

Recruitment of babies in vaccine trial: A challenge

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ABSTRACT

Introduction: The enrollment of children into clinical trials is challenging. India is increasingly recognized as a site for clinical research due to its large population and growing research capabilities, though data regarding barriers for recruitment into pediatric vaccine clinical trials are scarce. **Objective:** The objective of this study was to assess the barriers in recruitment and to find out parental factors for non-participation of their babies in the vaccine clinical trial. **Materials and Methods:** This was a prospective cross-sectional non-interventional study which was carried out in the pediatric clinical research unit of a tertiary care multispecialty teaching hospital in Pune. The study social worker visited postnatal ward to prime mothers regarding the pneumococcal vaccine clinical trial. Parents of babies aged 6–8 weeks, who were eligible for participation in the ongoing pneumococcal vaccine trial were explained the informed consent form of this clinical trial and their willingness for participation was sought. The reason for refusal of the parents, who declined the study participation of their baby, was documented. **Results:** Even though eligible inborn baby pool was large (n=384), only 148 (38.54%) inborn babies were brought to our clinical research unit showing a major barrier in the recruitment. Of 204 babies who presented to clinical research unit, 94 babies (46.08%) were enrolled in the ongoing clinical trial and the majority of them were inborn (89.36%), whereas only 10 of 56 (17.86%) outborn babies were enrolled. There was no gender difference noted in enrolled versus non-enrolled babies. There was no significant association between baby's gender and place of delivery. The major reasons for non-enrollment were "unwillingness" for participation in clinical trial (68.18%) followed by mothers going outstation, staying far away from our hospital, lack of time, and concerns due to research vaccine. **Conclusion:** Our study has shown that even though eligible inborn baby pool was large, only 38.54% of inborn babies were brought to our clinical research unit, thus a major barrier in recruitment. More effective counseling and recruitment strategies are needed to scale up the enrollment more so for the outborn babies.

Key words: Barriers, Recruitment, Vaccine trial

Immunization is a proven tool for controlling and eliminating life-threatening infectious diseases and is estimated to avert between 2 and 3 million deaths each year. It is one of the most cost-effective health investments, with proven strategies [1]. Significant advances in child health have resulted from the conduct of various drug and vaccine trials in pediatric age group. Well-known trials of polio vaccine and the subsequent rapid translation into practice were instrumental in the successful and almost complete eradication of polio [2,3]. The new vaccines are still being developed, tested in clinical trials, and brought into routine clinical practice.

The enrollment of children into clinical trials is challenging due to relatively small number of available participants. This is further complicated by the challenges of obtaining parental consent for the child to participate [4]. The slow recruitment can lead to prolonged study duration, increased resource use, and increased budget or premature termination of recruitment which can result in underpowered studies.

Studies have shown that parents balance risks and benefits when deciding about trial participation for their child [5,6]. Kong *et al.* have reported that the perceived barriers for clinical trial participation include potential side effects, being randomized to ineffective treatments, mistrust of the health-care system, and the inconvenience for visits [7].

India is increasingly recognized as a site for clinical research due to its large population and growing research capabilities, though data regarding barriers for recruitment into pediatric vaccine clinical trials are scarce. The present study was carried out to assess barriers in recruitment and to assess parental factors for non-participation of their babies in the vaccine clinical trial. This would help us in planning strategies for improving recruitment in future studies.

MATERIALS AND METHODS

This study was a prospective cross-sectional non-interventional study which was carried out in the pediatric clinical research

unit of a tertiary care multispecialty teaching hospital in Pune. The study was conducted from June 2018 to December 2018 when enrollment of babies aged 6–8 weeks old in a phase-four pneumococcal vaccine trial was carried out in the pediatric clinical research unit. The study was initiated after approval from the institutional ethics committee.

The study social worker visited postnatal ward to prime mothers regarding the pneumococcal vaccine clinical trial. She telephonically called parents of eligible babies to remind them to bring their babies for vaccination to our hospital once the baby was 6 weeks old (n=384). Few parents could not be reached, as they did not pick up phone or number was not reachable, few parents told that they were going outstation, few had taken vaccine outside, and few of them said that they would come, but did not come. Thus, of 384 inborn babies, only 148 parents brought their babies to clinical research unit.

Outpatient department (OPD) pediatricians were informed of the ongoing pneumococcal vaccine clinical trial and were requested to refer 6–8-week-old healthy babies to the clinical research unit. Babies, who were brought to the unit for the study recruitment, underwent screening for inclusion/exclusion criteria

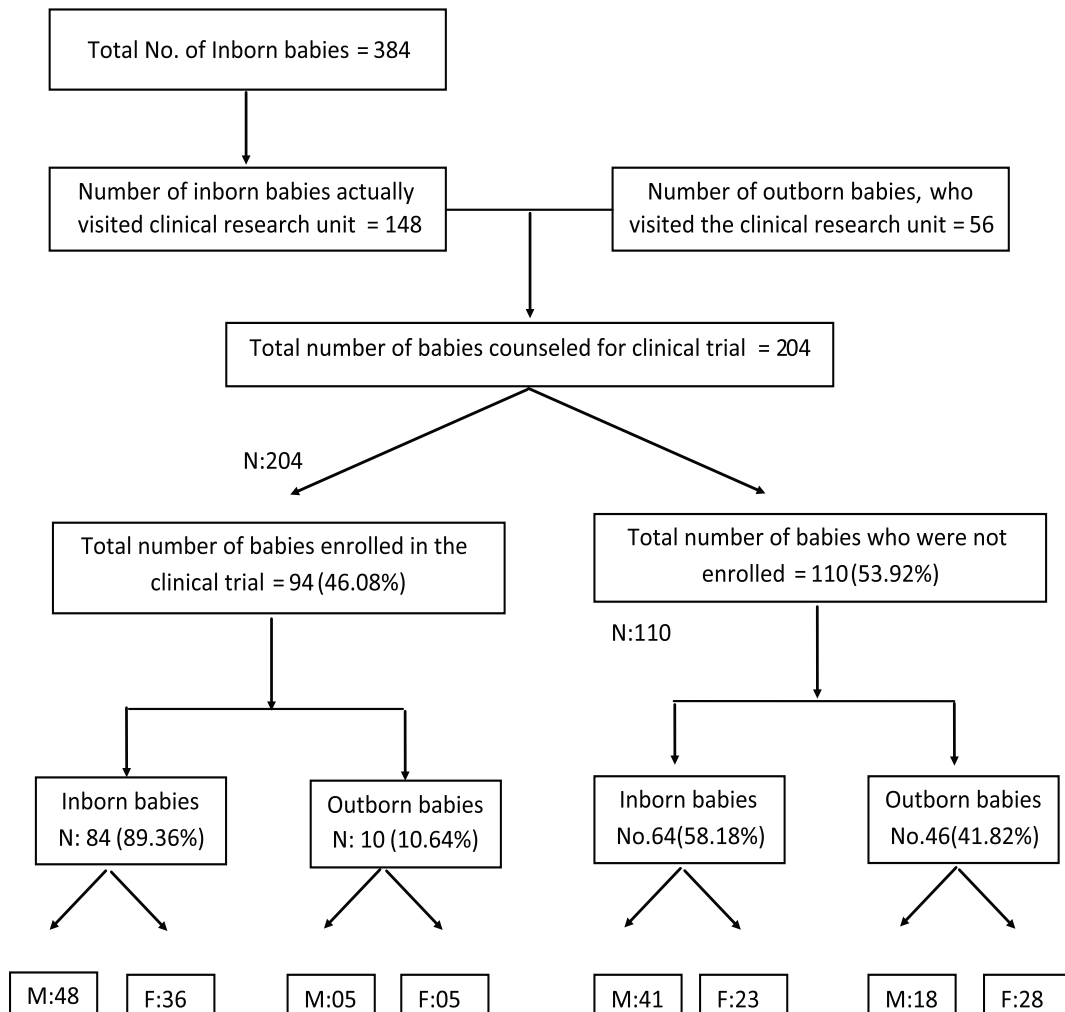
of the vaccine trial by the study physician. Babies who did not fulfill these criteria were excluded from the study and were referred back to OPD pediatrician for checkup and vaccination. The parents of eligible babies were explained the informed consent form of this clinical trial and their willingness for participation was sought (n=204).

The reason for refusal of the parents was documented and they were advised to take routine vaccination in the OPD (n=110). Thus, our study cohort included 148 inborn (our hospital deliveries) and 56 outborn babies (babies born in another hospital).

Statistical analysis was done using SPSS software with version 25.0. All qualitative variables were represented by frequency and percentages. Chi-square test was used to study the association between different variables in the study. Throughout results, 5% level of significance was used and all results were shown with 95% of confidence.

RESULTS

Flowchart of babies presented to clinical research unit for counseling and its outcome:



M: Male babies, F: Female babies, N: Number of babies.

The flowchart above shows that of 384 eligible inborn babies, only 148 (38.54%) babies were brought to clinical research unit and 84 babies of this cohort were enrolled in the study. Regarding outborn babies, only 10 of 56 (17.86%) babies were enrolled in the study. There was no gender difference noted in enrolled versus non-enrolled babies [Table 1].

The majority of enrolled babies were inborn (89.36%). There was no significant association between baby's gender and place of delivery.

Unwillingness for participation in clinical trial was the major reason for non-enrollment (68.18%) both in inborn and outborn babies. The association between non-enrollment and place of delivery of babies was not clinically significant [Table 2].

DISCUSSION

Clinical trials are considered the gold standard for generating evidence-based knowledge in medicine. Successful recruitment in pediatric clinical trials is one of the most challenging aspects of conducting clinical research in children. This study was carried out to evaluate recruitment barriers and to assess parental reasons for non-participation of 6–8-week-old babies in the vaccine clinical trial.

Our study has shown that even though eligible inborn baby pool was large (n=384), only 148 (38.54%) inborn babies were brought to our clinical research unit, thus a major barrier in recruitment. Vanhelst *et al.* have reported that Lasagna's law, i.e., the "number of patients in the predictive pool always exceed those eligible, which again exceeds those who consent during the recruitment period of the study" might have a greater impact on pediatric studies [8]. Thoma *et al.* have also reported that investigators greatly overestimate the pool of available patients who meet the inclusion criteria [9].

In this study, 94 of 204 (46.08%) babies were enrolled which were lesser than our previous study which had shown that 52% of parents were willing to enroll their babies in clinical trials [10]. Higher participation rate of 64.5% is reported by Gupta *et al.* [11], but the study by Vanhelst *et al.* has demonstrated only 32% of participation rate among healthy children as compared to 93% among ambulatory sick children [8].

The study shows that out of the babies who presented to clinical research unit for counseling for the clinical trial and enrolled in the study, 84/94 (89.36%) were inborn. This is probably due to the priming in the postnatal ward, reminder phone calls, and faith in the hospital/hospital physicians. Faith in doctor/hospital and doctor's influence are important reasons for enrollment in clinical trials as seen in various studies [4,12,13]. Hoberman *et al.* have observed that positive parental perception of the researcher is associated with greater likelihood to consent [12]. Good relationships and communication between parents and their clinician offer parents a sense of understanding, safety, and trust, as reported by Shilling and Young [13]. Unger *et al.* have reported that the physicians play a key role in helping patients, determine treatment choice, and patients often look to their physicians to inform them of clinical trials [14]. Thus, the parents of inborn babies are more likely to get enrolled as compared to outborn babies as seen in our study.

In this study, 56/204 (27.45%) babies were outborn and out of these, only 10/56 (17.86%) babies could be recruited in the study. The lower recruitment of outborn babies might be due to multiple factors such as lack of rapport with the parents or they were unaware of the clinical trials and had not come prepared, had no time for study procedures, and had concerns about research and its safety.

Various reasons for non-participation in clinical trials have been reported in earlier studies. Limkakeng *et al.* have shown that mistrust of researchers is a near-universal barrier to research participation across cultures [15]. Greenberg *et al.* have shown that for the study recruitment, contact from a "stranger" was much less preferred [4]. It has been reported that parents are unlikely to consent if they are not convinced by the study team that their children could benefit from being in the study [4,16]. Shilling and Young reported that parents of healthy children considering participation in vaccine research believed that children should only take part in research where the medical benefits outweigh any potential risk [13]. Vanhelst *et al.* have stated that the main improvement factor for enrollment was that the investigators should devote more time to parents, discussing pediatric clinical

Table 1: Babies enrolled in the study

Inborn/outborn	Male (n)	Female (n)	Total (%)	Chi-square value	p-value
Inborn	48	36	84 (89.36)	0.185	0.667
Outborn	5	5	10 (10.64)		
Total	53	41	94 (100)		

Table 2: Reasons for non-enrollment of babies

Reason for non-enrollment	Inborn babies (%)	Outborn babies (%)	Total number (%)	Chi-square	p-value
Not willing	42 (65.63)	33 (71.74)	75 (68.18)	12.28	0.423
Going outstation/stay far off	17 (26.56)	7 (15.22)	24 (21.82)		
Lack of time	2 (3.13)	3 (6.52)	5 (4.55)		
Because its research	2 (3.13)	3 (6.52)	5 (4.55)		
Other babyies had ventricular septal defect	1 (1.56)	00	1 (0.90)		
Total	64 (58.18)	46 (41.82)	110 (100)		

research studies [8]. Hence, to facilitate enrollment of outborn babies, we would have to establish good rapport with parents and rigorous counseling needs to be reinforced.

We did not observe any significant gender difference in clinical trial enrolment, i.e., 53 (56.38%) were male babies, in contrast to our earlier study which had shown that the parents were more likely to give consent for clinical trial participation for girl child [10]. Parents who refused study participation of their baby were asked reasons for non-enrollment, but most of the parents (68.18%) did not specify any particular reason for their unwillingness. The second most common reason for non-participation of babies was, going outstation and staying far away from our hospital. As per the prevailing custom in our state to have first delivery at maternal place, the mothers travel to and from their maternal house post-delivery, thus not available for entire study duration, poses an important sociocultural barrier for recruitment of 6–8-week-old babies.

Lack of time for the study procedures was another reason for declining enrollment by 5 (4.55%) parents as also shown in the previous studies [9,17]. There was concern about the research vaccine of 5 (4.55%) parents and so they did not enroll their babies in the study. Shah *et al.* have reported potential participants voicing their concerns about safety procedures as well as possible side effects and health risks [18]. Fear and uncertainty about new drugs and mistrust of system are reported as a barrier by Kong *et al.* [7]. Vanhelst *et al.* have shown that safety was the main concern for the parents of healthy children [8]. Fear of potential risks and a general distrust in research are also reported by Tromp *et al.* [19]. Our study was limited by its small sample size and also it was limited to only one clinical research site.

CONCLUSION

Our study has shown that only 38.54% of inborn babies were brought to our clinical research unit, thus a major barrier in recruitment which shows that Lasagna's law holds true for recruitment of babies in clinical trial. The inborn babies are more likely to come for counseling of vaccine clinical trial and get enrolled, as compared to outborn babies. The major reason for non-enrollment was "unwillingness" for participation in clinical trial. More effective counseling and recruitment strategies are needed to scale up the enrollment more so for the outborn babies.

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