Public engagement during a typhoid conjugate vaccine trial in Lalitpur, Nepal: experience, challenges and lessons learnt

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\SECTION{ABSTRACT}

Typhoid is a public health problem in Nepal. To generate evidence on the impact of Typhoid Conjugate Vaccine (TCV), a phase 3, double-blind, randomized controlled trial was conducted in Lalitpur, Nepal. 20,000 children aged between 9 months and ≤16 years were vaccinated with a new TCV, or control vaccine. Participants were actively followed for safety and efficacy over 2 years through passive surveillance (PS) clinics. Several challenges were encountered during vaccination and PS stemming from misinformation, misconception, and fear around clinical trials in the community. Public engagement (PE) activities were conducted across various tiers moving from decision makers in the first tier; to elected local representatives in the second tier; ending with interaction in community with parents/guardians of the targeted population. Prior and during vaccination, engagement was conducted to inform about the study and discuss the importance of vaccination. Post-vaccination, engagement was conducted to inform about PS clinics, alleviate study concerns and share study updates. Direct and continuous interaction with community stakeholders, including parents/guardians of the targeted population contributed to build trust around the study and community willingness to be involved. It helped to raise awareness, drive away misconceptions, and allowed adaptation according to feedback from community members.

\SECTION{INTRODUCTION}

Typhoid fever, caused by \textit{Salmonella enterica} serovar Typhi (S. Typhi) is a major cause of febrile illness. Annually, an estimated 12 million infections and over 128,000 deaths are attributed to the disease globally.\textsuperscript{1,2} In developed countries, disease rates have decreased with improvement in water and sanitation.\textsuperscript{1} However, it is still a public health problem in many low- and middle-income countries, like Nepal.\textsuperscript{3} With its high incidence, Kathmandu, the capital city of Nepal, has been labeled the enteric fever capital of the world.\textsuperscript{3}

To reduce the morbidity and mortality caused by S.Typhi, the Typhoid Vaccine Acceleration Consortium (TyVAC) aims to support the introduction of typhoid conjugate vaccine (TCV), for Gavi eligible countries with a typhoid disease burden\textsuperscript{4} using a World Health Organization (WHO) prequalified vaccine.\textsuperscript{4} TyVAC is funded by Bill & Melinda Gates Foundation and is led by the Center for Vaccine Development and Global Health at the University Of Maryland School Of Medicine, the Oxford Vaccine Group at the University of Oxford, and PATH.\textsuperscript{5}

TyVAC-Nepal is a phase 3, double-blind, randomized controlled trial with an aim to generate evidence on the impact of the TCV and conducted in Lalitpur Metropolitan City (LMC), Nepal.\textsuperscript{2} 20,019 children between the age of 9 months to ≤16 years of age were randomized in a 1:1 ratio to receive the Vi polysaccharide-tetanus toxoid conjugate vaccine (Typbar-TCV manufactured in India by Bharat Biotech) or the control vaccine, Group-A meningococcal vaccine.\textsuperscript{2} The vaccinated children were followed up for 2 years post-vaccination through passive surveillance (PS) for blood culture confirmed typhoid fever among the vaccinated children with self-reported fever of ≥2 days and/or a temperature of ≥38°C.\textsuperscript{6}

Clinical research industry has recently shifted its focus toward developing nations due to availability of treatment-naïve patient pool, trained professionals with superior clinical infrastructure and lower cost.\textsuperscript{7} In Nepal, clinical research is slowly attaining pace but is often met with distrust and negative opinions. Past audits of clinical trials have reported issues like conducting research without ethical approval, subject enrollment without informed consent, and data fabrication.\textsuperscript{8}

A phase 2 vaccination trial of hepatitis-E vaccine conducted in Nepal was forced out of the community after the local conflict, which foreshadowed ethical concerns claiming the residents wouldn’t have access to the vaccine after trial.\textsuperscript{9,10} The controversy heightened when the critics started to question whether adequate education on informed consent was provided to the trial participants.\textsuperscript{9} The public outcry to not allow the study in the community due to lack of information flow highlights the importance of educating public regarding trials. Later, the research was relocated to the population of soldiers from Nepalese Army.\textsuperscript{11} A negative community perception and distrust regarding research is prevalent in the Nepali community. Previous studies have suggested adequate and appropriate information-sharing with the community leads to improved public engagement and participatory research.\textsuperscript{12}

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enrollment in clinical trials, especially requiring community-based recruitment. A community-based study conducted in Nepal for lymphatic filariasis mass drug administration (MDA) highlighted the importance of public awareness campaigns to counter myths about side-effects of medications. Similarly, multiple level community engagement was highlighted as the most successful strategy to achieve immunization targets in Pakistan for TCV.

Community engagement in health research describes an array of activities that include information dissemination, consultation, and collaboration in decision-making, empowerment, forming stakeholder partnerships, and seeking guidance from community leaders. It involves a collaborative relationship between the research team and relevant stakeholders. Engagement helps to build community trust in research, facilitate participant enrollment, and assist in post-trial follow-up. Community stakeholder engagement has been recognized to be essential for both ethical research practice and trial feasibility by building community trust, generating awareness, and helping the researchers to ensure the trial procedures are acceptable in the local setting.

### How did engagement for TyVAC-Nepal start?

Public engagement (PE) for TyVAC-Nepal began with engaging the key official stakeholders from the National Committee on Immunization Practices, Child Health Division, WHO representatives and other national level stakeholders prior to starting the trial to inform them about the study.

In the community, PE was conducted in 3 tiers. Prior to vaccination, the first tier of engagement was held with the elected representatives of LMC which is divided into 29 municipal wards (the smallest administrative unit). Out of those 29 municipal wards, the first meeting was conducted with the ward chairpersons from the proposed 12 wards on 29th October 2017. TyVAC-Nepal started with the same municipal wards where the Strategic Typhoid Alliance across Africa and Asia (STRATAA) study was conducted, which aimed to measure the age-stratified burden of clinical and subclinical typhoid infection. Along with the chairpersons from 12 municipal wards, there were the mayor and deputy mayor, Ward Health Implementation Committee (WHIC) representatives, ward health officials and official representatives of the social service department of LMC in attendance. During vaccination, it seemed unlikely to achieve the vaccination target of 20,000 children from the initial 12 wards. Therefore, TyVAC-Nepal area was extended to include an additional 5 wards.

The second tier of engagement was conducted in all the respective 17 municipal wards and was attended by WHIC members of each ward, representatives from mothers’ and women’s groups, principals of different schools, representatives of community development committee, and also by ward chairperson and elected ward members.

Prior to vaccination, the third tier of engagement was conducted with mothers group and in schools. Post-vaccination, third level of engagement was attended by the parents/guardians of vaccinated children along with non-vaccinated community members. Likewise, school engagement with students and teachers was also held for third tier.

All the three tiers of TyVAC-Nepal engagement activities were continuously conducted before, during and after vaccination. The aim of conducting engagement before vaccination was to inform the target audience about the study. Post-vaccination, engagement was conducted to inform the target audience about passive surveillance clinics, clear the study concerns and doubts, and regularly update about the study.

### Experiences of public engagement in TyVAC-Nepal: challenges faced and strategies taken to overcome them

Public Engagement for TyVAC-Nepal was a continuous and dynamic process. The extensive PE activities conducted at various stages of the study with community stakeholders and the general population helped to connect the research team with the public. Vaccination was conducted for approximately five months from 20th November 2017 to 9th April 2018. Before and during the vaccination, engagement was conducted to inform the target audience about the study, burden of typhoid, and importance of vaccination. Post-vaccination, engagement was conducted to inform mainly about passive surveillance (PS) clinics, clear study related concerns and doubts and regularly update about the study. Although the vaccination target was achieved and the vaccinated children visited passive surveillance clinics, several challenges came up during the study period.

### Prior to vaccination

Stakeholder engagement conducted in Pakistan has been highlighted to improve coverage of TCV immunization where agreement and cooperation with the community stakeholders allowed to gain access to the community for successful vaccination campaign implementation. Similarly, in Nepal, prior to vaccination, engagement was conducted at LMC office. Some of the ward leaders were hesitant to permit vaccination program in their wards, which was not delivered by the Government of Nepal. Nonetheless, they allowed the PE team to approach the ward stakeholders (WHIC representatives, community development committee members, and tole health promoters (THPs)) in presence of the ward chairperson to hold engagement activities. After explaining them that the study was approved by Nepal Health Research Council and the study vaccines received license from Department of Drugs Administration and National Immunization Advisory Committee members supported the study, ward representatives permitted for vaccination in their wards. Each ward provided a venue for vaccination clinics and forwarded names of community volunteers who could be engaged in home-visits to inform people about the study. Involving volunteers from their own community for home-visits helped build trust in the community. They distributed study information sheets to households with targeted study population and invited parents to visit the vaccination clinics to get more information about the study and ask any questions if they had.
During vaccination

The main challenge for the PE team was to make parents understand about the importance of vaccination. For this purpose, engagement with the mothers’ and women’s groups was simultaneously conducted in all the wards. The PE team personally met parents who had questions about study vaccines and explained to them about typhoid fever and the importance of vaccinating children against typhoid.

During the third tier PE, it was found that people compared the TyVAC-Nepal study with MDA campaign run by the government for lymphatic filariasis. Huge round of misinformation was spread around the side-effects of albendazole and diethylcarbamazine given during MDA. A study conducted to explore the understanding of Nepali people about the nationwide MDA campaign recommended sound public awareness campaigns, as the MDA coverage was 95.5% but the compliance rate was low with only 71.6%. People mistook TyVAC-Nepal study as an experiment done on their children disguised as international aid and were fearful to vaccinate their children with a study vaccine not included in the national immunization schedule.

Before and during vaccination, the PE team remained in close contact with the elected authorities through first- and second-tier engagement and with the community members through third tier of engagement. The community engagement helped resolve the doubts of parents/guardians of the targeted population with reference to MDA campaign. It allowed time for the investigators for detailed explanation about the typhoid burden, the importance of MDA and the study objectives in community-friendly language.

Trust

Trust plays a critical role in the enrollment decisions of potential study participants. With skeptical parents doubting the study vaccines, involvement of the locals during the vaccination consent process helped in part to build a trusting relationship. Furthermore, involving trusted community figures (ward chairperson) who had vaccinated their children in TyVAC-Nepal in community engagement helped to build confidence amongst the community members. Additionally, the PE team started to involve the study medical doctors in public engagement covering various health topics, which helped to attain community trust as it encouraged direct interaction between the two parties.

News article

The biggest setback that the PE team faced was articles about the vaccination program in the national daily newspaper as a front-page headline. TyVAC-study was referred to as the study where vaccines manufactured by developed nations were used in Nepali children. The news articles mentioned Nepali children as guinea pigs used for experimentation. Misinformation and fear has been reported as the leading causes of low vaccination coverage. After the publication of the news, the parents whose children were vaccinated in the study, including the elected ward representatives started questioning the credibility of the vaccine, which made it difficult to go to the community and regain their trust. To tackle this issue, PE team engaged with the elected representatives first as they would be the ones who would eventually be questioned by the community. After regaining their trust, the PE team approached parents of vaccinated children and clarified their queries and reiterated the details of the study based on the checklist of likely questions prepared by the study investigators. During community-based engagement, elected representatives were invited to share their understanding and positive feedback about the study. This helped to refute the rumors about the study amidst the negative environment created by the news articles. At the same time, interim results of TyVAC-Nepal were shared in the community and with the national level stakeholders which spread positive messages about TCV.

Overtime, the PE team, learnt to avoid using the term “trial” or “experiment” during interaction. The PE team carefully reframed the randomized controlled “trial” as “study” because the community considered a “trial” to be experimentation on animals and was negatively perceived.

Participation

One of the major challenges faced was to convince the community members to attend the engagement events. To overcome this, the PE team started engaging with every mothers’ and women’s group in the community. The PE team started to conduct engagement activities at the same time the mothers’ and women’s group would normally meet, which allowed to address a large group in one sitting.

Age group of the participants

PE conducted in mothers’ and women’s group consisted mostly of elderly women or grandmothers of the vaccinated children. It was challenging to know if the women really grasped the messages. To make the best use of PE events, the team started mobilizing THPs, who were from the same community, to identify the parents of the vaccinated children and invite them to attend PE.

Gender differences in the participation

Low rate of male attendance at PE events was noted as significant for TyVAC-Nepal. Of a total of 224 engagement events (all levels), only first- and second-level PE events had male participation from men in official capacities within the community. None of the third-level PE events had male participation. Nepal is a patriarchal society, and it is mostly men who make decisions within the family including where to take the child when they get sick. Their absence in PE led to lack of information resulting in low vaccination coverage in some wards as the fathers decided not to vaccinate their children. It also resulted in low utilization of passive surveillance services.

Time

Arranging an appropriate time for PE was also a major constraint as working parents would only have weekends off, and during their free time, they would be busy doing their
household chores. To accommodate the maximum number of participation, multiple PE events were conducted, even on the same day. This helped the participants to choose the time that best suited them.

With an awareness of the religious and cultural calendar within the community, PE events were planned during festivals and public holidays to facilitate attendance. In general, vaccination rates were also higher during weekends and festival holidays. Therefore, the PE team facilitated this trend and met and engaged the community on those specific days to deliver study related information.

Logistics

For a phase-1 HIV vaccine trial in India, community friendly PowerPoint presentation was developed to make the community understand technical issues in a simple, visually appealing, and non-technical manner to ensure wider distribution of knowledge regarding the vaccine and trial. Likewise, for TyVAC-NP, PE team had developed handmade flipcharts and electronic PowerPoint presentations to initiate interaction. Engagement activities were conducted at venues with or without power-supply. At times, because of power outage, the PE team had to adapt and explain verbally despite prepared to use PowerPoint presentations. During the summers, while conducting PE in an open space, the events frequently had to be stopped midway because of unexpected rain. Furthermore, occasionally PE events were conducted in the living rooms, balconies and open spaces of the participant’s homes or temples because of unavailability of other venues. Flexibility was critical within the PE team to overcome these kinds of hurdles.

Expectations

The PE team had to manage unrealistic expectations from some attendees of engagement events. People’s misconception about the internationally funded study resulted in financial expectations of their hour long participation. The PE team provided snacks and refreshment to tackle this.

Repetition in PE topics

Some of the attendees of third-tier engagement complained that they were tired of hearing repetitive message. The PE team acknowledged this issue early and started to involve the study doctors to present on common health topics relevant to the community, other than typhoid.

School engagement

During the TCV immunization campaign in Pakistan, strategies to engage school principals, teachers, school administrators including students was done which helped to gain the confidence of the participants attending PE that ultimately boosted vaccination. Similarly, for TyVAC-NP study, school engagement with teachers and students in grades 7 and above was conducted. There were 2 major challenges during these events. First, not all students in the classes were part of the study, and therefore, if the discussion purely focused TyVAC-Nepal, it was difficult to maintain everyone’s attention. The second challenge was around how well they could relay the discussed information to their parents, example about the services available from the passive surveillance clinics. With time and experience, the PE team learnt that short but interactive sessions with children would keep them engaged. Teachers were also invited to attend the events which meant that when they were asked about the study, the key messages could be communicated to other students and parents too.

Conclusion

Public engagement has been a key achievement of the TyVAC-Nepal study. The continuous and direct interaction with the community stakeholders including parents/guardians of the vaccinated children, throughout the study helped to gain and maintain community trust. Adhikari et al. identified that day-to-day interactions helped to foster interpersonal trust between community members and research staffs. People’s trust in the vaccines has also showed to be directly linked with willingness to receive vaccines in past literature. Public engagement conducted for this study clearly shows that staying connected with the community stakeholders helped to gain trust and support for the study despite publication of negative news article in a national daily.

Involvement of the locals in the consent taking process during the vaccination phase of this study and periodic home visits by THPs helped in gaining community confidence. Networking with locally active groups and community workers has found to decrease vaccine refusals and gain trust. Involvement of active and systematic community established network contributing for clinical trials enrollment has already been acknowledged in past literature.

PE for TyVAC-Nepal was continuous process conducted before, during, and after vaccination in three-tiers. Interaction with stakeholders at different levels contributed to achieving the target of vaccinating 20,019 children. Meiring et al. have also highlighted the importance of delivering messages from grass-root to ministry level to aware about the trial and addressing misconceptions to make informed decisions.

For a HIV vaccine trial in India, using study information material in a non-technical and community friendly language has been recognized for successful trial. Likewise, for this study, community groups like mothers’ and women’s group were identified and approached to deliver community friendly messages using flip-charts and PowerPoint presentations. This helped to convey study related information with ease. Over time and with experience, the PE team learnt lessons that were adopted in subsequent PE events. Instead of using the words like “trials” or “experiment” that were negatively perceived by the community, the term “study” was used which was welcomed by the community.

Working in a community is not an easy task but the regular engagement facilitated effective communication with the research team and build trust. The constant effort to stay in
touch with the participants helped to achieve the target and overcome the challenges during the study period.

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Disclosure statement

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References

1. Meiring JE, Sambakunsi R, Moyo E, Misiri T, Mwaksegile F, Patel P, Patel P, Nduferankehande J, Laurens M, Gooding K, et al. Community engagement before initiation of typhoid conjugate vaccine trial in schools in two urban townships in Blantyre, Malawi: experience and lessons. Clin Infect Dis. 2019;68(2 Suppl):S146–S53. doi:10.1093/cid/ciy1110.
2. Shakya M, Colin-Jones R, Theiss-Nylund K, Voysey M, Pant D, Smith N, Liu X, Tonks S, Mazur O, Farroq YG, et al. Phase 3 efficacy analysis of a typhoid conjugate vaccine trial in Nepal. N Engl J Med. 2019;381(123):2209–18. doi:10.1056/NEJMoa1905047.
3. Karkey A, Aryal A, Basnyat B, Baker S, Kathmandu, Nepal: still an enteric fever capital of the world. J Infect Dev Ctries. 2005;2 (6):461–65. doi:10.3855/jidc.162.
4. Colin-Jones R, Shakya M, Voysey M, Theiss-Nylund K, Smith N, Pant D, Liu X, Tonks S, Mazur O, Farroq YG, et al. Logistics of implementing a large-scale typhoid vaccine trial in Kathmandu, Nepal. Clin Infect Dis. 2019;68(2 Suppl):S138–S145. doi:10.1093/cid/ciy1125.
5. Patel P, Patel P, Meiring T, Misiri T, Mwaksegile F, Gordon MA. Stories from the field on the ground in Malawi—first typhoid conjugate vaccine study in Africa. Am J Trop Med Hyg. 2019;100 (6):1299–300. doi:10.4269/ajtmh.19-0014.
6. Shakya M, Voysey M, Theiss-Nylund K, Colin-Jones R, Pant D, Adhikari A, Tonks S, Mujadidi YF, O’Reilly P, Mazur O, et al. Efficacy of typhoid conjugate vaccine in Nepal: final results of a phase 3, randomized, controlled trial. Lancet Glob Health. 2021;9(11):e1561–e1568. doi:10.1016/s2214-109x(21)00346-6.
7. Ibnas M, Asim M, Mekkodathil A, Sathian B. Practical challenges and obligations for conducting clinical trial in Nepal: a call for improvement. NEPIOL 2019;9(3):769–71. doi:10.3126/nje.v9i3.25804.
8. Basu S, Lurie P. Correspondence hepatitis E vaccine. N Engl J Med. 2007;356(23):2421–22. doi:10.1056/NEJMc070884.
9. McNair S. A shot to change the world: an analysis of process and partnership in U.S. military vaccine research [Doctoral dissertation]. Boston (USA): Harvard Medical School; 2015.
10. Mills EJ, Singh S. Health, human rights, and the conduct of clinical research within oppressed populations. Global Health. 2007;3(10). doi:10.1186/1744-8603-3-10.
11. Andrews J. Research in the ranks: vulnerable subjects, coercible collaboration, and the hepatitis E vaccine trial in Nepal. Perspect Biol Med. 2006;49(1):35–51. doi:10.1353/pbm.2006.0001. PMID: 16489275.
12. Sahay S, Kumar M, Srikrishnan AK, Ramanathan V, Mahendale S. Experiences in recruiting volunteers through community-based initiatives in Phase-1 vaccine trials in India. Hum Vacc Immunother. 2014;10(2):485–91. doi:10.4161/hv.26799.
13. Adhikari RK, Sherchand JB, Mishra SR, Ranabhat K, Wagle RR. Awareness and coverage of mass drug administration for elimination of Lymphatic Filariasis: a community based cross sectional study in Nepal. J Community Health. 2014;40(1):34–40. doi:10.1007/s10900-014-9891-1.
14. Qamar FN, Batool R, Qureshi S, Ali M, Sadaf T, Mehmoon J, Iqbal K, Sultan A, Duff N, Yousaafzai MT. Strategies to improve coverage of typhoid conjugate vaccine (TCV) immunization campaign in Karachi, Pakistan. Vaccines (Basel). 2020;8(697):1–12. doi:10.3390/vaccines8040697.
15. Musesengwa R, Chimba MJ. Experiences of community members and researchers on community engagement in an ecohealth project in South Africa and Zimbabwe. BMC Med Ethics. 2017;18 (76):1–15. doi:10.1186/s12910-017-0236-3.
16. Adhikari B, Pell C, Cheah PY. Community engagement and ethical global health research. Global Bioethics. 2020;31(1):1–12. doi:10.1007/s11874-020-17035-0.
17. Ahmad T, Haroon H, Ahmad K, Shah SM, Shah MW, Hussain A, Jalal S, Ahmad W, Khan M, Harapan H, et al. Hepatitis E vaccines: a mini review. Biomed Res Ther. 2021;8(9):4514–24. doi:10.15419/ bmrat.v8i9.690.