

Trials and tribulations of conducting interventional studies in urban slums of a developing country: Experiences from Kolkata, India

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Experimental studies involving human subjects provide most internally valid evidences in epidemiological research due to their robust methodology. While conducting population-based interventional studies, to achieve external validity, inclusion of information from vulnerable groups like urban slum-dwellers of the developing world, in the epidemiological estimates is of paramount importance. The challenges faced while conducting 2 consecutive large-scale, community-based vaccine trials in urban slums of Kolkata, India are presented in this article. Interventions in these communities often get constrained by issues pertaining to human rights and benefits, socio-cultural factors, political environment, methodological shortcomings in addition to the challenges in ensuring community participation. While conducting these trials although we intermittently faced obstacles, by virtue of having a long term and robust surveillance system and developing a trusted relationship between the researchers, community leaders and residents we were able to come up with a commendable community participation which culminated into the success of the interventions. Bridging the gap between research and field operations by incorporating knowledge gathered from interventional studies and making strategies to improve health conditions of these informal settlers is a major unfulfilled agenda. We believe the lessons learnt during our research will help researchers while developing efficient interventions in similar setting.

Introduction

Relatively unhealthy human settlements capable of rapid and enormous growth and characterized by altered physical and social environment are known as “slums.”^{1,2} The United Nations describes slums as communities with social and residential insecurity, poor housing conditions, overcrowding, poor sanitation and limited access to safe water.^{2,3} In their 2003 global report, the “United Nations Human Settlement Program” reported that more than one third (32%) of the global urban population and nearly 3-fourth (78.2%) of the urban residents of least developed countries live in slums.¹ Therefore, scientific validity of any interventional study cannot be established without inclusion of representatives from these communities in the study population.⁴ While community-based studies have facilitated better understanding of the health status and amplified public health knowledge among these slum-dwellers, there still remains a huge gap between their knowledge and its application for personal health improvement.^{5,6,7}

The principal challenge for efficiently conducting an interventional study in the slums involves incorporating information from these communities in the epidemiological estimates of disease parameters and enabling these informal settlers to access the benefits of the proven interventions.⁸ Thus, in spite of preventing innumerable cases of infectious diseases in cost-effective manners, vaccine trials and mass vaccination campaigns often have to face obstacles due to disbeliefs and wrong perceptions.⁹ Here we are presenting our

experiences while conducting 2 vaccine trials in the slums of Kolkata, India.

Methods

Study conduct

Typhoid and cholera are infectious diseases of immense public health concern in India including Kolkata. The National Institute of Cholera and Enteric Diseases (NICED), Kolkata in collaboration with International Vaccine Institute (IVI), Korea conducted consecutive large scale intervention trials of 2 vaccines against typhoid and cholera, for which pre-vaccination surveillance to estimate the disease burden was initiated in 2002 in selected slum areas in Kolkata.⁹ The projects involved assessing the protection afforded by vaccines against typhoid and cholera along with studying the socio-economic effects of vaccination in high-risk communities.^{9,10} The trials were approved by the NICED Institutional Ethics Committee, Health Ministry Screening Committee of the Government of India and the Institutional Review Board of IVI and were financially supported by the Bill & Melinda Gates Foundation through the Diseases of the Most Impoverished (DOMI) Program and the Cholera Vaccine Initiative.

Study area and population

About 14 million people reside in Kolkata and its suburbs, making it the third largest metropolitan city in India. (2008;^{11,12} Kolkata municipal area is divided into 141 civic administrative units called wards. There are 5500 slums in the city where more than one third residents live. (2008;^{11,12} Study population included residents of overcrowded hutments, sometimes poorly constructed along narrow, sewage littered pathways of 3 administrative wards. The typhoid study was conducted in a segment of ward 29 and the entire ward 30, while the cholera study site included entire wards 29, 30, and 33. A *de jure* census was initially conducted in January 2003 to collect personal and socio-demographic information.⁹ During baseline census, about 57000 residents were registered for the typhoid study and 105000 for the cholera study. Most of

the household head (75%) were able to read and write. Only 15% of the residents had access to safe drinking water (tap or tube well) and 8% had good sanitation system (flush toilet in the house). The study population was monthly updated to incorporate migrations (in and out), births and deaths.

Disease surveillance

Surveillance for febrile illness and diarrheal diseases was incepted in April 2003 in the project health clinics and 2 adjacent hospitals, Infectious Diseases Hospital and Dr B C Roy Memorial Children Hospital. These project health clinics were set-up within the community where residents could seek care for fever, diarrhea and related ailments. Physicians, data operators and attendants staffed the clinics, where clinical information and biological samples were collected from consenting participants. Venous blood samples were obtained from patients having fever for ≥ 3 days for culture and Widal test to diagnose typhoid cases and rectal swabs were obtained from patients with ≥ 3 loose stools in last 24 h, to isolate *Vibrio cholera*.^{(9,13,14,15} Community health workers conducted monthly home-visits to identify and motivate cases of fever and diarrhea to get tested. Subjects diagnosed with typhoid or cholera were reimbursed with their treatment cost.⁹ Government hospitals, municipal health-centers and local private practitioners were duly informed and were involved in motivating the subjects to participate in the surveillance and vaccination.^{9,13,14,15}

Interventions

The cluster-randomized double blind, placebo controlled typhoid vaccine trial was conducted among approximately 60000 residents between November 27 and December 31, in 2004. The clusters were pre-defined contiguous geographic areas.¹⁵ Non-pregnant, non-lactating, otherwise healthy, afebrile residents of the study area, aged ≥ 2 y were eligible. 18869 individuals received the Vi polysaccharide typhoid vaccine and 18804 received the hepatitis-A vaccine as the active control.^{9,15} Post-vaccination typhoid disease surveillance continued for 2 y thereafter.¹⁵ During this period

cholera surveillance also continued and 3 more field health clinics were established in ward 33 and another one in the expanded part of ward 29.

The cluster randomized, double blind, placebo controlled, phase III trial of an oral cholera vaccine was conducted in 2006 among non-pregnant, healthy residents of the study area, aged ≥ 1 y. In the cholera study clusters were dwellings (premises) defined as huts, groups of huts or a multi-story building with several households sharing the same water pipes, bathrooms and latrines, as assigned by the Kolkata Municipal Corporation.¹⁴ 31932 consenting individuals received 2 complete doses of the bivalent, modified killed-whole-cell oral cholera vaccine and 34968 individuals received 2 doses of the heat-killed *Escherichia coli* strain K12 as the placebo.^{14,16,14} Both vaccine and placebo were supplied by Shantha Biotechnics, Hyderabad, India. Doses of the assigned agents were administered at a minimum interval of 14 days, the first being given between July 27 and August 13, and the second between August 27 and September 10 in 2006.^{9,16,14} Post-vaccination cholera surveillance continued till 30th September, 2011, followed by a closeout census.

Challenges

Our study had to overcome several scientific, socio-cultural, financial, political and logistic challenges. An account of our experiences is presented here, contextualized with evidences from available literature, such that anyone planning to conduct an intervention involving communities of informal settlers may be prepared to deal with such challenges.

Mistrust, disrespect and wrong perceptions

Proper conduct of an intervention requires a long-term trustworthy and respectful relationship between the investigators and the residents. There could be a gap in understanding between investigators and participants, because subjects may perceive no direct benefit, no opportunity to participate in the decision-making and often minimal or no feedback is

provided to them about the outcomes.⁵ Inequalities regarding socio-physical environment, perspectives, priorities and values between researchers and participants may widen this gap.^{5,4,17} Efforts to develop a trusted relationship with the participants lengthens the study period.⁵

To overcome those barriers, in a step-wise approach, project-related discussions with community leaders were held. In turn, community leaders actively supported the development of rapport between investigators and residents. Project health workers were recruited from the study area. Disease surveillance for both diseases was initiated 2 and 3 y prior to the typhoid and cholera vaccine trials respectively. Collectively these provided us ample opportunity and time for establishing a cordial and trusted relationship with the residents. Moreover, by providing primary care in cases of medical emergencies and being available at the field health clinics throughout the study period, our study physicians became respected individuals in the community.

During these trials, rumors abounded regarding the effect and quality of the interventional products. To combat these we had to carefully prepare our study area for the intervention. Residents of our study area were motivated by project staffs who were their neighbors. Concerned authorities were well-informed and all necessary approvals, including regulatory were sought, which somewhat lengthened the timelines. Local opinion leaders and religious heads were actively involved for social mobilization. Prior notifications were also given to the local police, civic administrative bodies and the human rights commission.

Randomization and maintenance of blinding

In a field setting, randomization of the study intervention across the arms of the study and maintaining the randomization structure and blinding are big challenges.¹⁸ We faced difficulties in maintaining the randomization and blinding due to socio-political pressure. It was difficult for the investigators to explain the subjects especially to people with poor literacy, about the importance of not specifying the identity of the product

(vaccine/placebo) that any individual was receiving and local political pressure for unblinding was always there. However, we were able to explain the crux of blinding and final outcome of the study through regular small focused group meetings and interactive sessions with participants and local opinion leaders. We also convinced them that the control group would eventually be offered the vaccine after the trial.^{16,14,15}

Informed consent

While conducting an intervention trial, researchers need to mention all study related aspects in detail to the participants in a language that they understand clearly. This is to make sure that, the potential subject understands his/her responsibilities, potential risks and benefits related to the study before providing consent. This whole process makes the information sheets very lengthy. It was extremely difficult for us to work in the aforementioned settings with such lengthy documents. The information sheets were translated into 3 local languages (Bengali, Hindi and Urdu) and back-translated. Explaining the informed consent process and the study details to the participants^{18,19} were very important because the slum dwellers being less educated and economically underprivileged, might view it as an opportunity to obtain free treatment.⁵

The basic challenge was to make sure that the subject paid adequate attention to the intricate details and understood the whole document clearly. As these contained a lot of information subjects or their legally authorized representatives often became impatient. The recruitment processes took place in noisy environment, which were typical in slums and caused much inconvenience for the subjects to concentrate adequately on the provided information before giving the consent. There were always possibilities that in the long run these shortcomings might generate misunderstanding between participants and investigators. The time required for the whole process was also a critical issue especially in hot summer months and monsoon season when participants were packed inside hot and humid rooms. To make the participants feel comfortable, temporary huts were set up near the

intervention centers, where participants could wait. Instructions were given to the community health workers and project physicians not to lose patience and explain all queries raised by the participants.

Identification and follow-up

After being enrolled for the study many subjects may migrate to other places and information about them may not be available. This may result in serious threats for both internal and external validities of the interventional studies conducted in these settlements.^{4,5,17} These losses to follow up were not uncommon in our study. With the help of the robust surveillance system, the proportion of this loss remained relatively low.

Accurate identification of subjects during intervention and follow-up was a major task. Falsifications of identity to avail the benefits by persons who migrated out of the study area or resided outside the study area were also noted. During the baseline census we distributed identity cards to households that helped us to prevent falsification. Computers containing the regularly updated database were installed in the field health clinics, allowing further identity verification.

Literacy

Poor literacy is another major issue often observed while conducting studies in slum areas of developing countries. Often the dwellers of these areas do not have the necessary minimum literacy to understand their role, autonomy and responsibilities while participating in an interventional study.^{5,20,21} Informing them about the intervention and its prospects along with associated potential risks and benefits was not easy because of poor literacy and awareness. Illiterate subjects provided thumb impressions and the accompanying literate impartial witnesses, whose presence was made mandatory during the recruitment procedure, signed the informed consent documents. We gave special attention to the illiterate subjects to make sure that accurate information about the study was provided to them and their literate impartial witnesses. It was difficult to make the less educated subjects understand the importance of complying with the study protocol and adhering to

the dosing schedule, hence compliance and adherence were also affected by literacy. Since the cholera vaccine was given in 2 doses, 14 d apart, it sometimes became difficult to bring back the subjects for the second dose. Here again the local leaders and health workers played an important role in motivating the subjects to receive the second dose.

Socio-economic issues

Diversity of the slum dwellers in terms of castes, economic and social inequalities, cultural and religious beliefs may become important barriers in conducting externally valid interventional research in these poor-resource settings.^{5,21} Constraints that may affect participation and adherence of the subjects include familial, employment-related and social obligations.⁶ Availing free treatment in the study clinics may be viewed as a social stigma.²² Recruitment of subjects and their adherence to the study protocol commonly suffer from issues related to their economic condition. Compensation in an interventional study is provided to the study subjects to make up for their loss of wages and travel expenses for participating in the study. Often motivation of the subjects for participation in an interventional study becomes focused on the compensation rather than the risks and benefits. Participation of the eligible subjects may thus be influenced by the socio-economic situation of the decision-makers of the households which may in turn affect the validity of the research.⁵

The situation in all 3 study wards was similar during our study period. The project health clinics were usually visited by individuals from the lower socio-economic strata of the locality. Reimbursement of the treatment cost for the typhoid and cholera positive cases often raised issues related to falsification of medicine bills. Individuals from poor socio-economic class, who resided outside the study area started visiting the clinics and later were inclined to take part in the vaccination trial also. The long duration of pre-vaccination surveillance and strength of our population database updated regularly through active surveillance helped us to solve these socio-economic issues considerably.

Political issues

Lack of adequate political will and receptivity for research among the community leaders are issues commonly affecting the smooth conduct of interventional studies in the slum areas.^{18,23} Our study also suffered from similar shortcomings when political views and turmoil continuously threatened smooth conduct of our study starting from selection of our field supervisors and health workers to motivating the subjects to attend the vaccination centers on scheduled dates. Local councilors were closely involved in the conduct of the study. As a result, we had to be cautious to make sure that personal political views do not affect the participation of the individuals during intervention.

Health related issues

Urban slum areas are characterized by poor hygienic conditions, improper sanitation, overcrowding and limited access to safe water, making the residents more vulnerable to several communicable diseases. Unhealthy environment and frequent suffering generate many health related misperceptions and disbeliefs among the dwellers. These issues preclude their spontaneous participation in interventional studies and even after taking part in the study their adherence to the study protocol may become affected.⁶ Occurrences of unrelated events are often correlated by them as the harmful effects of the interventional products, thus may hamper proper conduct of the studies.

In our study several potential subjects were either lost to follow up or prevented from participation due to health conditions that were unrelated to the vaccination. Family members were skeptical to allow the elderly and young children to participate in the study due to the fear that vaccination might introduce some health problems to them. Laboratory testing for typhoid could not be done in some subjects because they thought providing blood samples for the laboratory testing will make them more anemic. By virtue of our long-term and robust surveillance we were able to keep the proportion of this non-participation negligible with respect to our large sample size.

Disease perception

Perceptions about the magnitude and gravity of the diseases are remarkably distorted among the slum-dwellers owing to the non-recognition and underreporting of these diseases in the slum areas. A previous study indicated that only one-sixth of cholera cases in India had been reported to WHO²⁴ and years of conveying such a wrong message has removed the notion of cholera as a major killer disease from the public memory. This might have indirectly hindered participation in the cholera vaccine trial, thus we attempted to educate the medical practitioners as well as the population about the disease from the very beginning of the surveillance phase.

Conclusion

There is a world-wide agreement on the enormous benefits of vaccines for mankind. It had been estimated that over 350 candidate vaccines against nearly 100 different infectious diseases were in the development pipeline.²⁵ Currently available vaccines are the result of interventional research in which vaccine trials play an essential role. We observed several barriers while conducting the vaccine trials in our study area and we believe that such problems have also been faced by others working in similar research settings. In fact, a majority of the large scale field trials are conducted in poor resource settings where most of the people have poor literacy. At the onset, residents are to be educated about the trials and what it entails to be a participant. Participation in the trial should not mean as an opportunity to get free medical and participants should sign the consent form after extensive community education.

The lessons learnt in these community-based studies involving underserved urban slums are crucial as they provide important information on the health and living conditions of the residents of these settlements which may be useful in designing socio-culturally appropriate and economically viable interventions for the improvement of health conditions in these communities. Additionally, incorporation of the duly collected data as obtained from public health research conducted in

these communities, with the existing health information may enhance the external validity of the estimated population and disease parameters.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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