RESEARCH NOTE

REVISED Recruitment strategies used to enrol healthy volunteers in the first pneumococcal human infection study in Africa: Lessons from Blantyre, Malawi

[version 2; peer review: 1 approved, 2 approved with reservations]

Edna Nsomba[1*], Anthony E. Chirwa[1*], Clara Ngoliwa[1,2], Vitumbiko Nkhoma[1], Pemphero Liwonde[1], Edward Mangani[1], Modesta Reuben[1,2], Lorensio Chimgoneko[1], Lumbani Makhaza[1], Evaristar Kudowa[1], Marc Y R Henrion[1,3], Neema Toto[1], Stephen B. Gordon[1,3*], Dingase Dula[1*], Malawi Accelerated Research in Vaccines, Experimental Laboratory Systems (MARVELS) consortium

[1]Clinical and Experimental Medicine, Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre, Southern Region, P.O. Box 30096, Malawi
[2]Department of Medicine, Queen Elizabeth Central Hospital, Blantyre, Southern Region, P.O. Box 95, Malawi
[3]Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, L3 5QA, UK

[*] Equal contributors

v2 **First published:** 24 Apr 2024, **9**:216
https://doi.org/10.12688/wellcomeopenres.19271.1
Latest published: 26 Feb 2025, **9**:216
https://doi.org/10.12688/wellcomeopenres.19271.2

Abstract

Background

Human Infection Studies (HIS) also known as Controlled Human Infection Models (CHIM) are a relatively new concept in African countries to clinicians, scientists, and communities alike. We have introduced HIS/CHIM studies to Malawi during the last four years by developing an experimental human pneumococcal carriage model. This CHIM was used to test the efficacy of a licensed 13-valent Pneumococcal Conjugate Vaccine (PCV13) against experimental nasal pneumococcal carriage. Traditional and digital recruitment strategies into this novel trial were explored.

Objectives

To describe various methods of recruitment in this first CHIM study in Malawi.

Open Peer Review

Approval Status ? ✓ ?

	1	2	3
version 2 (revision) 26 Feb 2025	? view	✓ view	? view
version 1 24 Apr 2024	? view	? view	

1. **Dorcas M Kamuya**, Kenya Medical Research Institute (KEMRI) - Wellcome Trust Research Programme, Kilifi, Kenya
2. **Oren Ziv**, Ben-Gurion University of the Negev, Beer-Sheva, Israel
3. **Patrick Harris**, University of Queensland, Queensland, Australia

Methods

The clinical trial within the context of which these data were recorded was registered with the Pan African Clinical Trials Registry (REF: PACTR202008503507113) on 03 August 2020. The project was conducted at the Malawi Liverpool Wellcome Programme (MLW) in Blantyre, Malawi between April 2021, and September 2022. Source populations were college students and community members within Blantyre. Recruitment strategies included sharing study information in written or visual form, community sensitization meetings, snowball contacts (word of mouth from previous volunteers), branded clothing and participating in radio and television programs.

Results

299 volunteers attended screening clinic, of whom 278 were recruited. Sixty-six recruited volunteers (23.7%) were college students and 212 (76.3%) were from the community. Snowball word-of-mouth contacting was the most successful recruitment strategy, with 201 (72.3%) participants recruited using this method. 195 (70.1%) were men of whom 149 (76.4%) joined the study through snowballing.

Conclusion or recommendation

Using a variety of recruitment strategies led to successful recruitment in this novel controlled human infection study. Most participants were recruited through snowballing.

Keywords
Controlled Human Infection Model, Streptococcus pneumoniae, Carriage, Conjugate Vaccine, Clinical trial

This article is included in the Malawi-Liverpool Wellcome Trust Clinical Research Programme gateway.

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding authors: Edna Nsomba (ensomba@mlw.mw), Anthony E. Chirwa (achirwa@mlw.mw)

Author roles: Nsomba E: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Chirwa AE**: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Ngoliwa C**: Conceptualization, Data Curation, Methodology, Writing – Review & Editing; **Nkhoma V**: Conceptualization, Data Curation, Methodology, Writing – Review & Editing; **Liwonde P**: Conceptualization, Data Curation, Investigation, Writing – Review & Editing; **Mangani E**: Conceptualization, Data Curation, Investigation, Validation, Writing – Review & Editing; **Reuben M**: Conceptualization, Data Curation, Methodology, Writing – Review & Editing; **Chimgoneko L**: Conceptualization, Data Curation, Writing – Review & Editing; **Makhaza L**: Formal Analysis, Software, Validation, Visualization, Writing – Review & Editing; **Kudowa E**: Formal Analysis, Software, Validation, Visualization, Writing – Review & Editing; **Henrion MYR**: Formal Analysis, Software, Validation, Visualization, Writing – Review & Editing; **Toto N**: Conceptualization, Data Curation, Methodology, Validation, Writing – Review & Editing; **Gordon SB**: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Dula D**: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing;

Competing interests: No competing interests were disclosed.

Grant information: The work presented was supported by Wellcome [Grant number 211433].
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Nsomba E, Chirwa AE, Ngoliwa C *et al.* **Recruitment strategies used to enrol healthy volunteers in the first pneumococcal human infection study in Africa: Lessons from Blantyre, Malawi [version 2; peer review: 1 approved, 2 approved with reservations]** Wellcome Open Research 2025, **9**:216 https://doi.org/10.12688/wellcomeopenres.19271.2

First published: 24 Apr 2024, **9**:216 https://doi.org/10.12688/wellcomeopenres.19271.1

REVISED **Amendments from Version 1**

We have added new references to describe CHIM studies which have been conducted in Africa and revised the discussion section by putting additional quantitative information.

Any further responses from the reviewers can be found at the end of the article

Introduction

Rationale

Human Infection Studies (HIS), also known as Controlled Human Infection Models (CHIM), involve introducing a pathogen to a healthy individual under carefully monitored conditions. These studies continue to make important contributions to prevention and treatment of many infectious diseases by offering researchers a platform to evaluate the efficacy of vaccines in protection against infections as well as the immune response generated. The study of vaccines for malaria and influenza have been significantly advanced by CHIM studies[1]. Following a scale up in production, CHIM studies are now possible at a very much greater scale[2]. High Income Countries (HIC) have utilized these studies to understand biology and develop vaccines for pathogens of clinical and population health importance such as human influenza viruses, respiratory syncytial virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Staphylococcus and Neisseria species. High literacy levels, equitable access to health care, advanced technology, superior physical and digital health services infrastructure, and high socio-economic status have facilitated the success of these novel studies in HICs.

In Africa, not so many countries have conducted CHIM studies so far. Malawi, Kenya, Uganda, and Tanzania are four countries that have established HIS in Africa (Malawi: *Streptococcus pneumoniae* challenge[3], Kenya[4]: *Plasmodium falciparum* challenge, Uganda: Schistosoma challenge[5]). One of the contribution of Kenyan Malaria CHIM study was that it allowed for an early assessment of vaccine efficacy in a population with the same generation background as the eventual target population. This study built a strong and grounded understanding of the ethics of research used in CHIM models which has helped to inform the future of CHIM models in similar settings. Current CHIM studies in other African countries continue to build on these efforts[6].

Other countries such as Zambia[7], are following with other study pathogens, and priming their populations for introduction of these novel studies[7]. Typically, HIS are conducted first in a HIC and after the technology, standard operating procedures and safety have been established, transferred to a collaborating Low-Income Country (LIC). For example, pneumococcal human challenge trials were conducted in Liverpool for a decade following which technology and standard operating procedures were transferred to Malawi for feasibility testing[8]. Similarly, a study of blood-stage controlled human Plasmodium *falciparum* malaria infection that is ongoing in Tanzania, originated from Oxford University[9]. As CHIM studies expand and clinical researchers continue to gain more experience, other population at risk have been included. Recently, in Malawi a CHIM study in people living with HIV (PLHIV) was implemented using the same experimental design well-established at the Malawi-Liverpool Wellcome Programme and at Liverpool School of Tropical Medicine[10]. This has laid a foundation for future at-risk population CHIM models in similar settings.

The first workshop to be convened on human challenge work in Malawi by a technical working group, which included the authors, met in 2017[11]. Clinicians, scientists, ethicists, and community leaders discussed the potential benefits of human infection studies (accelerated vaccine development, capacity building) and risks (safety, acceptability, ethical concerns)[11]. The workshop report highlighted: excellent international clinical standards, local capacity building and ownership, a rigorous informed consent process, mitigation of challenges with transport and access to health facilities, appropriate economic compensation, and managing community and media perceptions as key issues to address to ensure success of human infection studies in a setting like Malawi[11].

Next, the researchers conducted a study exploring acceptability of human infection studies using focus groups and key informant interviews with Blantyre-based research staff, medical students, and community representatives, clinicians, ethics committee members, and district health government officials[11]. Overall, HIS studies were favourably perceived and potentially beneficial provided the following conditions were met; voluntary and informed consent, rigorous inclusion/exclusion criteria, provision of medical check-ups and monitoring, appropriate compensation, and robust community engagement[11].

Acceptability work paved way for feasibility testing of the human challenge model among 24 healthy volunteers, whose experiences with the trial from recruitment methods, compensation, inoculation with live bacteria, study procedures (nasosorption, nasal scrape with rhino probe, nasal wash, throat swab, saliva collection quarantine and residential stay post-challenge, were sought after trial completion[12]. Motivation for joining the study despite initial reservations included altruism, patriotism, and monetary gains[12]. Although the participants did not experience adverse events in the short duration of the study (21 days) they were concerned about future unanticipated risks[12]. The volunteers admitted that the concept of human challenge trials was completely novel and recommended extending information and education about the model to the wider Malawian population[12].

In the present paper, we discuss experiences and lessons we have learnt about recruitment through the process of scaling up from a feasibility study in tens of participants to a randomized controlled vaccine trial requiring screening of more than 250 participants.

Objectives

We describe methods used in recruiting participants in a pneumococcal CHIM study in Blantyre Malawi and highlight lessons learned in the process. The objective of the pneumococcal CHIM study was to test the efficacy of a licensed 13-valent Pneumococcal Conjugate Vaccine (PCV-13) against experimental nasal pneumococcal carriage.

Study site. This study was conducted in Blantyre, southern region of Malawi among health participants who took part in the first Controlled Human Infection Model study to assess the efficacy of PCV-13 vaccine.

Study Population. The efficacy of Pneumococcal Conjugate Vaccine (PCV-13) against experimental nasal pneumococcal carriage study recruited healthy participants aged between 18–40 years from surrounding communities and colleges. The study protocol and results can be accessed on https://wellcomeopenresearch.org/articles/6-240 and https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(23)00178-7/fulltext respectively.

Methods

Trial design

This was a qualitative description of recruitment methods used to recruit participants in a double-blinded, parallel-arm, randomized controlled trial investigating the efficacy of PCV13 or placebo (allocation ratio PCV13: placebo 1:1) against experimental pneumococcal carriage of *Streptococcus pneumoniae* serotype 6B (SPN6B). The study protocol has been published in Wellcome Research Open.

Methods

Data collection and analysis

The information in this study was collected retrospectively by calling all participants who consented and participated in the pneumococcal CHIM study. This was because in the main study (PCV-13 study) participants' information on how they heard about the study was not collected and documented. The main study was approved by ethics committee. Participants were asked to recall how they heard about Pneumococcal CHIM study and this information was documented on an excel sheet. We analyzed the data by counting each category of the planned sensitization methods.

Sensitization meetings: Sensitization meetings were conducted at eight surrounding colleges in Blantyre namely Malawi College of Health Sciences, Malawi University of Business and Applied Sciences, formerly The Polytechnic, Kamuzu University of Health Sciences, Malawi Institute of Journalism and Malawi Institute of Tourism. Each sensitization meeting was attended by approximately 50 students. Additional sensitization meetings were conducted at the Malawi-Liverpool-Wellcome Programme main site and invited research and clinical staff. Individuals interested in the study provided their telephone numbers to the study staff and verbally consented to be phoned to schedule an information session at the clinic. Sensitization meetings were interrupted from July to August 2021 by school closures due to the fourth COVID wave but resumed in September 2021.

Snowball recruitment: Snowball recruitment or sampling, also called chain-referral sampling, is an informal spread of study-related information to potential participants by word of mouth[13]. Snowball recruitment in this study occurred naturally without study staff influence. Potential participants and existing participants shared study information with their peers, who came to volunteer for the study as a result.

Radio and Television: While initially the study team was careful to perform only targeted sensitization during the feasibility study, the proven safety of the model demonstrated for over three years provided later confidence to expand awareness of human infection studies to the wider community. In May 2022, four weekly radio broadcasts about human infection studies and the PCV13 study were conducted by study clinic and laboratory team members. The broadcasts were one hour long, with a text and phone dial in segments for listener engagement. These broadcasts were all live and recorded in both English and Chichewa. There was very high engagement from the listeners during the radio programmes. Similarly, a television programme was recorded with a live studio audience and aired twice in June 2022. The live audience engaged well with the study team and asked relevant questions.

Digital media: The study team recorded a video for MLW's YouTube channel describing the importance of human infection studies in Africa and detailing the PCV13 trial. In addition, a digital study flyer was circulated on WhatsApp.

Increased visibility: The study team utilized branded clothing for participants and staff members to increase visibility and generate interest about the study.

Clinic recruitment: Recruitment to the pneumococcal CHIM study itself was as follows. Potential participants who showed interest were invited via telephone to an in-person information visit (visit A) to the research clinic. The information visits were conducted in groups and lasted approximately an hour. During this visit, A study nurse or clinician provided detailed information about the study including screening, vaccination, inoculation, quarantine, and safety procedures and follow up. Risks were discussed in detail. Materials used to collect samples were also demonstrated. At this stage, participants did not require to disclose whether they will join the study or not but were encouraged to think about it and to decide later. At the end of the visit, the potential participant's information, including their name, contact number, age, sex, residence, and their information sources regarding the study were recorded. Information sources included college sensitization campaigns, snowballing, adverts, social media and digital programs on radio and television. In addition, information to define the participants' community category was collected. They were defined as college students or not a college student (referred to as 'the community').

During a second visit intended to obtain individual consent (visit B), data were collected to show how many participants from each category showed interest in joining the study and how many of each category were both eligible and were successfully recruited, consented and vaccinated.

Following screening and recruitment, participants underwent randomization, vaccination, inoculation and follow up including residential stay and exited the study. Study procedures are summarized in Figure 1.

Ethical approvals

The CHIM study including recruitment strategies was approved in Malawi by the National Health Sciences Research Committee on 1 May 2020 (REF: 16/07/2519) and Pharmacy Medicines and Regulatory Authority (REF: PMRA/CTRC/III/10062020121) and in the United Kingdom by the Liverpool School of Tropical Medicine on 23 April 2021 (REF: 20-021). The trial was registered with the Pan African Clinical Trials Registry (REF: PACTR202008503507113) and can be found on https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=12124.

Results

A total of 299 participants were screened for the study, of which 278 were recruited. 209 (69.9% and 195 (70.1%) of the screened and recruited volunteers, respectively, were males.

Screening and recruitment by recruitment strategy

Snowballing: 215 of 299 (71.9%) screened indicated that they were motivated to join through snowball recruitment. Of these, 201 were eventually enrolled in the study. 21 volunteers were excluded for not meeting one or more of the inclusion criteria (Table 1).

Sensitization: 82 of 299 (21.4%) screened were motivated after a sensitization event (Table 2a and Table 2b).

Radio and television: This strategy motivated only one individual to screen and enrol in the study (Table 2a and Table 2b).

Poster: Only one individual was screened and enrolled after seeing a study poster (Table 2a and Table 2b).

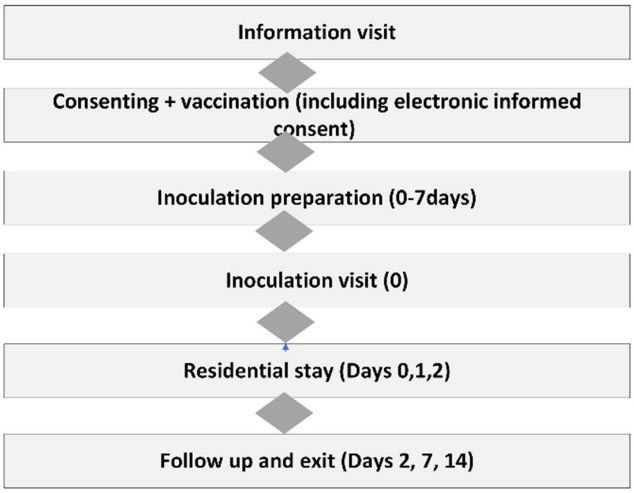

Figure 1. Summary of recruitment and follow up procedures in the main trial; PCV13 trial. This figure is an original figure produced by the author(s) for this review article.

Participant feedback on exiting the PCV13 study

213 participants accepted to be interviewed regarding their experience in a CHIM at study exit. Responses were recorded using a Likert scale survey. The majority either strongly agreed or agreed that study processes from informed consent, through recruitment, safety monitoring, compensation and quarantine-were a positive experience. 95.3% stated that they would recommend study participation to a friend (Table 3).

Discussion

In this article, we describe recruitment methods utilized in a pneumococcal human infection study. We sought to detail the contribution of various recruitment strategies to recruit and enroll healthy participants in a CHIM study in Blantyre, Malawi. Among the recruitment strategies used in this study, an overwhelming number of participants were recruited via snowballing or word of mouth networking. 215 out of 299 participants who were screened representing 71.9% joined through snowball method. Out of these 201 were enrolled in the study. The higher enrolment efficiency of snowballing was because study related information was widely shared to potential study participants prior to information visit at the clinic. The advantages of prior sharing of information relieved potential participants of stress and anxiety because of the assurance from other participants who had passed through the same process. Snowballing strategy reduced the number of community sensitization meetings because the study had enough number of people who have attended information visit way before the target period.

Snowballing is often more cost-effective than other recruitment methods, particularly when traditional advertising like posters, using television or radio are costly or unavailable. The snowball method reduced the need for large-scale recruitment campaigns because the participants did much of the recruitment themselves.

PCV-13 study had a good participant retention and snowball recruitment method partly contributed to it. Evidence shows that because participants are recruited through referrals from people they trust, such as friends and family, they may be more likely to engage and remain committed to the clinical trial[14].

The drawback to snowballing recruitment was that participants recommended the study to relatives and friends from the same location and with similar characteristics[15]. This has the potential to over-represent specific social and demographic group. This let to other participants from other location from hearing about the study. This is the first study of its kind of which we are aware. The strengths of this study are that several institutions and potential volunteer groups were observed, and many methods of recruitment were attempted. Some of the limitations are that not all of the recruitment processes and decision making can be observed and we could not explore further on the snowball method. Also, it can be difficult to ascertain the accuracy of the information that participants share with others.

We suggest that hearing about the study from a former or current volunteer may reinforce trust in the safety of the study in

Table 1. Inclusion and Exclusion Criteria.

Inclusion criteria	Exclusion criteria
• Adults aged 18–40 years • Fluent spoken and written Chichewa or English • Own a cell phone	• Previous pneumococcal vaccination • HIV-infection seropositive • Close physical contact at-risk individuals • Allergy to penicillin/amoxicillin • Acute illness • Chronic illness that may impair immune response or impair ability to comply with study procedures and safety • Pregnancy • History of drug or alcohol abuse • History of Smoking • Unable to give informed consent • Participant is positive for *Streptococcus pneumoniae* serotype 6B

Table 2a. Screening methods by sex.

	Total screened (N=299)	Snowball n (%)	Sensitization n (%)	Radio and television n (%)	Poster n (%)
Male	209	160 (76.6)	48 (23.0)	1 (0.4)	0 (0.0)
Female	90	55 (61.1)	34 (37.8)	0 (0.0)	1 (1.1)

Table 2b. Recruitment methods by sex.

	Total recruited (N=278)	Snowball n (%)	Sensitization n (%)	Radio and television n (%)	Poster n (%)
Male	195	149 (76.4)	45 (23.1)	1 (0.5)	0 (0.0)
Female	83	52 (62.7)	30 (36.1)	0 (0.0)	1 (1.2)

potential volunteers and encourage them to join. There has been evidence suggesting this in participant studies in Malawi and in Kenya. We also suggest that in future CHIM studies, it is very important to begin with community engagement activities and adopt snowballing as the main strategy.

On reflection, we consider that the tools used by the study team to inform and educate the community about the study may not have been well understood or accepted by the targeted audience and may need to be reviewed. In a different view, a malaria controlled human infection study conducted in Kenya, community engagement facilitated understanding of the study process, especially in participants with low levels of education[16].

While radio and television, done in both English and Chichewa, attracted an audience and active participation, this did not directly translate to an increased number of volunteers. The suitability of the messaging tools needs further exploration. Engaging former and current volunteers to participate in study sensitization activities may need to be considered.

Our study recruited more male than female volunteers. Possible reasons for this could be greater autonomy and decision-making power regarding consent to research participation among men than women in Malawi, although this was not formally explored in this study. Another reason could be that the information visits reached more men than women and via snowballing they predominantly enlisted their friends, mostly men too. Thirdly, if the study was viewed as risky, males may have had a greater risk tolerance. Targeting women through women church groups and community village banks might increase participation of women in CHIM studies in Malawi.

Conclusions

In conclusion, engaging current and former volunteers in novel trials like human infection studies is a possible strategy that

Table 3. Participant feedback at study exit.

Column1	Strongly agree n(%)	Agree n(%)	Neutral n(%)	Disagree n(%)	Strongly diasgree n(%)
The approach used for study recruitment was appropriate	146(68.5)	62(29.1)	5(2.3)	0	0
The information provided before consenting was appropriate	155(72.8)	58(27.2)	0	0	0
The medical questions and tests used before consenting were appropriate	142(66.7)	66(31.0)	5(2.3)	0	0
There was sufficient time to consider the study before consenting	147(69.0)	60(28.2)	5(2.3)	1(0.5)	0
The finger print scanner was acceptable way to confirm my identification	164(77.0)	46(21.6)	3(1.4)	0	0
The clinical team treated you with respect and kindness.	173(81.2)	39(18.3)	1(0.5)	0	0
The safety monitoring procedures for the study were appropriate	151(70.9)	59(27.7)	3(1.4)	0	0
The study follow up procedures did not cause inconvenience	122(57.3)	73(34.3)	14(6.6)	4(1.9)	0
The accommodation provided after inoculation was satisfactory	146(68.5)	54(25.4)	11(5.2)	2(0.9)	0
The meals provided at the accommodation were satisfactory	155(72.8)	49(23.0)	8(3.8)	1(0.5)	0
The location of the accommodation was convenient	137(64.3)	65(30.5)	8(3.8)	3(1.4)	0
The compensation provided by the study was appropriate	99(46.5)	72(33.8)	34(16.0)	5(2.3)	3(1.4)
I would recommend participant in this study to a friend	142(66.7)	63(29.6)	7(3.3)	1(0.5)	0

can encourage community acceptance and participation in settings like Malawi. It is very important that researchers must consider snowballing limitations carefully and take steps to mitigate them such as employing strategies for a diversified sample. More work needs to be done to explore how increased participation from women can be ensured.

Data availability

Underlying data

Figshare: Underlying data for 'Recruitment methods and participant experiences in the first controlled human infection study in Blantyre, Malawi.' https://doi.org/10.6084/m9.figshare.22567513.v1

This project contains the following underlying data:

- Data file 1. (The attached file contains the following information: VisitA_month: Date of information visit, VisitB_date: Screening visit, Age, Sex, Recruitment and, Vaccination status, Study completion status, Column I to U represents Likert scale of participant experiences with summary of findings in Table 3 in this article.)

Extended data

Figshare: Extended data for 'Recruitment methods and participant experiences in the first controlled human infection study in Blantyre, Malawi.' https://doi.org/10.6084/m9.figshare.22567513.v1

This project contains the following extended data:

- Data file 1 (Description of data.)

Software availability

Data was collected electronically using Open Data Kit (ODK) on an Android device. To complement ODK functionality, an additional in-house application was used called ODK lookup updater application, which helped to enforce data validation at the point of data collection.

Data was validated at the point of entry using field restrictions embedded within the form to avoid collection of invalid and out of range data for numeric fields. Skip logics were also

built into the form to eliminate collection of irrelevant or redundant data. Form level calculations were used to evaluate and validate data like eligibility criteria to avoid human error in decision making for such critical study decisions. And finally, an inhouse application was used for cross form verification of previously collected critical participant information.

Acknowledgements

We would like to thank all our participants and the Malawi Accelerated Research in Vaccines, Experimental and Laboratory Systems (MARVELS) consortium consisting of:

Laboratory team: Tarsizio Chikaonda, Christopher Mkandawire, Simon Sichone, Raphael Kamng'ona, Mphatso Mayuni, Percy Mwenechanya, Godwin Tembo, Kondwani Jambo and Bridgette Galafa, Faith Thole; **Field Research Assistant**: Tina Harawa; **Data team**: Joel Gondwe, **Pharmacy:** John Ndaferankhande, Aggie Zambasa, Bright Lipenga. **Collaborators**: Markus Gmeiner, Mike Parker, Vella Kaudzu, Andrew Pollard, Rob Heyderman, Jason Hinds, Mark Alderson, Chris Bailey, Marien de Jonge, Robert Kneller, Jeremy Brown, Peter Banda, David Goldblatt, Richard Malley, Jeff Weiser, Jonathon Grigg, Henry Mwandumba and Debby Bogaert.

Authorship: The two first authors (Edna Nsomba and Anthony E Chirwa) contributed equally to this paper. The two senior authors (Stephen B Gordon and Dingase Dula) also contributed equally.

References

1. Etefia E, Inyang-Etoh P: **Malaria vaccine development: challenges and prospects.** *Medical and Pharmaceutical Journal.* 2023; **2**(1): 28–42.
Publisher Full Text
2. Kapulu MC, Kimani D, Njuguna P, *et al.*: **Controlled Human Malaria Infection (CHMI) outcomes in Kenyan adults is associated with prior history of malaria exposure and anti-schizont antibody response.** *BMC Infect Dis.* 2022; **22**(1): 86.
PubMed Abstract | Publisher Full Text | Free Full Text
3. Morton B, Burr S, Chikaonda T, *et al.*: **A feasibility study of controlled human infection with *Streptococcus pneumoniae* in Malawi.** *EBioMedicine.* 2021; **72**: 103579.
PubMed Abstract | Publisher Full Text | Free Full Text
4. Hodgson SH, Juma E, Salim A, *et al.*: **Lessons learnt from the first controlled human malaria infection study conducted in Nairobi, Kenya.** *Malar J.* 2015; **14**: 182.
PubMed Abstract | Publisher Full Text | Free Full Text
5. Egesa M, Ssali A, Tumwesige E, *et al.*: **Ethical and practical considerations arising from community consultation on implementing controlled human infection studies using *Schistosoma mansoni* in Uganda.** *Glob Bioeth.* 2022; **33**(1): 78–102.
PubMed Abstract | Publisher Full Text | Free Full Text
6. Hodgson SH, Juma E, Salim A, *et al.*: **Lessons learnt from the first controlled human malaria infection study conducted in Nairobi, Kenya.** *Malar J.* 2015; **14**: 182.
PubMed Abstract | Publisher Full Text | Free Full Text
7. Chilengi R, Simuyandi M, Chibuye M, *et al.*: **A pilot study on use of live attenuated rotavirus vaccine (Rotarix™) as an infection challenge model.** *Vaccine.* 2020; **38**(46): 7357–7362.
PubMed Abstract | Publisher Full Text
8. Morton B, Burr S, Jambo K, *et al.*: **A pneumococcal controlled human infection model in Malawi: transfer of an established pneumococcal carriage model from Liverpool, UK to Blantyre, Malawi – A feasibility study [version 2; peer review: 2 approved].** *Wellcome Open Res.* 2020; **5**: 25.
PubMed Abstract | Publisher Full Text | Free Full Text
9. Gordon SB, Rylance J, Luck A, *et al.*: **A framework for Controlled Human Infection Model (CHIM) studies in Malawi: report of a Wellcome Trust workshop on CHIM in Low Income Countries held in Blantyre, Malawi [version 1; peer review: 2 approved].** *Wellcome Open Res.* 2017; **2**: 70.
PubMed Abstract | Publisher Full Text | Free Full Text
10. Doherty K, Dula D, Chirwa A, *et al.*: **Experimental pneumococcal carriage in people living with HIV in Malawi: the first controlled human infection model in a key at-risk population [version 1; peer review: 3 approved].** *Wellcome Open Res.* 2024; **9**: 2.
PubMed Abstract | Publisher Full Text | Free Full Text
11. Kapumba BM, Jambo K, Rylance J, *et al.*: **Stakeholder views on the acceptability of human infection studies in Malawi.** *BMC Med Ethics.* 2020; **21**(1): 14.
PubMed Abstract | Publisher Full Text | Free Full Text
12. Toto NM, Gooding K, Kapumba BM, *et al.*: **At first, I was very afraid"-a qualitative description of participants' views and experiences in the first Human Infection Study in Malawi [version 2; peer review: 2 approved].** *Wellcome Open Res.* 2021; **6**: 89.
PubMed Abstract | Publisher Full Text | Free Full Text
13. Valerio MA, Rodriguez N, Winkler P, *et al.*: **Comparing two sampling methods to engage hard-to-reach communities in research priority setting.** *BMC Med Res Methodol.* 2016; **16**: 146.
PubMed Abstract | Publisher Full Text | Free Full Text
14. Jong ST, Stevenson R, Winpenny EM, *et al.*: **Recruitment and retention into longitudinal health research from an adolescent perspective: a qualitative study.** *BMC Med Res Methodol.* 2023; **23**(1): 16.
PubMed Abstract | Publisher Full Text | Free Full Text
15. Heckathorn DD: **Comment: Snowball versus respondent-driven sampling.** *Sociol Methodol.* 2011; **41**(1): 355–366.
PubMed Abstract | Publisher Full Text | Free Full Text
16. Vaswani V, Saxena A, Shah SK, *et al.*: **Informed consent for controlled human infection studies in low- and middle-income countries: ethical challenges and proposed solutions.** *Bioethics.* 2020; **34**(8): 809–818.
PubMed Abstract | Publisher Full Text | Free Full Text

Open Peer Review

Current Peer Review Status: ? ✓ ?

Version 2

Reviewer Report 04 April 2025

https://doi.org/10.21956/wellcomeopenres.26260.r120636

?

Patrick Harris
UQ Centre for Clinical Research, University of Queensland, Queensland, Australia

Human challenge studies are a relatively new concept in the African context, yet understanding the effect of new interventions in these populations is important. Hence this study adds to our understanding of how these studies can be effectively delivered in this setting. The study presents meaningful data and appears to have been well conducted . The data are available and the conclusions are justified - although the results are largely descriptive. The finding that snowballing was the moist efficient strategy for enrolment is notable.

Specific comment:

- The term "sensitization" is used throughout, but the exact process is not described in detail. Some additional information on how this was done would be useful

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: AMR research, trials, genomics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 02 April 2025

https://doi.org/10.21956/wellcomeopenres.26260.r119636

?

Dorcas M Kamuya
Kenya Medical Research Institute (KEMRI) - Wellcome Trust Research Programme, Kilifi, Kenya

Recruitment strategies for research participants in clinical trials and in controlled human infection studies/models (CHIM) in particular is an area of great interest in bioethics and engagement discourses. A description of effective strategies for controlled human infection studies would provide much needed information for sites that are considering these types of studies, and highlights the important contribution that this publication would make. However, there are some major revisions that would need to be addressed if the work described is to meet the criteria for quality and rigorous qualitative research

1. **Background sectio**n: whilst it provides good information about the 1sy pneumococcal CHIM study in Malawi and previous work, it does not at all highlight the issue of recruitment strategies in CHIM (or even in clinical trials or research studies), and why that is an area of interest for the current research. It is thus not clear why recruitment is a topic of interest in this manuscript.

2. **Methods**: Following above, the entire methods section is about the methods that were used in the main pneumococcal CHIM study.; only one paragraph/sentence mentions that the qualitative study recruited participants from the main study. This methods section should be about the qualitative study methods and analysis approach and should include information such as a) the recruitment methods that was used in the qualitative used b) justification for the respondents that were recruited, for example, why did the qualitative study also not include those that participated in sensitization meetings but did not participate in the CHMI study ie why did it limit itself to only those that participated in the CHMI study? c) why were exit interviews an appropriate method for the qualitative research? what informed the choice of this method? and what is its limitation d) Likert scale questions were used, why was this chosen yet there is criticism of using likert scale questions especially in LMICs e) what approach (in person? telephone interviews?) and who collected the data? f) how was data quality counterchecked?

3. Data analysis: How was the qualitative data analysed? what variables were considered and what informed the selection of those variables?

4. *NB: Qualitative research requires transparency about the entire research (which assists in assessing the quality/rigour of the research and of the reported results), but the current manuscript seems not to address many of these (please check the criteria for reporting qualitative research that is included in guidance of most journals including WellcomeOpen)

5. Reflexivity and positionality of the researchers is missing - this is part of being transparent and includes explicitly descriptions of any researcher biases and how these were addressed across the qualitative research cycle.

6. Since description provided in the methods section relate to the recruitment methods of the main CHIM study(and not of the qualitative research), I suggest that all that information is moved to the results section. The methods section should then be a description of the qualitative research methods (as alluded in 2 above)

7. **Ethics review** - the approval described in this research seems to be that of the main CHMI study, what about the qualitative research of it? Kindly clarify and also describe how consent was sought for the qualitative research.

8: **Results section:** Here present the methods that were used to recruit participants in the main study and information about what informed the choice. Given that several strategies, including expensive one such as radio were used, why was a plethora of strategies considered?

9. Were there participants who reported participating in several recruitment strategies? how was this handled in analysis?

10. The participant feedback at exit seems to be highly positive, is there a reflection of a) how social desirability might have influenced responses and link back to researcher positionality b) whether this method of collecting data was the most appropriate -ie a critique of the method since on other settings narratives have been used to describe experiences of participating in CHMI studies

11. **Discussion**: it would be important to discuss the findings with references to some of the ethical and social science theories e.g. snowballing and social capital, trust, network analysis and what informs us about what was going on etc.

12. Also some information on what sort of information was shared by those that recruited others through snowballing - for example were some over-emphasize on the benefits and not the risks of participation?

13. A reflection of what '*effective recruitment strategy*' means would be very helpful. Meeting target numbers is not the same as effective recruitment, particularly if people do not know that they are in researcher/trial and what is involved in the research.

14: The *ethics of using current and former research participants to recruit in studies* - also need to be articulated, both the positive and the negative implications and how these can be balanced.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Bioethics, ethical issues in Human Infection studies, community engagement

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 31 March 2025

https://doi.org/10.21956/wellcomeopenres.26260.r119635

Oren Ziv
Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel

The authors have made the necessary changes to the paper. I have no more comments. Good work.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: otolaryngology, epidimiology, PCV's

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 12 June 2024

https://doi.org/10.21956/wellcomeopenres.21354.r82654

?

Oren Ziv
Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel

The article discusses Human Infection Studies (HIS) in low-income countries(LICs), focusing on their implementation in Malawi, Kenya, Uganda, and Tanzania. HIS involve introducing a pathogen to a healthy individual under controlled conditions to study disease and develop treatments. The paper details recruitment methods for a pneumococcal HIS in Malawi, including sensitization meetings, snowball recruitment, and media campaigns. It highlights the success of snowball recruitment and identifies challenges such as the need for better-targeted messaging and increased female participation. Ethical approvals and participant feedback are also addressed, with most participants having a positive experience and recommending the study to others.

Strengths
1. Comprehensive Recruitment Methods.
2. Feedback: High levels of participant satisfaction and willingness to recommend the study

suggest good management and ethical conduct.
3. Pioneering Study in Malawi: This study sets a precedent for conducting HIS in Malawi, contributing valuable insights for future research in LICs.
Weaknesses
1. Limited numbers of participants.
2. The study recruited significantly more males than females, which can be a confunder.
Overall, it is a very nice paper, written well, and designed well.
Minor revisions to be made:
1. Need to add a section that should address the study's limitations (number of participants, time extra).
2. In the discussion there need to be a compression of the results in this study to other countries in which similar studies were conducted.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: otolaryngology, epidimiology, PCV's

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 12 June 2024

https://doi.org/10.21956/wellcomeopenres.21354.r82660

? **Dorcas M Kamuya**
Kenya Medical Research Institute (KEMRI) - Wellcome Trust Research Programme, Kilifi, Kenya

Controlled Human Infection studies are increasingly being introduced in LMICs including in Africa. They raise a plethora of social, ethical, scientific and cultural issues. A growing body of literature is helping to unpack these issues; the paper therefore feeds into this body of work. The area of recruitment strategies has perhaps not been well addressed, this paper helps fill this gap. There are a few areas I raise below that could strengthen the paper.
1. References are few, yet there is a body of work on this area across Africa, that can be drawn up on.
2. First paragraph 2nd sentence - could you provide some examples and references of how HIS studies have led to prevention and treatment of infectious diseases - these outcomes seems not to be directly related to CHIM, but I could be wrong
3. 2nd paragraph - Malawi, Kenya etc - also include what contribution such CHIM studies conducted in African countries have made (as you did in the previous sentence for HIC).
4. Objectives these are not clearly defined. what was the objective of the present study (ie not the objective of this paper). Also, could add the overall research question of the study.
5. add information on the study site and within that include the description of the CHIM. Please also note that the section on trial design is not really part of qualitive method and would fit well under the study site description.
5. Under methods - include information on how the data for this paper were collected, analysed etc. The methods that are currently described are those of the recruitment strategies - these should be provided either under results section (where you then start by describing the different recruitment strategies used for the CHIMN study) or - depending on how the info is framed - can be described under study site - where info about the CHIM study would be included. Also would be great to include information in why the CHIM study targeted University students and not the general population
6. It is very interesting that the snowballing was by those that attended the information giving sessions - where any information materials given to them to share within the populations they come from? In case not, was there an attempt to find out what information was shared (in our setting in Kenya, we realised that most info shared at that stage were about the health benefits, the compensation amounts and the risks of the study, with a greater emphasis on financial compensation - did similar issues also arise in your setting?). This is really important as later under results, it is reported that 71.9% of those that were screened 'indicated that they were motivated to join through snowball recruitment'. What information were they given to motivate them to join the study? also what does motivation in this instance mean - noting also that it has been used under sensitization as well? is it motivation or encouraged?
7. The discussion section of the paper needs strengthening (major revisions). It would be important to situate the recruitment strategies within wider debates of recruitment in clinical trials (if indeed none of the strategies have been discussed within CHIM studies). Interrogate the strategies - their strengths and weaknesses, and position such critique within for example some of the well known ethical principles and frameworks including for example = that of relational autonomy, networks and value of social groups (pros and cons). Also, you can be reflective here and suggest what this means for similar studies in Malawi and elsewhere.
8. As suggested in point 5 - this paper can be strengthened by integrating the recruitment strategies descriptions with the quantitative information provided under results.
9. could the authors whether the ethics approvals quoted are for the main CHIM study or are for this descriptive mixed methods, alternatively could include the approval for this specific study

10. would be great to include the link to the Youtube video about CHIM. Is it translated to English for wider audience? Also include a sample consent form as an attachment.
Finally, with strengthening of this paper as suggested above, it would make an important about recruitment strategies for CHIM in LMICs, and provide a critical reflection for other sites to consider too.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Bioethics, ethical issues in Human Infection studies, community engagement

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 19 Feb 2025

Edna Nsomba

1.References are few, yet there is a body of work on this area across Africa, that can be drawn up onReferences are few, yet there is a body of work on this area across Africa, that can be drawn up on

- Thank you very much. We have reviewed more literature on this and what we are finding is this there are not many CHIM studies except for the two added.Please refer to the two research papers on Malaria CHIM study in Kenya and the first at risk population CHIM study conducted in Malawi have been added on page 7.If you have any references in mind, we will be happy to add them.

2. First paragraph 2nd sentence - could you provide some examples and references of how HIS studies have led to prevention and treatment of infectious diseases - these outcomes

seems not to be directly related to CHIM, but I could be wrong

- A reference on how HIS studies have led to prevention and treatment of infectious diseases has been added on page 7.

3. 2nd paragraph - Malawi, Kenya etc - also include what contribution such CHIM studies conducted in African countries have made (as you did in the previous sentence for HIC).

- Please refer to references on page 6

4. Objectives these are not clearly defined. what was the objective of the present study (i.e. not the objective of this paper). Also, could add the overall research question of the study.

- We acknowledge this.Please refer to page 8 of the manuscript.

5. add information on the study site and within that include the description of the CHIM. Please also note that the section on trial design is not really part of qualitive method and would fit well under the study site description.

- Thank you for pointing this out.The section has been revised. Please refer to a description made on page 8.

6. Under methods - include information on how the data for this paper were collected, analysed etc. The methods that are currently described are those of the recruitment strategies - these should be provided either under results section (where you then start by describing the different recruitment strategies used for the CHIM study) or - depending on how the info is framed - can be described under study site - where info about the CHIM study would be included. Also would be great to include information in why the CHIM study targeted University students and not the general population

- Thank you for pointing this out.Please refer to page 8 on data collection and analysis.

7. It is very interesting that the snowballing was by those that attended the information giving sessions - where any information materials given to them to share within the populations they come from? In case not, was there an attempt to find out what information was shared (in our setting in Kenya, we realised that most info shared at that stage were about the health benefits, the compensation amounts and the risks of the study, with a greater emphasis on financial compensation - did similar issues also arise in your setting?). This is really important as later under results, it is reported that 71.9% of those that were screened 'indicated that they were motivated to join through snowball recruitment'. What information were they given to motivate them to join the study? also what does motivation in this instance mean - noting also that it has been used under sensitization as well? is it motivation or encouraged?

- During our community engagement sessions in colleges, we distributed participants information sheets (PIS) in both English and local language (Chichewa). Potential participants could also share these PIS to their families and friends to read. We would like to acknowledge that we did not find out from the participants what kind of information they got from their colleagues. This has been included in the discussion as a limitation.

8. The discussion section of the paper needs strengthening (major revisions). It would be important to situate the recruitment strategies within wider debates of recruitment in clinical trials (if indeed none of the strategies have been discussed within CHIM studies). Interrogate the strategies - their strengths and weaknesses, and position such critique within for example some of the well known ethical principles and frameworks including for example = that of relational autonomy, networks and value of social groups (pros and cons). Also, you can be reflective here and suggest what this means for similar studies in Malawi

and elsewhere.

- This is acknowledged and we have done the revisions.Please refer to page 13 for a revised discussion version.

9.As suggested in point 5 - this paper can be strengthened by integrating the recruitment strategies descriptions with the quantitative information provided under results.

- This is noted. Please refer to first paragraph of the discussion section for an addition of the quantitative information.

10.could the authors whether the ethics approvals quoted are for the main CHIM study or are for this descriptive mixed methods, alternatively could include the approval for this specific study.

- The approvals quoted are for the main CHIM study because this study did not have a separate protocol.

11. would be great to include the link to the Youtube video about CHIM. Is it translated to English for wider audience? Also include a sample consent form as an attachment.
Finally, with strengthening of this paper as suggested above, it would make an important about recruitment strategies for CHIM in LMICs, and provide a critical reflection for other sites to consider too.

- The link to the tube video and a sample consent form are attached.The you tube video is in English and currently translation to Chichewa (our local language) is underway through our science and communication department.

Competing Interests: No competing interests were disclosed.