Author's response to reviews

Title: Lessons and implications from a mass immunization campaign in squatter settlements of Karachi, Pakistan: an experience from a cluster-randomized double-blinded controlled trial [NCT00125047]

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Version: 3 Date: 7 April 2006

Author's response to reviews: see over
April 2006

Dear Editors,

Thank you very much for considering our manuscript for possible publication in the BMC Trials. On behalf of the authors I would like to thank the reviewers for their valuable comments and the time they spent while giving their input. I am sure that this has improved the quality of the manuscript a lot and would be more beneficial for the readers and those involved in future field trials in developing countries.

We have very carefully read the comments of the reviewers and have addressed them point by point. The comments have been incorporated in the manuscript and the location is mentioned below for your consideration.

We submitted the revision once on April 4, 2006 but we received some suggestions from some of the co-authors later, which we thought would improve the quality of the manuscript and added them later. This version is the latest and can be considered as an updated one. We hope that in the larger interest of information dissemination this would be acceptable to you.

Please feel free to contact if you have any questions.

Sincerely,

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Reviewer's report
Title: Lessons and implications from a mass immunization campaign in squatter settlements of Karachi, Pakistan: an experience from a cluster-randomized double-blinded controlled trial [NCT00125047]
Version 1: Date: 12 March 2006
Reviewer: Jonathan A Sterne

Reviewer's report:
General
This paper reports methods and baseline data from a cluster-randomised trial in Pakistan. It is potentially suitable for publication in Trials. However, the inclusion of further relevant information about the design and conduct of the trial, the characteristics of participants at baseline, and the adverse effects observed could make the paper considerably informative.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached) The CONSORT statement now provides the standard for reporting randomized controlled trials, and has been modified to deal with cluster randomized trials (BMJ 2004; 328: 702-8). However it is often difficult, given the severe space constraints on articles in medical journals, to report all the relevant information. Therefore, articles such as this are an opportunity to report in more detail on the conduct of relevant aspects of the trial. The authors could improve greatly, for example, on the reporting of methods of randomization.

How was the randomization sequence generated? How, precisely, were the randomization strata defined (these could be displayed in a table or depicted in a figure)? Figure 2 has been added

Authors’ Response: The study incorporated a cluster-randomization after stratification that was based on the sizes of the cluster (large vs. small) and by the area (Sultanabad vs. Hijrat). Both stratification and the randomization were done by a statistician who is not involved in the disease surveillance of the study. A consort diagram has been added in the manuscript.

What steps were taken to ensure that the allocation sequence was concealed? (In the context of this trial, this would mean that it was impossible for anyone to interfere with the chosen allocation, for example by re-randomizing because they did not like the chosen allocation). We have added the comment in the text, page 12 line 16

Authors’ Response: Randomization was done by a senior statistician (Prof. Allan Donner, Canada) outside the study setting. Only codes (C,M) were shared with the local investigators who were conducting the trial. Labeling of the vaccine was done at Rixensart. Since this was less likely that the investigators would know the nature of the vaccine therefore the chances of re-randomization were minimal. To make sure that this would not happen even at individual level each team was given a single vaccine code (for that particular cluster) and the team carried with the same vaccine through out the campaign. Continuous supervisory visits by external monitors were made to ensure all procedures were followed according to the protocol. We can’t see any opportunity for a protocol violation or for that matter a motive as the vaccine assignment was blinded and the code remains unknown in the site.

How many clusters and individuals were randomized to the two groups? (This could be reported without revealing which group contained the Vi PS vaccine and which the hepatitis A vaccine). This information has been added please see figure 2
Authors’ Response: The area was divided in to 60 geographic divisions called cluster. Equal
count number was randomized from each stratum to each vaccine group.

Who conducted the procedure of labeling the vaccines as C or M, and what procedures were used
to ensure that the identifying information was not passed to any of the investigators or study
personnel? This has been added to text Page 8 line 15

Authors’ Response: Vaccines were labelled in Rixensart, Belgium. The local investigators as
well as the monitors are not aware of the vaccine codes. Please refer to response to earlier
comment.

Similarly, I suggest that in the revised version of the paper the authors consider how they could
report in more detail on other information about the conduct of the trial that is required by the
CONSORT statement.

Authors’ Response: Based on the suggestion the revision was done following the Consort
statement where applicable. Since the manuscript doesn’t report results of the trial, inclusion of
some of the components was not possible, such as analysis etc.

There is evidence that the primary outcomes reported in final trial reports are often not those
specified in the protocols. Therefore I suggest that the authors include information on what
outcome measures will be used to assess vaccine efficacy, and how it is planned that these will be
measured.

This has been added to the text, page 14 line 2

The authors give some information on the numbers of adverse events. I suggest that they also
explain precisely how adverse events were defined, how their occurrence was ascertained and
recorded, and how many of each type of event occurred. It would be acceptable to report this
information for both vaccine groups combined.

This has been added to the text page 11 line 1 and page 15 line 23

Minor comments
Abstract: much of the information contained in the “conclusions” section should in fact be in the
“results” section. Addressed

Page 5 paragraph 1: I completely agree that vaccine research and development agendas are
tailored to the needs of wealthier countries, but I do not think that it is “especially true” that
persons living in slums in South Asia are at a disadvantage compared to other impoverished
people in low income countries. Addressed

Page 5 paragraph 2: this needs rephrasing because it sounds as if all persons approached gave
consent. Results presented later make it clear that this was not the case. Addressed

Page 11 paragraph 2: was there any particular reason that the letters C and M were chosen?
Response: No, any letter could be given as codes to the vaccines. This was by chance that C and
M were given.

Page 12 paragraph 2: define the abbreviation AE before you use it for the first time. Addressed
Page 9 line 24

Page 13 paragraph 3, and Table 1. Consider presenting this information in the form of (the upper
part of) a CONSORT flow chart. Addressed
Page 16 paragraph 3: it would be helpful if, as well as outlining positive lessons learned and successful aspects of the trial, the authors also identified problems that occurred, how these were addressed and how, with hindsight, they such problems might have been avoided. **Addressed**

**What next?** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.
Reviewer’s report

Title: Lessons and implications from a mass immunization campaign in squatter settlements of Karachi, Pakistan: an experience from a cluster-randomized double-blinded controlled trial [NCT00125047]

Date: 16 March 2006 Version: 
Reviewer: Christian Gluud

Reviewer’s report:

General

Mohammad Imran Khan and colleagues describe in the manuscript the logistics, the feasibility, and some safety aspects of a cluster randomized trial conducted in squatter settlements of Karachi, Pakistan. In the clusters, the investigators compare ‘Vi’ typhoid polysaccharide vaccine (experimental intervention) versus hepatitis A vaccine (control intervention). The trial is part of the Diseases of the Most Impoverished (DOMI) typhoid fever programme started in 2001, a prestigious project having received substantial funding from several important sources. Starting such a trial must have demanded lots of energy and skills. Most of the text reads well and I guess I have a good impression of the complexities the investigators had to overcome to reach this far. I have a number of comments that I suggest the authors’ address. The trial has been registered – but I lacked relevant information on this trial at the trial register.

• Major Revisions

1. The interest in assessing the experimental intervention would benefit in clarity from having a systemic review backing the complexity in deciding to use the intervention. How many trials have been conducted with this vaccine versus placebo? What are their findings with relative risks and 95% confidence intervals on which outcomes? How many trials have been conducted with this vaccine versus other vaccines for typhoid fever? What are their findings with relative risks and 95% confidence intervals? I suggest that the authors identify such systematic reviews or conduct them themselves.

Response:


We have added this information to the text page 5 line 14

2. Why was this ‘Vi’ vaccine chosen and not a more long-term effective ‘Vi’ vaccine?

Response:

Currently two typhoid fever vaccines are internationally licensed Ty21a and Vi polysaccharide (PS) vaccine. A recent Cochrane review on typhoid fever vaccines found that the two vaccines i.e. Ty 21 and Vi have similar results with Vi having an advantage of heat stability and single dose regimen. ViPS was thus chosen for use in the DOMI trial as it would suit the public health program for immunization in the
countries of south east Asia. The use of Vi requiring a single, injectable dose was thought to be logistically easier than use of Ty21 which requires three doses.

We have added this paragraph to the text page 5 line 16

3. The relevance in assessing the experimental intervention versus the control intervention would similarly benefit in clarity from having a systemic review backing the deciding for using this control intervention. How many trials have been conducted with this hepatitis A vaccine versus placebo? What are their findings with relative risks and 95% confidence intervals? How many trials have been conducted with this vaccine versus other vaccines for hepatitis A? What are their findings with relative risks and 95% confidence intervals? I suggest that the authors identify such systematic reviews or conduct them themselves.

Response: Craig and Schaffner in 2004 reviewed the preventive strategies for control of HAV. Hepatitis A vaccine has been shown to be highly protective against active disease. Two large efficacy trials were conducted; one in Thai villages and the other in a religious community in New York, all of which had sustained high rates of transmission of hepatitis A. Vaccination efficacy rates of 94 to 100 percent were recorded in these challenging circumstances. However we have to emphasize that the objective of our study was not to assess the HAV vaccine but to provide information on the programmatic use of a typhoid fever vaccine.

4. What is the chance that hepatitis A vaccination would offer any benefit in this population? I suspect that the chance of any beneficial effect – due to the fact that a high proportion of children already have been exposed to hepatitis A – is close to negligible?

Response: There is no scientific evidence that vaccine for HAV would benefit populations with previous exposure but at the same time it has been reported that HAV vaccine has had a tremendous effect on the epidemiology of HAV in areas where it has been used. Since Pakistan is an endemic area for HAV and direct benefit of the vaccine to the recipients may be questioned but the herd effect of the vaccine to stop the transmission would have long term implications for the study participants and the setting. During discussions with the community there was a strong feeling that a biological active control would be preferable to an inactive control. Both groups will ultimately receive the benefits of the Vi vaccine as well as the HAV vaccine as a cross-over vaccination is planned at the end of the surveillance period.

This information was added to the text page 9 line 8

5. This trial was approved by a number of ethical committees from several organizations/countries. It is not fully clear to me why this has happened. I suggest that the authors give a detailed description of the ethical considerations they have, eg, the description included in their protocol.

Response: Please find attached appendix A from the protocol that mentions ethical considerations of the project. Since the project encompasses a wide geographic region

and an international group of investigators we obtained approval from WHO. IVI is located in Seoul Korea and approval from the IVI institutional review board was obtained. Local ethical approval was obtained from the national Ethical Committee of Pakistan.

5.1 In planning a clinical trial of a new intervention, two issues should be addressed. The first is the question of whether the use of the new intervention is justified. The second is the choice of the appropriate control group. Both issues are dependent on the knowledge about the therapeutic value of the treatments to be compared (see points 1-4 above). This is an important reason why clinical trials should be preceded by systematic reviews to assess the status of knowledge. The trial would not be justified if one of the treatments to be assessed is known to be superior to the other. A clinical trial is only justified if the participant and the clinician are not certain about which treatment to choose from the available options. If they are uncertain (indifferent) about the relative value of the treatments, it is time for a trial. This is not only because the trial will help resolve this uncertainty but also because it is the fairest way to choose the preventive strategy.

Response: We agree with the comment that equipoise is a precondition in the ethical conduct of efficacy trial. Our study is a demonstration project to evaluate the effectiveness of typhoid vaccines in an impoverished setting with very high typhoid fever incidence. National decision makers stated this evidence would be essential for the introduction for of a typhoid fever vaccine programs in Pakistan (DeRoeck, J Health Popul Nutr. 2004 Sep;22(3):322-30)

This has been added to the text page 6 line 6

6. Following the same logic, I would also like to see described in more detail what was the information (written and verbal) given to the a) community leaders, b) the parents, c) the guardians, as well as d) the participants on benefits and harm of experimental and control interventions.

Response: Please see the attached appendices B, C and D. these guidelines and information material was distributed during various phases of the trial. These were translated in the local language for the ease of understanding. This has been added to the text, page 10 line 1

7. How was the sample size of this trial calculated. In a ‘sister’ (or aunt?) publication (Acosta et al, Tropical Medicine and International Health 2005; 10:1219-1228) we learn that 60 clusters with 30,000 participants was the goal of this trial, - but neither in this publication, nor the present manuscript, nor at the NCT-registration site do I find description of the sample size calculation.

Response: please see the appendix from the protocol that gives the description of sample size for the trial from the protocol. This has been added to the text page 7 line 16

8. We now learn that about 21,059 children lived in the 60 clusters, but only 12,830 were randomised. This represents only 43% of the target. This aspect needs to be discussed including an assessment of the impact on the potential conclusions top be drawn.

Response: After the pilot phase an update census was conducted to capture the current residents in the study setting. The number 21,059 is based on census update database who resided in 60 geographic clusters. Cluster was the unit of randomization. We
were finally able to reach 12,830 children, who received vaccine according to their cluster of residence.

9. The authors should report the trial and the flow of patients according to instructions in the CONSORT Statement/CONSORT diagram.

**Response:** We have added the chart with some missing information as not all components of the CONSORT chart apply to this paper. The consort chart is required for the reporting of trial outcomes. The aim of our publication is to report on operational aspects of a very large vaccine trial. A complete consort chart will accompany the report on trial results.

10. What was the role of the pharmaceutical sponsor in designing this trial?

**Response:**
The trial was sponsored by IVI through funds generously provided by the Bill and Melinda Gates foundation. Vaccines were generously provided by GSK free of cost. Neither BMGF nor GSK were involved in the study design, implementation or will they be involved in the analysis of the trial. BMGF and GSK have been informed about the progress of the trial in regular intervals.

11. What was the role of the pharmaceutical sponsor in reporting this trial?

**Response:** None

12. What are the risks of breaking the code in the trial due to the use of similar code letters in the two groups of clusters? Would the investigators do the same if they were to plan the trial today?

**Response:** The simple design is least likely to result in mix-ups. While there is a theoretical advantage of reduced opportunities for unblinding with multiple code groups the potential for mix-ups also increases. We believe that the most simple and basic design is most appropriate for complex settings such as slums in Pakistan. We are not aware that unblinding has occurred (the trial is still ongoing). This has been added to the text page 8 line 17

13. Maybe the reporting of adverse events should await breaking of the code, so that beneficial and harmful effects can be assessed in the same report. Accordingly, the present publication could focus on justification of the trial as well as design and feasibility issues.

**Response:** We agree that it is too early to analyse AEs. We only report on the feasibility of AE detection.

14. As this manuscript deals with feasibility why not give the data on resource use for immunization mentioned op p.15? **This has been added Table 3**

**Cold chain**

There was no important deviation of the cold chain at any storage site. The temperatures recorded at the vaccination posts were +3°C to +20°C (mean +4°C). These were maintained by 4 or 5 ice packs per cool box. The highest temperatures were observed during the busy hours when cool boxes were opened frequently. Temperatures were never above 8°C for more than 2 hours and were within the manufacturer’s recommended guidelines. Thus, no vaccine had to be discarded because of temperature variation.
**Resources and supplies**
On an average, 389 children were vaccinated per day and each vaccination team worked 7 hours a day for 33 days. A total of 12,837 vaccine doses were opened during the vaccination campaign. Seven doses were not used because the needle was injected in the vein.

15. There was a significant migration between the clusters. How were the expectations during the planning of the trial regarding migration? What are the consequences for this cluster randomized trial of the observed substantial migration? How are the authors planning to deal with this problem during data analysis?

**Response:** We conducted two censuses during the preparation phase of the trial mainly to understand the typhoid fever incidence and the mobility of the study population. The mobility was acknowledged in the sample size calculation. During the preparation of the analytic plan several possible migration patterns were considered, including migration within a cluster, migration into another cluster with the same vaccine code, migration into a cluster with a different vaccine code, and migration out of the study area. Depending on the pattern the study participant will be censored at the time of migration which will be established through interviews following the exit census.

- **Minor Essential Revisions**

16. All randomized trials are of course controlled, so please do not use the pleonasm ‘randomized, double-blind controlled trial’ but rather ‘randomized, double-blind preventive trial’, which I think will be more descriptive. **Addressed we believe that RCT refers to randomized clinical trial?**

17. On p.6 local EPI needs explanation first time. **Addressed expanded programme of immunisations**

18. On p.8 DSMB needs explanation first time it is used. **Addressed data safety monitoring board**

19. If reporting of adverse events stay in this manuscript, please consider: The reporting of adverse event will be wrong, because only a fraction of those vaccinated were checked for adverse events. Calculation of proportions (%) should use the correct denominator – and the total number with adverse events should be calculated based on extrapolation.

**Response:** Adverse event documentation was either solicited (total of 240 household visits) and non-solicited (those who reported adverse event either to the vaccination posts on the succeeding day or the health center that was functioning 1000 – 2200 hrs everyday). We think if there were adverse event following immunization this must have been reported to our surveillance system of adverse events. The relative number of individual AEs is based on the total adverse events captured through all sources, therefore we think we can use the total number of vaccine recipients as the denominator.

20. The three patients with serious adverse events ought to be described. **Addressed**

Three persons were hospitalized post immunization. One child developed petechial haemorrhages and later was found out to be having a bleeding disorder. Another child was admitted with fever and was diagnosed as having culture proven typhoid. The third one had developed an injection abscess. The main adverse events reported included fever (48), local pain (56) and local swelling (15).
21. Tailored GCP – what is meant by that?
   We omitted this expression

22. The authors may be right that the number of refusals may be lower during a non-trial mass vaccination campaign – but why? **Addressed**
   **Response:** The blinded nature of the trial nature may have contributed to relatively high rate of refusals. Parents and guardinas often feel uncomfortable with the uncertainty of blind RCT. As a matter of fact many clinicians feel the same. In our experience with blinded and unblinded trials participation is much higher in unblinded trials.

   **What next?**: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions
   **Level of interest:** An article of importance in its field

**Quality of written English: Acceptable**

**Statistical review:** No, the manuscript does not need to be seen by a statistician.
Appendix A: ETHICAL CONSIDERATIONS

Protocol Review
Before initiation of the Vi Demonstration Project the working protocol requires clearance by Pakistan’s Ethic Committee and Institutional Review Board (IRB). Additionally, the protocol will be submitted to IVI’s and the WHO’s IRB for approval. Then investigators and sponsor representatives should sign it.

According to the international standard guidelines on IRB, an annual review will take place to evaluate if the research has been conducted according to the protocol which was approved by initial review. Investigators will submit a progress report, which includes: report of adverse events occurred, subject recruitment status etc.

Ethical Guidelines
The principles that govern biomedical research involving human subjects are of application to this project. The Declaration of Helsinki (appendix 2) and the International Conference on Harmonization’s Good Clinical Practice Guidelines (ICH-GCP) will be followed, aiming to provide assurance that the rights, integrity, and confidentiality of trial subjects are protected and that results reported are credible and accurate. The Investigators’ responsibilities will follow the WHO guidelines for GCP. It is also expected that local ethics committees will follow guidelines set forth by WHO to ensure quality of the ethical review.

Data & Safety Monitoring Board (DSMB)
These multi-centric cluster randomized trials will be audited by the Data & Safety Monitoring Board (DSMB). The DOMI DSMB is constituted by:

Dr. Bernard Ivanoff, chairman (WHO-Vaccines & Other Biologicals, Geneva)
Roger Glass (CDC-USA),
Dr. Jack Lee (Westat-Korea) and
Ellwyn Griffiths (WHO-Geneva).

The DSMB in collaboration with the PIs will designate an independent on site clinical monitor. The DSMB will give recommendations on Continuing, modifying or stopping the trial. Specific DSMB activities are:

a) To review the study protocol with special attention to safety monitoring procedures and make recommendations for addition and adjustment;

b) Could recommend increasing the sample size (number of clusters) as a result of an interim analysis carried out by the independent statistical consultant group (Prof. Allan Donner).

c) The chairman will review quarterly all serious adverse events SAE related or not to vaccination (see section on SAE : who and when to report);

3 The Declaration of Helsinki. Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and amended by the 29th World Medical Assembly, Tokyo, Japan October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983, the 41st World Medical Assembly, Hong Kong, September 1989 and in South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.


6 WHO. Operational Guidelines for ethic committees that review biomedical research: TDR/PRD/ETHICS/2000.1
d) The clinical monitor and the chairman will hold the codes for the trial;
f) In some circumstances it might be necessary to break the codes, for example when an individual become seriously ill and knowledge of the intervention received may be needed to apply the appropriate treatment, or in case of frequent and serious adverse reactions. The DSMB has the mandate to stop the study if there is evidence of a substantial risk of adverse reactions associated with any of the vaccines under the study.

Informed Consent
Three different consents will be sought in the project
1. Trial participation
2. Specimen collection
3. Home visits

Inform consent procedures will follow the WHO/TDR Guidelines for Standard Operating Procedures for Clinical Investigators described in pages 10-12

Trial participation informed consent
Informed consent for the cluster-randomized Vi vaccine and Hep A vaccine demonstration project will undergo the following process:
1. A series of meetings with the elected community leaders, local Nazis and community elders will take place between November and December 2002, where the general background, objectives and plans for the vaccination campaigns will be explained. Project information on: nature and purpose of vaccination; expected risks and benefits and procedural details entitled in participation, will be provided to community leaders by project medical personnel (appendix 4). This English version will undergo cultural translation and adaptation. Appendix 4 (pending) shows the translated version of the trial information.
2. A series of community information and dissemination meetings, including cluster-level meetings will take place December 2002 – January 2003, in order to get general verbal consent for the Vi -Hep A vaccination schedule and its cluster design.
3. This verbal consent will be further ascertained at the time when the vaccination schedule will be conveyed to the community via the health workers, study physicians and family physicians, 1 month prior to vaccination.
4. At the time of the vaccination campaign, there will be a verbal ascertained of the family’s understanding of the vaccination program and willingness to participate. Once verbally ascertained, the parent/guardian will be requested to affix his/her signature or thumb print on the requisite section in the vaccination record book, duly witnessed and signed by an independent community representative.

Specimen collection & Home visits consent
In the case of blood drawing for further studies (Vi and hepatitis A immunogenicity) and home visits (typhoid fever cases follow-up; risk assessment for controls of the case-control study and for vaccination safety documentation), individual written inform consent will be obtained. The subset of study participants that will be randomly be identified for the immunogenicity testing and safety monitoring (n=240), will be individually approached prior to vaccination. The process of vaccination, home follow-up, sequence of blood sampling at day 0, 6 weeks and 24, will be explained. The English and translated version (pending) of the information provided to the participants is attached in appendix 5 and 6. In the event the family agrees to participate, an individual signed and witnessed informed consent will be obtained from the parent/guardian on the day of vaccination.

Confidentiality
Participant confidentiality in publications, reports and clinical or biologic specimens collected during the conduct of the trial and following completion of the trial, will be ensured. Clinical or biologic

specimens will have an ID number or laboratory number only. The list linking names of the participants to the ID or laboratory number will be kept separately. Access to both electronic and hard copy data will be restricted to authorized senior study personnel only.

**Potential Risks and Risk Minimization**

**Vaccination**

Both the Vi polysaccharide vaccine (Typherix ®) and the control vaccine, hepatitis A vaccine (Havrix®) are licensed and known to be safe. Most reported adverse events have been mild and did not last more than 24 hours. (See section of adverse events. Adverse events, if deemed related to vaccination process (e.g., abscess at vaccination site or post vaccination rash) will be treated at the project health facilities. In case a life-threatening event occurs, trained projects physicians at the Vaccination Centers will treat these and transportation to a hospital will be guaranteed.

**Blood collection**

The potential risk to the participants will be minimal, since all clinical procedures (venous blood collection) will be performed by adequately trained and experienced personnel under regular supervision. There is a small risk associated with phlebotomy for patients who are required to give a blood sample. This may include pain, redness and, very rarely, local infection at the phlebotomy area.

**Risk/Benefit Ratio**

The benefits to participants of the study are direct and are listed above. The risks are minimal. During the study the potential direct benefits to participants meeting the clinical case definitions for typhoid fever include: free and accurate diagnosis of the disease through laboratory investigation, followed by proper outpatient treatment and, when needed, referral to the hospitals. Those receiving Vi or Hepatitis A vaccines will be highly protected against these diseases.

*Choice of the control intervention*

Hepatitis A vaccine was chosen as the active control in consensus with the PI and other local investigators, for the following reasons:

1) To provide benefit to the control arm. It was acknowledged that protective sero-prevalences could be high at young ages, in the study area.
2) The hepatitis A was considered an adequate control intervention, to facilitate masking of the trial

**Protocol modification**

Any amendment to the trial, as the trial progresses, must be discussed by the investigator and IVI concurrently. If agreement is reached concerning the need for an amendment, such amendment will be produced in writing and be made a formal part of the protocol. Any amendment requires Ethics Committee approval.

An administrative change to the protocol is one that modifies administrative and logistics aspects of a protocol and that does not affect the study participants’ safety, the objectives of the trial and its progress. An administrative change may require Ethics Committee notification.

The investigator is responsible for insuring that changes in approved trial, during the period for which Ethics Committee approval has already been given, may not be initiated without Ethics Committee review and approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

**Trial Interruption**

The trial may be discontinued for administrative reasons and/or on advice of IVI, the investigators and/or the local Ethics Committee.

If a trial is prematurely terminated or suspended, IVI shall promptly inform the investigators and the local Ethics Committee of the reason for termination or suspension.
**Stipends for Participation**
The majority of study participants will not receive stipends for participation in the vaccination trial. A subset of 240 study participants that will provide blood for the Vi immunogenicity testing will receive vitamins or food immediately after the blood collection process.

**Compensation**
Both the Vi polysaccharide vaccine (Typherix ®) and the control vaccine, hepatitis A vaccine (Havrix®) are manufactured under GMP conditions, licensed in many countries and known to be safe. Rare allergic events have been reported. If a study participant develops a vaccine-related serious adverse event as confirmed by the DSMB, medical treatment will be provided according to local treatment guidelines and cost of such treatment will be charged to GlaxoSmithKline Biologicals.
Appendix B HOME VISIT INFORMED CONSENT

1. Date of consent (dd/mm/yy) ........................................
2. Name of subject: ..................................................
3. Subject ID : ......................................................
4. Age: a) _______ (years)
5. Address
   a)Area/Commune ___  b)Village: ______  c) Block: ______
   e)Household Number ______
   f) Street (Complete) __________________________________

Your community and you have agreed to participate in a research project to reduce the incidence of typhoid in the area by evaluating the usefulness of a vaccine to prevent typhoid fever. We request now for your permission to evaluate and visit you at home in order to obtain information on: risk factors associated with typhoid fever in this area; disability associated with typhoid fever and cost of the disease.

1. The activity involves: interviews at home and collection of stool sample.

2. The scope, aims and purpose of the home visits. To confirm residence of patients, to evaluate clinical prognosis of patients with typhoid fever and to identify risk factors of typhoid fever in this area. We also want to calculate the cost impose to those suffering of typhoid fever. Stool specimens will be collected to identify typhoid fever healthy carriers.

3. Foreseeable harm and possible level of risk. We will be asking the participants to discuss some personal issues related to health practices. Answering these questions could cause some minor discomfort for the participants. There are no physical risks associated with this project.

4. Likely or expected benefits. There will be no direct benefit to you as a result of participating in this study. However, results of this study will improve our knowledge on the typhoid fever. These data may then be useful in terms of planning control measures in the future.

5. Subjects will be notified of new information. The community will be informed on the progress and results of this investigation.

1. Confidentiality will be maintained. All the information you give us will be kept in a locked cabinet. Only our staff will have access to it. We will not give it to anyone to the extent permitted by applicable laws and regulations. Under certain circumstances data can be made available to regulatory authorities, DSMB and ERC. If the results of the trial are published, the subject’s identity will be kept confidential.

6. Explanation laboratory procedures and care for research-related illness. The following laboratory procedures will be sought: stool culture to determine the presence of the bacteria that caused typhoid fever. If the culture is positive our project will contact you and will provide you the adequate treatment.

7. Your participation is voluntary and refusal to participate will involve no penalty. You are free to accept or reject to be visited at home. If you decide not to participate you can
continue participating in the vaccine evaluation. After enrolment you will be able to withdraw your self from the study at any moment.

8. If you agree to participate, please indicate by placing your signature or the impression of your left thumb at the specified space below.

9. Thanks you for your cooperation

10. No anticipated financial expense is expected for participating in the project. No pro-rated payment will be given.

Thanks you for your cooperation

_________________________   _________________________
Signature:             Signature of the investigator
of the guardian (under 18 years)
of the participant (≥18 years)

Date: ____________________

____________________
Signature of witness

Date: ____________________

The patient agreed to participate □ yes □ no    If no, explain the reason below

____________________________________

____________________________________
Appendix C: *Information that will be provided to the community*

**The project involves research.** We ask the community to participate in a field trial to reduce the incidence of typhoid fever in the area. The study duration is 3 years. Approximately 35,000 children aged 2-16 will participate in this project.

**The scope, aims and purpose of the research.** Typhoid fever causes much sickness in the community; such as sustained fever, weakness, and abdominal pain. We have medicine to treat it but we want to prevent the community from becoming sick. In other countries, they have been using a vaccine, Vi, to prevent typhoid fever, mainly in school children and during epidemics. We want to know if Vi vaccine can be given here. To find out this, we will give some people Vi vaccine and the others a vaccine to protect against hepatitis A; the assignment will be random. Because we need to obtain valid results, participants will be not told in which group they are in and efforts will be made so that the treating doctors and investigators are unaware of what group they are in. The vaccine injection is similar and will be labeled with codes only. We will follow up the participants at the health centers to see whether they become ill or not with typhoid fever. After 2 years of follow-up the vaccine codes will be unveiled.

**The vaccines.** Typhoid fever Vi vaccine and hepatitis A vaccines are licensed vaccines from GSK. Both come in syringes and they are given intramuscularly. At the end of the study the children that initially received hepatitis A vaccine, will receive a 2nd does of hepatitis A vaccine (normal schedule involves 2 doses) and Vi vaccine. Those that received initially Vi vaccine will get 2 doses of hepatitis A vaccine with an interval of 6 months.

**Foreseeable harm and possible level of risk.** We anticipate no harm because these vaccines have been used in other countries for several years. Nonetheless vaccines can produce some minor side effects like local pain, and fever. The investigator’s contact information will be available at the health centers for participants that present adverse events, following vaccination. Life-threatening events have been rarely seen with these vaccines. In case a life-threatening event occurs, trained projects physicians at the Vaccination Centers will treat these and transportation to a hospital will be guaranteed. Any serious adverse event related to the vaccination process, as determined by a board of specialists that monitor the trial, will be treated under national treatment guidelines, and costs will be assumed by the vaccine manufacturing company.

Pregnant women will not take part in this project. There is not enough information on safety of these vaccines to the unborn child. Women at risk of pregnancy will be asked verbally on their pregnancy status, before vaccination. Any women who discovers that she was pregnant at the moment of receiving the project vaccines should inform the investigators. Health project personnel will visit her periodically during her pregnant months.

**Home visits and specimen obtention.**

A small proportion of participants will be visited by project health personnel to obtain information on safety of the vaccine. These same participants will be also asked to allow us to take a sample of blood to evaluate the performance of the vaccine.

A small proportion of participant that may or may have not experienced typhoid fever in the previous days will be visited by health project personnel to obtain information on risk factors and disability associated with typhoid fever and cost of the disease.

If you happen to be selected for one of the above we shall inform you in detail on the procedure and seek for your written consent.
**Likely or expected benefits.** Those receiving Vi or Hepatitis A vaccines will be highly protected against those diseases. Diagnosis of febrile patients and treatment for confirmed typhoid fever cases will be free of charge.

**Alternative procedures, treatments or preventive strategies.** The best way to prevent typhoid fever is to drink and eat food which are free of the pathogens.

**Subjects will be notified of new information that might affect their participation.** We will be closely watching the progress of all the population in our study. We will notify you if we detect any problems. The community will be informed on the progress and results of this investigation.

**Confidentiality will be maintained.** All the information you give us will be kept in a locked cabinet. Only our staff will have access to it. We will not give it to anyone to the extent permitted by applicable laws and regulations. Under certain circumstances data can be made available to regulatory authorities, DSMB and ERC. If the results of the trial are published, the subject’s identity will be kept confidential.

**Explanation about medical treatment and care for research-related illness.** As usual you will be receiving medical attention and treatment through the health facilities. If you develop typhoid fever, we will collect this information so that we can see whether this strategy is good. The following standard laboratory procedures will be performed: blood culture, stool culture, antibody detection. Additional special molecular methods such as detection of bacterial DNA & detection of host response to infection will be tested. Clinical specimens can be used for investigating other infections if necessary.

**Payment.** No anticipated financial expense is expected for participating in the project. No pro-rated payment will be given.

**Participation is voluntary and refusal to participate will involve no penalty.** All participants/parents/guardians will be asked verbally and individually if they have been previously informed of the trial and are willing to participate, and if so they will sign the Vaccination Record Book, prior to vaccination.
Appendix D Determination of Sample Size

This project will utilize cluster randomization procedures to allocate typhoid Vi or hepatitis A vaccines. To mimic a public immunization program for typhoid fever, a group of households will represent the cluster and hence the unit of randomization. A sensitivity analysis was performed and what follows is a conservative estimate of sample size. A total of approximately 24,710 children will be needed in order to have 80% power to detect a 50% vaccine protection at a 5% level of significance. This sample size calculation assumes a minimum cumulative typhoid incidence of 2.8 per 1000 (during 2 years).

Using the Hayes and Bennet formula\(^8\), the total sample size per arm is determined as follows:

Testing type for vaccine effectiveness: one-sided (alpha=0.05),
Minimum power to achieve: 0.8 (=1-beta),
PE(Protective Efficacy): 0.5,
Study Duration in Years: 2,
Incidence of interest: Cumulative,
Between cluster coefficient of variation (CV): 0.5,
Cluster size (N\(_c\)): 580,
Zalpha: Quantile of standard normal distribution whose cumulative probability is alpha, and
Zbeta: Quantile of standard normal distribution whose cumulative probability is beta.

Under the assumptions above, number of clusters per arm is given as

\[ 1 + (z_{alpha}+z_{beta})^2 \left( \frac{(p_1+p_2)}{N_c} + CV^2 \left( p_1^2+p_2^2 \right) \right)/\left( p_1-p_2 \right)^2. \]

Assuming an annual attrition rate of 10% a total sample of 24,710 children is needed. The estimated 2-16 year old population of the study site is 35,000. The first 30 clusters (Sultanabad and Hijrat colonies with a population of 17,000 children) will be randomized initially and the others 30 clusters (Bilal colony with an estimated population of 18,000 children) will be randomized one year later (after the first year pre-vaccination surveillance). This “staggered enrolment” of clusters is frequently done in community intervention trials for feasibility reasons and to increase power and has no methodological drawbacks except for extending the length of the trial as a whole (Prof. Allan Donner, personal communication). Sample size will be revisited after the first year disease surveillance is completed in Bilal colony, in order to determine the need to enroll other clusters, if one of the critical design assumption is in error; for ex., if the cumulative typhoid fever incidence in the control group is below what was initially assumed in the estimation of the trial power.

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