father and mother) while 63 (31.4%) children

were accompanied by the mother alone and 8 (4.0%) children by the father alone. The willingness to give consent by single parent was 50 (70.0%),while it was 86 (66.15%) if accompanied by both parents; and refusal to consent was 21 (30.0%) and 44 (34.0%) among single and both parents, respectively.

The median age of father who approached the site was 32 years (range 19–47 years) while the median age of the father who took part in the study was 33.18 years and who refused their child to be enrolled was 31.18 years. The median age of mother who approached the study site was 28 years (range 19–43 years) and the median age of mother who accepted their child to be enrolled for study vaccination was 28 years while the median age of mother who refused was 27 years.

There were 35 (17.4%) fathers under 10 years of formal education (SLC), and out of 35, 29 (82.9%) consented while 6 (17.1%) did not consent for study participation. Fathers with above SLC education were 166 (82.6%) and out of which 107 (64.5%) consented their child participation while 59 (35.6%) refused. There were 49 (24.3%) mothers under 10 years of formal education, and out of 49, 37 (75.5%) consented while 12 (24.5%) did not consent for study participation. Mothers with above SLC education were 152 (75.7%) and out of which 99 (65.1%) consented their child participation while 53 (34.9%) refused. The main professions of father were service jobs 74 (36.8%), while mothers were home makers 107 (53.2%). There were 153 (76.1%) participants from nuclear family and 48 (23.9%) from joint family enrolled in the study. There were 50 (24.9%) participants from native Kathmandu valley while 151 (75.1%) migrated to the Kathmandu valley. (Table 1)

There were 39 (19.4%) parents who had additional companion with them and 63 (31.3%) did additional consultations before consenting for the study. Most of the queries regarding test vaccine and study came from mothers 124 (61.7%) followed by fathers 70 (34.8%) and others 7 (3.5%). (Table 2)

The major concern shown was related to safety (185 (92.0%)), followed by concern about any other additional dose in future and cost of vaccines if they have to buy outside the clinical trial (8 (4.0%)). (Table 3)

Discussion

Children are unique subpopulation with special developmental and physiological differences from adults, therefore, clinical trials in children are essential to develop age-specific, empirically verified therapies and interventions to determine and improve the best medical treatment available.[16] Due to the vulnerable nature of this population group, the balance between risk and benefits needs to be assessed very carefully. A vaccine trial in pediatric population is conducted after its safety is well established in the adult population. Most of the immunizations are conducted in infancy and childhood to decrease the morbidity and mortality of childhood diseases, which necessitate children participation in vaccine research. Participating in any clinical trial including vaccine trial is an important and personal decision, and participation in these clinical studies can help to improve the health of children around the world.[17,18]

This study included 201 parents/LARs, who approached Kanti Children Hospital site in Kathmandu, directly came either from the community through community workers or from the routine immunization clinic of Kanti children's hospital with the interest to get their children enrolled in a vaccine clinical trial. In Kathmandu, the capital of Nepal, both mixed and diverse populations resides and our study population represents the same heterogeneity. These people had equal chance to come to the trial site with interest in participation and this is the real reflection of the community interest. It is hard to find enough participants in the vaccine trial in low-income countries due to various apprehensions toward clinical trials. A recent study from developed countries reported that only 18.4% parents were willing to enroll their child in a COVID 19 vaccine clinical trial,[19] which shows the difficulties of enrolling pediatric population in clinical trials. A study conducted by Akmatov et al. (2017)[20] among participants over the age of 65 years for participation in a possible study on influenza vaccine trial found that refusal to participation was mainly associated with the invasive nature of medical study procedures, such as blood-draws, followed by long duration of the study period. MaëlleDetoc et al. (2019) conducted an online survey in France among adult participants and reported that 48% of the survey respondents were likely to participate in a clinical trial against COVID-19.[12] Rahejaet al., conducted a survey among 400 participants above 60 years around Atlanta, and found that 64.34% adults were willing to participate in new vaccine trial and moreover 75% of them never participated before.[14] Though our study subject was very different, i.e., Typhoid vaccine, but it reported better acceptance of the study vaccine, which was 136 (67.7%) whereas the denial rate reported was 65 (32.3%). Typhoid is an endemic disease in Nepal and there is awareness about the typhoid among population, particularly in Kathmandu; the capital city. This might have played a significant role. Beside that Information of this vaccine trial was cascaded through community workers and therefore, those who were interested in study vaccine, might have visited the site so the acceptance rate might have been more than in general at population level.

We collected the demographic data and other common variables reported in literature from the participants who visited the Vi-DT typhoid conjugate vaccine clinical trial site and described the characteristics and concerns of Parents/LARs, which played important role in decision making to get their children enrolled in new vaccine trial. Among the 201 parents/LARs who visited our site, majority of the children 130 (64.6%) were brought by father and mother together. About 46 (73.0%) of the mothers who came alone for their child's enrollment in the trial though it was statistically insignificant. There was no statistically significant difference among children accompanied by single (either father or mother alone) or both parents for participating in trial (p value = .324).

The median age of father was 32 years (range 19–47 years). The median age of the father who agreed or refused to enroll their child in the study was 33.18 and 31.18 years, respectively, which showed higher acceptance rate for trial participation with increasing age (p = .018). In contrary, Botelho-Nevers et al. found the acceptance was significantly higher among

Table 1. Socio-demographic characteristics of 201 participants.

	Consented for trial Vaccine	Not Consented for trial Vaccine	Total	*p value*	OR with 95% CI
Categories	N (%)	N (%)			
Total parents (n=201)	136(67.66%)	65(32.33%)	201(100.0%)		
The child was brought by					
Father	4(2.0%)	4(2.0%)	8(4.0%)	0.350	
Mother	46(22.9%)	17(8.5%)	63(31.4%)		
Both	86(42.8%))	44(21.9%)	130(64.6%)		
The child was brought by					
Singly (either father or mother)	50(70.0%)	21 (30.0%)	71(33.8%)	0.536	
Both	86(66.2%)	44(33.8%)	130(64.2%)		
Father's Age (median age of32)					
Up to 32 years	68(60.7%)	44(39.3%)	112(55.7%)	0.018	2.095 (1.12 - 3.89)
More than 32 years	68(76.4%)	21(23.6%)	89(44.2%)		
Father's education					
Up to SLC	29(82.9%)	6(17.1%)	35(17.4%)	0.103	0.375 (0.14 - 0.95)
Above SLC	107(64.4%)	59(35.6%)	166(82.6%)		
Father's profession					
Service	50(67.6%)	24(32.4%)	74(36.8%)	0.819	
Agriculture	5(83.3%)	1(16.7%)	6(3.0%)		
Business	47(65.3%)	25(34.7%)	72(35.8%)		
Foreign Employment	34(69.4%)	15(30.6%)	49(24.4%)		
Mother's age (median age 28)					
Up to 28 years	65(60.2%)	43(39.8%)	108(53.8%)	0.015	2.135 (1.15 - 3.94)
Above 28 years	71(76.3%)	22(23.7%)	93(46.2%)		
Mother's Education					
Up to SLC	37(75.5%)	12(24.5%)	49(24.3%)	0.153	0.606 (0.29 - 1.25)
Above SLC	99(65.1%)	53(34.9%)	152(75.7%)		
Mother's profession					
Service	21(67.7%)	10(32.3%)	31(15.4%)	0.177	
Agriculture	2(33.3%)	4(66.7%)	6(3.0%)		
Business	37(64.9%)	20(35.1%)	57(28.4%)		
Home maker	76(71.0%)	31(29.0%)	107(53.2%)		
Family type					
Nuclear/Broken	109(71.2%)	44(28.8%)	153(76.1%)	0.053	0.519 (0.26 - 1.01)
Joint	27(56.2%)	21(43.8%)	48(23.9%)		
Place of origin					
Inside Kathmandu	26(52.0%)	24(48.0%)	50(24.9%)	0.006	2.477 (1.15 - 4.79)
Outside Kathmandu	110(72.8%)	41(27.2%)	151(75.1%)		

Table 2. Characteristics and Decision making process among 201 participants.

	Consented for trial Vaccine	Not consented for trial Vaccine	Total	*p* value	OR with 95% CI
People accompanying with parents					
None	107(66.0%)	55(34.0%)	162(80.5%)	0.319	1.491 (0.67 - 3.29)
Yes	29(74.4%)	10(25.6%)	39(19.5%)		
Parents consulted for decision making					
Yes	50(79.4%)	13(20.6%)	63(31.3%)	0.017	2.326 (1.15 - 4.68)
No	86(62.3%)	52(37.7%)	138(68.6%)		
People to inquire about the study vaccine					
Father	45(64.3%)	25(35.7%)	70(34.82%)	0.585	
Mother	87(70.2%)	37(29.8%)	124(61.6%)		
Others	4(57.1%)	3(42.9%)	7(3.4%)		

Table 3. Parental concern about trial vaccine among 201 participants.

	Consented for trial Vaccine	Not consented for trial Vaccine	Total	*p* value
The concern shown for				
Safety	129(69.7%)	56(30.3%)	185(92.0%)	0.029
Frequency	5(62.5%)	3(37.5%)	8(4.0%)	
Cost	2(25.0%)	6(75.0%)	8(4.0%)	

younger population (38.5 vs 54.9 years old) in a study related to COVID-19 vaccine conducted in France in 2018.[21] The median age of mothers was 28 years (range 19–43 years) who accompanied the child for study participation. Study reported higher acceptance rate among older mothers as compared to younger ones (p = .015). (Table 1)

All parents who came with the interest to know about vaccine trial were educated. Among the enrolled participants, fathers' education was under SLC 82.9% (n = 29) while 64.4% (n = 107) was above SLC. With the reported statistical significant difference (p = .03) showed that lesser the education level of the father, more is the acceptance rate for enrolling in study vaccination which is contradictory to the finding by Cobb et al. in 2014.[22]

While analyzing mother's education, we found that lesser the mother's education more was the chances of enrolling the child in the trial vaccination though it was not statistically significant (OR .606; 95%CI (.291–1.259), p = .15).

Parents from different professions came to the trial site including parents from medical background 10 (4.0%), who enrolled their child in the clinical trial, but the overall study didn't report any profession specific preference for or against trial participation. When it comes to the structure of the family, it was found that the parents from joint family were more reluctant to consent than parents from nuclear family (OR .5195%CI: .266–1.013). It may be due to hesitancy of the parents to keep forward their views among the senior member of the family or influence of various family members which negatively impacted parent's decision to enroll.

There was about 2.5 times more participation from the people who were migrated to the valley in enrolling their child than native inhabitants (OR: 2.47 (95% CI: 1.279–4.795 and p = .006). This could probably be due to easy adaptation characteristics of the people who are originally outsider and came to Kathmandu. They may be more enthusiastic for newer innovation or more anxious of health issues related expenses, which are difficult to bear. Thus burden of disease and economy may also have influenced them to take part in vaccination clinical trials.

Our study observed that there were 162 (80.5%) parents who did not bring any other companion with them while 39 (19.5%) brought some friends or relatives with them while coming for participation. Parents accompanied by others were more willing to have their children enrolled in our vaccine trial study rather than those who came alone (OR: 1.491; 95% CI: .677–3.281). This may be due to endorsement of their decision to participate by accompanied friends and relatives, which gave them more confidence to participate. When parents came with their friends rather than elderly family members, it was easier for them to make decision. This could be due to ease of communication and discussion with peers rather than elderly people. We also observed that there were parents who consulted other medical experts for making decision of getting their child enrolled in the study. There were 63 (31.3%) parents who consulted with other medical experts, while 138 (68.7%) did not consult with others. It was found that those who consulted other medical experts for vaccination were more keen to take part in the vaccine trial than those who did not (OR: 2.326; 95% CI: 1.154–4.686, p = .017).

Study done in Australia had shown the acceptance of children in clinical trial was mainly associated with personal characteristics like physical, psychological, patient centered attitudes of any individual and may be dependent on the age, religion they belong and social taboos they have.[23] This is in agreement with our study as well. Almost all parents had some concern about the trial vaccine. Most of the parents were concerned about the

safety of the vaccine, though a few had shown concern about the cost of the vaccine if they had to buy themselves out of this study and frequency of vaccination. They were concerned for the need of booster dose in future, if any. Though Akmatov et al. (2017) found blood sampling to be the factor for unwillingness to participate in the vaccine trial,[20] our study interestingly showed, parents did not show any concern about sampling. It might be due to proper explanation about the need and benefit of blood sampling while explaining the participant information sheet as a part of Informed consent process.

This study had few limitations. We included parents/LARs, who approached Kanti Children Hospital site in Kathmandu with the interest to get their children enrolled in a vaccine clinical trial. Those who didn't have interest at all might not have come to the trial site. So this study highlight factors among interested participants, but not at population level. Sample size was small which could potentially increase variability and bias. Structured information was collected based upon pre-set questionnaire; therefore, there might be other factors which could have contributed to decision making by parents. Additional research with large sample size in diverse geographical setting may be needed to further understand the factors and barriers which influence the parents' decision to get their children enrolled in any vaccine trial.

Conclusion

This study showed that age, education level, family structure, advice from family, and friends and medical guidance play important roles in willingness of parents to get their child enrolled in the trial. If proper counseling is done, fear of blood sampling is not a big factor which is contrary to the belief among clinical researchers. Safety of vaccine, frequency of vaccination, and cost of vaccine were the main concerns of the parents, which need to be addressed extensively while planning for any clinical trials in children. Field health workers due to their regular interactions within well-defined catchment areas could play an important role in spreading the awareness and educating the families/societies regarding the importance of conducting clinical trials among vulnerable populations and generating local data, which ultimately benefits public health decisions in terms of policy making and implementation.

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Conceptualization RHC and SA; Data curtain RHC, SA, GKR; Formal Analysis SP, BRG; Methodology: RHC, SA, SP; Supervision GKR,TS; Validation TS, TAW,SS; Original Writing RHC, SA; Writing review and editing PR, NJS, BP, PJ, BRG, TAW, SS.

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