

# Exploring willingness to participate in future Human Infection Studies in Lusaka, Zambia: A nested qualitative exploratory study

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## Research article

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# Abstract

**Background:** Human Infection Studies (HIS) involve intentional infection of volunteers with a challenge agent or pathogen in controlled conditions with the aim of developing vaccines. Though sub-Saharan Africa carries the highest burden of vaccine-preventable diseases, the region is only now being primed to conduct HIS relevant to its population. Given the imminent introduction of HIS in Zambia, we sought to understand potential participants' willingness to volunteer for such studies.

**Methods :** We used a qualitative exploratory approach to understand potential participants' perceptions on HIS participation using the example of typhoid. Healthy adults, recruited using random selection from higher learning institutions in Lusaka, participated in 15 in-depth interviews (IDIs) while others were purposefully included in five focus group discussions (FGDs).

**Results :** Participants considered typhoid a serious disease with potential for life-long consequences and death. After sharing audio visual materials introducing the concepts of HIS, some participants expressed unrestricted willingness to participate, others said that they needed to consult parents and professors, and some expressed fear of death and illness. Though willing to be quarantined for up to six months, participants expressed concerns regarding separation from family and duties, having insufficient information to decide, inadequate access to care, severe disease, life-long injury or side-effects, death, and vaccine failure. These concerns along with possibility of underlying conditions that compromise individual immunity, competing priorities, parental refusal, and distrust of study or vaccine efficacy could lead to refusal to participate. Reasons for willingness to participate included monetary compensation, altruism and being part of a team that comes up with a vaccine.

**Conclusions:** Though afraid of deliberate typhoid infection, potential participants are willing to participate if given adequate information, time to consult trusted persons, compensation and assurance of adequate care.

## Background

Typhoid fever accounts for an estimated 128 000 deaths each year in Low and Medium Income Countries (LMICs) [1, 2] with children below the age of five and those going to school most affected [3]. Fecal-oral transmission of *Salmonella enterica* serotype Typhi (*S. typhi*)[4] causes approximately 12 million typhoid infections globally per year. While clean water, sanitation and hygiene (WASH) are sufficient to interrupt transmission, LMICs struggle to keep up with the increasing demand for WASH by a rapidly growing urban population [5]. Thus, vaccines remain the most viable short to medium term option for diarrhoeal disease control. However, vaccines developed in non-endemic countries have proven to be less effective in LMIC settings [6] highlighting the urgent need to develop new effective vaccines and improve already existing ones among disease-endemic populations.

Though sub-Saharan Africa carries the highest burden of vaccine-preventable diseases, it is only now that the region is beginning to conduct Human Infection Studies (HIS) relevant to its population. HIS can

accelerate vaccine development by facilitating an understanding of pathophysiology and mechanics of immune response under highly controlled conditions and to efficiently test vaccine or drug efficacy. The intentional infection of healthy study participants with a viable challenge agent or pathogen under highly controlled conditions [6], could potentially raise public concerns, queries, and ethical complexities particular to LMIC settings; including concerns around communal pressure to participate, local language wording in information sheets, beliefs on blood collection, adequacy of infection control measures in the community, and appropriateness of compensation given levels of poverty [7]. Additionally, the daily risk posed in some LMIC environments makes it difficult to control HIS participants' exposure to additional diseases or the spread of infection into the larger community without residency requirements [7]. Gathering public opinion of HIS including ethical and scientific concerns among potential participants is an important step in establishing a platform to conduct HIS in LMICs.

Given the imminent introduction of enteric HIS in Zambia, we conducted a qualitative exploratory study nested within an immunological study that compared naturally-induced immune responses with those from deliberate typhoid infection among Zambian patients and British volunteers respectively. In our nested qualitative study, we explored knowledge regarding typhoid and perceived risk as these elements could influence willingness to participate in HIS. Additionally, we explored knowledge of HIS, and reactions when introduced to the concept behind HIS among potential participants in Lusaka, Zambia. Gathering would-be participants' perspectives can aid the process of developing practical and ethical guidance cognizant of societal values and constructions of risk around enteric HIS [8, 9]. Extending these findings to further public engagement activities can build and enhance study accountability to the community being served [7].

## Methods

We conducted 15 in-depth interviews (IDIs) and 5 focus group discussions (FGDs) among healthy adults recruited from higher learning institutions. Using random sampling, students at higher learning institutions around University Teaching Hospitals were invited to participate in IDIs. Participants for the FGDs were purposefully sampled to include medical and non-medical students. The characteristics of interest included being an adult aged 18 or above, attending university or college at selected institutions, and consenting to a blood draw for the immunological study. Each Focus Group had at least eight students from different fields of study, three groups were single-sex, and two were mixed-sex groups.

The study was conducted in two universities and two colleges. Medical students were randomly selected from the University Teaching Hospital (UTH) and non-medical students from the University of Lusaka, the Lusaka Business and Technical College, and the National Institute of Public Administration. Healthy volunteers were selected using a script written in Python 3.6 for a simple random sampling of all students residing within the selected institutions of higher learning. Selected participants were approached by the study staff and invited to learn more about the study at the UTH research site. Consenting individuals participated in one-on-one interviews at the study site within the UTH. Study staff stationed at the selected higher institutions of learning invited students to learn more about the study using sensitization

talks. Potential participants meeting the study eligibility criteria and providing informed consent were invited to participate in FGDs.

Study staff gave sensitization talks to both the randomly and purposefully selected students and provided a general overview of the study. They proceeded to provide further information on the study to those who were willing to consider participating in IDIs and FGDs. IDIs and FGDs were conducted in participants' preferred language with their consent including for audio-recording to ensure that information was accurately captured. The RAs took notes to supplement the recorded data. The question guides asked what participants knew about typhoid including transmission, what they knew about HIS and, if they would participate or allow a relative to take part in a HIS. After determining what participants knew about HIS, they were shown a video on HIS [10] to allow them to make a more resolute decision of whether or not they would participate or allow participation in a HIS.

## Analysis

Thematic analysis was conducted to identify the perceptions of the students on participation in a HIS. The data analysts listened to the audio recordings and read the transcripts repeatedly to familiarize themselves with the data. Transcripts were imported into Nvivo and coded using inductive and deductive reasoning. Codes were further categorized into the themes and organized in Word for this paper.

## Results

A total of 15 participants, two women (13%) and 13 men (87%) with an average age of approximately 28 years participated in the IDIs. Focus group discussants included 24 men and 27 women with an average age of 22 years.

All participants were enrolled in certificate, diploma, or degree programs, in development studies, education, business and entrepreneurship, information technology, law as well as medicine, public health, and other health sciences.

## Perceptions Of Typhoid

Most participants knew about typhoid fever with a few confusing it for other diseases such as bilharzia. Participants who had knowledge about typhoid knew that it is spread through an oral fecal route and one needed to have ingested the bacteria *Salmonella Typhi* to get the infection:

*“So typhoid is a bacterial infection. It's caused by salmonella typhi and it is spread by the oral fecal route. Yeah, it can cause diarrhea, fever and the like, yes... People get it when they put something contaminated with salmonella in the mouth.”(IDIp13, medical student)*

Those less knowledgeable thought that typhoid could be transmitted by contact with fluid or faecal matter from a person who has typhoid.

Participants considered typhoid a serious disease with potential for life-long consequences and death. They thought that people, particularly children of low socio-economic status living in high density areas with no proper sanitation and no access to clean water were at risk of typhoid as below:

*"I think the majority of those infected are children. Other than the fact that they are children and their immune systems are not yet developed, they are also prone to it because children lack knowledge on hygiene to be able to say 'this is dirty' and 'this is what.' That's why I feel like it is more common in children who have naturally low immune systems. Also, people who have low economic status are prone to poor hygiene." (IDp14: Medical student)*

*"Okay, so mostly aah, probably from my reading, it's usually gotten from places that are highly populated with very poor sanitary conditions especially in Africa because we are economically challenged. So you look at countries or areas that are economically challenged with large population and then with poor sanitation. You also find it usually among children because they play in dirty environments. So whenever I think of typhoid or a person with typhoid, I start picturing them living in an area which is financially challenged with poor sanitation, yes, and all that." (IDp10: Medical student)*

## Knowledge Of Human Infection Studies

Most participants had limited knowledge about HIS until they watched the video on HIS and its requirements. While medical students had some idea about HIS, others knew nothing at all about it which is to be expected given the newness of HIS implementation in LMICs as illustrated below:

*"Really I don't have much knowledge on them [HIS] but I have heard about them." (IDp9: Medical student)*

*"I have never heard about it." (IDp8: Medical student)*

## Willingness to participate in a HIS

Once educated on typhoid HIS using audio-visual materials, some participants expressed unrestricted willingness to participate. Some participants were so eager that they wanted precise information on when the studies will begin while others insisted we contact them when these studies commence so that they can volunteer in them. Under this broad category of willingness to participate in a HIS, the theme of motivation emerged along with sub-themes related to monetary compensation, altruism, patriotism, and perceived community and family benefits. The other theme that emerged was of 'other considerations when contemplating participation', with sub-themes such as information to aid decision making, assurance of provision for health care in the event of illness, and perceived risk and burden of participation. Participants also understood that with some HIS there may be need to be kept in-residence for a few weeks at a study facility.

Some participants said that they would look at the pros and cons of participating in a HIS and the experience and expertise of the research team because it affects their safety.

Participants had various views concerning allowing family members to take part in a HIS sharing similar concerns regardless of relationship to the family member. Some said that they would allow participation because family members have free-will and they are free to make their own decisions if they are informed. One participant said they would be proud if a child took part in such a study and that they would allow them to participate because it would not only benefit the family but the community as well.

*“For me actually I would feel motivated to see my child (adult child) – since I am the father myself - to see my child who is participating in such program. I would look at it as my child being educated in that perspective or that field and my child would bring back that knowledge back into the house and not only my house but to the community as well which will bring change.” (FGD#4p3:non-medical student)*

Others said they would deny the family members permission because they would be scared of not knowing what will happen at the end of the study, either positive or negative. Some said that they would need to get more information in order to decide whether or not to allow them to take part as below:

*“I would have a lot of questions to ask and some level of uncertainty deciding to take part in the Human Infection Challenge Study. And I would like to find out more about what the organization conducting the research is all about. Personally I would be a bit nervous about it before finding out what the organization doing research is all about.” (FGD#5p6: non-medical student)*

When asked about the concerns they would have if husbands, wives, and children above 18 had to take part, they stated various concerns including damage to their relationship since they would be far apart. One participant said that,

*“Relations will be put on hold, because distance and silence kills a relationship” (FGD#4p4: non-medical student).*

Some participants aired concerns about the couple’s sex life after the participant returns home as the partner may fear that the participant is still infected and could infect them during sexual intercourse. Some men said that they would not allow their wives to participate because the wife has to cook and take care of the children at home.

## **Motivations for participating in HIS**

Participants said that they would be motivated to participate for the financial benefit, the love for others and to be part of a team that developed a new vaccine. Other than personal benefits, participants anticipated community and family benefits which motivated them to participate.

## **Monetary Compensation**

The participants clearly stated that they would participate for the monetary compensation given for the risk, side effects, and time lost during study participation. When asked about who should manage the money they receive as compensation, some participants thought that their parents, siblings, and grandparents would be best suited to manage the funds because they would look at the big picture and invest it. Others said they would manage it themselves given that they are the ones who put their lives at risk and bore the pain and discomforts of being in the study.

*...“You know everyone in this world thinks about finances and all that, yeah?”... (ID1p12: medical student)*

*... “But if it were up to me I think I will do it for the money ... for the money ... ye”... (FGD#2p5:non-medical student)*

One participant said he would give the money to an orphanage if after the trial he does not get sick because he would be getting money for free as below:

*“I would give to an orphanage. If I am not sick and they give money, it is like they have given it [money] for free because I didn’t get sick and I am fine. Then why will I use that money for nothing when there are people in need of that same amount?” (FGD#5p3:non-medical).*

## **Altruism - For The Love Of Others**

Some participants anticipated that while they may not directly benefit from participating, their loved ones would gain from a new and more effective vaccine which motivated them. They said that they would participate for the love they had for others.

*“... Okay, it feels good because at least I’m volunteering, I’m bringing up for the future generation. I might not benefit right now but it’s for the greater masses out there ... I am a driving tool coming up with ways which at the end of the day, will actually save lives...” (ID1p15: medical student)*

One participant said she would participate because of her experience when she visited her family in the Congo where she saw people were dying of Ebola. She did not want to imagine other people dying when a solution like a vaccine can be provided:

*“... Yes I was against it [the study on Ebola vaccine]. Right now, the disease [Ebola] is in my home town. In my province, people are dying and if they tell me to try it, I will do it, I will try it. I have seen people die. A husband dies and gives it to the wife, who passes it to the son and it goes on passing from one to another in the family. So if they bring it [HIS] and say, “Let us try it on you; we inject you with Ebola and then try the cure on you and see if it will work,” I will do it because I know it is a bad disease. Even if I know that there is an available cure, I want to try the new one and if it doesn’t work, I will go for the standard one. Yes, that is what I would do ...” (FGD#2p12:non-medical)*

## **Patriotism**

Participants were excited to volunteer in a HIS to contribute to science and be part of a team that comes up with a vaccine in Zambia. Interestingly, some participants said they would participate in HIS for the betterment of (health) research which would put Zambia on the global map.

*"... I will do it for the research. Meaning it is something new; it has never happened in Zambia, right?! So, it will market the country; like now, they are now producing their own thing. So, I will do it to try it out..." (FGD#2p5:non-medical)*

*"... One reason specifically is that I want to be part of the team that can make a difference in changing the current catastrophe of typhoid. So it's not just about having knowledge about it but also be part of a team that finds solutions to typhoid ..." (IDp14:medical student)*

## **Perceived community concerns and family members benefits**

Some participants indicated that monetary benefit to their families would drive them to take part in a study even if the family was worried for their health and possible death as below:

*"... So I think my family would benefit; if the vaccine works and one of them get sick, it would help them. And if they compensate me by giving me a lot of money and some of them [family members] would go to school and get nice things – then that would be good ..." (FGD#2p3:non-medical)*

*"... But obviously their concern would be, "Are you going to survive, is it safe?"..." (FGD#2p2:non-medical)*

Other participants said they did not care what the community had to say regarding their participation with some specifying that the vaccine, if developed, would be of benefit to their community so it was worth volunteering even if the vaccine does not work. For example, one female discussant said that:

*"...I think if the vaccine works when they try it on me, they will make more and bring it to the community who will benefit because there will be less typhoid. But if it doesn't work that means nothing [bad as there is no ready alternative anyway]." (FGD#3p1:non-medical)*

## **Other considerations when contemplating participation in HIS**

Several other factors influenced decision-making with regard to HIS such as the adequacy of information provided to an individual who would like to participate, risk-benefit ratio, and what relatives have to say about their volunteering for a HIS.

## **Information provided to aid decision**

Participants said that they needed sufficient details about the study for them to make an informed decision. They said it was imperative that participants of a study fully comprehended the study

procedures and the risks involved or anticipated. Hence, study personnel need to be honest and practice full disclosure so that volunteers know for what exactly they are signing-up. The participants suggested that providing this information would prepare the person mentally and that it was important for their sanity and wellbeing during the time they are enrolled:

*“There should be an education or something like that where people are informed and taught for them to be willing to participate. Because people can’t just come and they are told we have to try it on you. If they are more informed about it, they will be willing to do it.” (FGD#2p10:non-medical)*

*“... Like she is saying that you have to be fully honest with the patient with the things they are going to go through as you are doing the trial...” (FGD#2p5:non-medical)*

## **Assurance of provision for health care in the event of illness**

The other consideration was the kind of health care that would be assured to them during such studies. Participation was contingent on having study personnel who are well trained to give them the required care in the event that they fall sick:

*“... Yes, because you might find that the staff are just junior trainees – we don’t want that because this is life we are dealing with. We want qualified people who can handle the issues at hand and I would want them to talk to me one-on-one, to take me through each step you know...” (FGD#4p1:non-medical)*

## **Perceived risk and burden of participation**

Participants argued that because HIS is used to evaluate candidate vaccines, it was to a certain extent not safe. They perceived themselves at risk just by virtue of participation and were scared of dying should there be a failure of standard treatment (rescue). They expressed concern about the side effects and adverse events including death as a result of the various study procedures including the trial vaccine itself:

*“... Possibility of having an infection in the time of isolation and if the drug really works, that’s it, yeah ...” (ID/p6:medical student)*

For some participants, potential concerns and fears were alleviated by the fact that the disease in question was curable and said it would have been different if the HIS was, for instance about HIV, which is not curable:

*“... Because that is not aggressive like HIV or Ebola. Typhoid is a small disease. They can do it because it can be cured; it is not like when you have it you can pass away directly. They can cure it. So, if it is for a good purpose, we would accept to participate ... It is like malaria. (Fellow participants laugh) Yes - malaria is bad but there is actually a cure for malaria. It is not like HIV when you have it you don’t get cured. So if anything goes wrong, I will go to other doctors and they will provide medicine for me. (All Laugh) Yes...” (FGD#2p12:non-medical)*

## Unattractive features of residential stay

Some other considerations had to do with leaving home or school and being confined to a study facility for reasons of infection control and disease monitoring. Participants said that it had to be worthwhile to stay in such a place away from family. They wondered whether or not the facility would have social amenities or entertainment. They asked questions such as, “Will we be allowed to have visitors or to see our loved ones?” Some participants also preferred a facility which does not look like a hospital or hospital ward but was more homely and comfortable:

*“... They will have to let me be free to move around ... I have to be watching movies, I have to be doing all that ... (laughs) yeah, at least so that I wouldn't be bored ...”(IDIp5:medical student)*

*“... It shouldn't be in any way related to how the wards are (hospital ward) where you are very congested ... It should be a decent place, where someone can sleep, the room should at least have a TV for people to watch ... At least food should be there, it should be a good place ...” (IDIp15:medical student)*

## Discussion

This study revealed that participation in a HIS for a well-educated would-be participant in Zambia was almost guaranteed if expectations such as provision of adequate information and assurance of safety were met. Participants were willing to take part as long as they were provided with adequate information to make an informed decision. Other participants indicated that not only would they participate for their own sake and monetary compensation but also for the love of others and to contribute to science, motives also expressed by studies in other LMIC settings [11, 12].

Participants emphasized that for an individual to participate, they needed to be provided with adequate information to make an informed decision. They stated that information provided should include the level of discomfort, the possible risks, and benefits to them as an individual. While these are standard components of an information sheet, experiences elsewhere highlight the need to inform participants that there may be no direct benefit to them from their participation rather the benefit is at community level through scientific innovation and enhanced public health [7, 13, 14]. Also participants need to know what to expect during the study period including confinement to clear infection if they withdraw from HIS to ensure participant and community safety.

Information requirements for HIS are complex and long and thus most researchers target educated participants [7] bringing its own ethical issue of representation and unjust exclusion of those not educated [6]. Researchers must therefore devise ways in which participants from all walks of life, regardless of education, can access HIS information in a simple and precise way and can ask questions in myriad ways to enhance retention of information and comprehension [7, 13, 15]. Even with full information, some participants said they would seek permission from significant others raising questions of autonomy and individual consent. In such circumstances, “group informed consent processes to complement individual sessions” may be necessary [12]. This is so that individuals' confidence in the processes of a given study is boosted.

Some participants reported that they needed to understand the level of risk that is involved in HIS for them to decide whether or not to take part. This is similar to a study done by Hassar et al, who argue that volunteers considered risk before participation in a study [16]. If risk is not clearly stated by researchers and understood by the possible participant, recruitment may be affected as people may resist participation due to unnamed and unnecessary fears. Thus, all fears that are attached to participating in HIS need to be addressed during sensitizations, engagement and study participation to improve understanding and ease recruitment and retention. Also, because of the influence of significant others on individual decision-making, risk communication during sensitization and community engagement is important to ensure community-level comprehension [17].

For some pathogens such as typhoid, participants may need to reside in a study facility, equipped with provisions to be closely monitored for symptoms or reactions to drugs or the pathogen to ensure early and effective treatment [7, 13]. Infection control measures at the facility further contain the pathogen thus preventing and protecting third parties from getting unwanted infections. Similar to requirements reported from Kenya [18], facilities need to cater to more than medical concerns to include comfort, entertainment, family visitations (if possible), and provision to meet pressing worldly obligations such as examinations and funerals. These provisions bring with them considerations of measures that protect participants from infections carried by visitors and the visitors, infection from the facility [6]. Additionally, women may have other requirements such as for menstrual hygiene management, contraception, and a room-mate to feel safe.

Among the various motives for HIS participation, monetary compensation ranked high suggesting the need to establish what is fair compensation in the Zambian context, a matter we will discuss in-depth in another publication. However, desire for monetary compensation did not preclude volunteerism. Some participants also expressed altruism, patriotism, and perceived community and family members' benefits as motivations for HIS participation. Similar to other studies, it is evident that people do have altruistic reasons for taking part in clinical trials including HIS. These reasons include and are not limited to contributing to science or the health of other people, scientific interest, and curiosity [19, 20].

## **Strengths And Limitations**

Our study has some limitations, the main one being that interviewees and discussants were asked about anticipated participation. As such, they were not able to speak from experience in a HIS which, as shown in Kenya [7], can change perceptions and expectations through the course of HIS participation. Also, we asked well-educated individuals rather than community members for their perceptions on HIS, perceived risks, and benefits. Given community safety concerns and role in individual decision-making, communal views including from those less educated will be important. Nonetheless, our study provides insights from individuals who likely comprehend HIS and, aligns with international recommendations in literature to first recruit students. Students are most likely to represent healthy volunteers for HIS and, in countries where HIS is yet to be introduced, may more accurately convey their experience and decrease the risk of circulation of misinformation.

# Conclusions

This study on views of would-be participants for HIS in Zambia provides the basis to prepare the ground for implementation of HIS that meet participant expectations without compromising research ethics or findings.

# Abbreviations

HIS  
Human Infection Studies  
LMICs  
Low and Middle Income countries  
HIV/div>  
Human Immune deficiency  
IDI  
In-depth Interview  
FGD  
Focus Group Discussion  
RAs  
Research Assistants  
UTH  
University Teaching Hospital

# Declarations

Ethics approval and consent to participate

The University of Zambia Biomedical Research Ethics committee (Ref no. 010-09-18) gave ethical approval for the study and the Zambia National Health Research Authority gave authority to conduct the research. University authorities gave permission to recruit at their institutions.

Availability of data and materials

The data used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests" in this section

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• Authors' Contributions

RM, AS, MC, MS and JC were involved in the initial conception of the study. EK-N recruited and interviewed the participants with input from EN and MC. EK-N also performed the analysis with input from CM and AS. EK-N drafted the manuscript with input from AS and MS. All authors reviewed and approved the final manuscript.

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