OPEN LETTER

Considerations in planning a controlled human infection model in at-risk groups in sub-Saharan Africa: the case for pneumococcal challenge in people living with HIV in Malawi and a report of stakeholder consultation

[version 1; peer review: 1 approved, 5 approved with reservations]

Klara Doherty[1,2*], A Chirwa[2*], Shalom Songolo[2], Alice Kusakala[2], E Nsomba[2], Pemphero Liwonde[2], Daniela Ferreira[1,3], Henry Mwandumba[1,2], K Jambo[1,2], S Gordon[1,2]

[1]Liverpool School of Tropical Medicine Department of Clinical Sciences, Liverpool, England, UK
[2]Malawi-Liverpool Wellcome programme, Blantyre, Malawi
[3]University of Oxford Oxford Vaccine Group, Oxford, England, UK

[*] Equal contributors

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Abstract

Controlled human infection models offer a unique opportunity to understand infectious disease pathogenesis and have accelerated vaccine development and evaluations in malaria and typhoid. One major limitation of most CHIMs is that they are typically conducted in healthy young adults who are generally the population least affected by infectious disease, and who exhibit distinct disease profiles to more at-risk populations such as people living with HIV, young children, and older adults. However, the added value of studying these populations with high relevance is only desirable if it can be done safely, robustly and acceptably. We present a framework to guide the conduct of a controlled human infection model in people living with HIV using a case-example of an experimental human pneumococcal carriage model in a setting of high disease-burden and transmission.

Plain language summary

Controlled human infection models (CHIMs) are a research method in which an infection is safely introduced into volunteer participants to better in order to understand the infection and test vaccines against it. These models are more efficient than traditional clinical studies because they require fewer participants. Most CHIMs have focused on

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1. **James D Kellner**, University of Calgary, Calgary, Canada
2. **Emmanuella Driciru**, Uganda Virus Research Institute, Entebbe, Uganda
MRC/UVRI and LSHTM Uganda Research Unit (Ringgold ID: 47968), Entebbe, Uganda
3. **Paul Kaye**, Hull York Medical School, University of York, Heslington, UK
Hull York Medical School (Ringgold ID: 12195), University of York, York, UK
4. **Stephen Lockhart**, Hurst Grange Associates, Berkshire, UK

healthy young adults, who are not the ones most affected by infectious diseases and have a distinct infection profile and vaccine response compared to population with a greater burden of infectious disease such as older adults and people living with HIV. Recently researchers have started to include these high-burden populations in CHIMs but safety and ethics are critical considerations before embarking on such studies. We propose a framework for safely and ethically conducting CHIMs in people living with HIV in order to advance research in this key population. We use a case example of a CHIM of pneumococcal carriage in the nose of people living with HIV in Malawi.

Keywords
pneumococcal infections, HIV infections, vaccines, Malawi, Streptococcus pneumoniae

5. **Diane Gbesemete**, University of Southampton, Southampton, UK
6. **Andrew Gorringe**, UK Health Security Agency, London, UK

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

Corresponding author: Klara Doherty (kdoherty@mlw.mw)

Author roles: Doherty K: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Chirwa A**: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Songolo S**: Data Curation, Writing – Review & Editing; **Kusakala A**: Data Curation, Writing – Review & Editing; **Nsomba E**: Data Curation, Writing – Review & Editing; **Liwonde P**: Data Curation, Writing – Review & Editing; **Ferreira D**: Conceptualization, Supervision, Writing – Review & Editing; **Mwandumba H**: Supervision, Writing – Review & Editing; **Jambo K**: Conceptualization, Supervision, Writing – Review & Editing; **Gordon S**: Conceptualization, Funding Acquisition, Resources, Supervision, Writing – Review & Editing

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Introduction

Controlled human infection models (CHIMs) involve the deliberate introduction of an infectious agent to volunteer participants in order to study infectious disease pathogenesis or test a therapeutic intervention. In recent years CHIMs established in high-income, low endemic regions have been transferred to endemic settings to study the diseases in the populations most affected[1–4]. A malaria CHIM established in Oxford and Maryland has been transferred to malaria endemic settings in Kenya, Tanzania, and Gabon, to study the disease in those with prior immunity and to make the findings relevant to those most affected[4–6]. Similarly, an experimental human pneumococcal carriage model (EHPC) established in Liverpool has been transferred to Malawi where post-vaccine persistence of pneumococcal carriage has hindered vaccine effectiveness[7,8].

CHIMs have typically been conducted in healthy, young adult volunteers. These are generally the population least affected by infectious diseases, and so efforts are being made to increase the relevance of CHIM models. For example, the UK EHPC model has been used to study pneumococcal carriage in older adults, which has indeed demonstrated a distinct infectious disease process compared to young adults[9]. The next step for CHIMs in sub-Saharan Africa should also focus on more at-risk populations. Careful consideration of safety, public perception, and justification of the research is crucial. In Malawi, people living with HIV (PLHIV) are a key population to study pneumococcal disease and carriage and an EHPC in PLHIV in Malawi is now ongoing[10].

Our review of the published literature demonstrates no other CHIM in PLHIV, and no framework for CHIMs in PLHIV. Ethical frameworks and considerations for CHIMs in general have been explored, but do not address CHIMs in a potentially vulnerable population[4,11–14]. CHIMs must be justified by value of the research and must present an acceptable risk both to participants and the wider community. Here we adapt the ethical frameworks developed by Binik (2020) and Miller and Grady (2001), which evaluate CHIMs in the general population, to apply them to a potentially vulnerable population such as PLHIV[13,14]. We explore the case for undertaking a CHIM in PLHIV using the EHPC in PLHIV in Malawi as a case-example. Additionally, we present feedback from two patient and public involvement and engagement (PPIE) workshops in Malawi in which attendees were invited to share views on CHIM in PLHIV.

A considerations framework for controlled human infection models involving people living with HIV

Our proposed framework consists of four ethical questions, each encompassing several considerations (Table 1).

1. Is the scientific rationale for a controlled human infection model in PLHIV justified, and does the research have translational value for the populations affected?

PLHIV are a key population in addressing the burden of pneumococcal carriage and disease in settings with high HIV prevalence such as Malawi. PLHIV exhibit higher rates of pneumococcal carriage compared to HIV-uninfected and paradoxically exhibit even higher rates once established on antiretroviral therapy[7,15]. Pneumococcal carriage is a prerequisite for invasive pneumococcal disease (IPD) and despite the positive impact of antiretroviral therapy in reducing risk of IPD,

Table 1. Framework for planning a controlled human infection model in an at-risk population such as PLHIV.

Ethical question	Considerations
1. Is the scientific rationale justified and does the research have translational value for the populations affected?	• Justification of the research question in the at -risk population • Adequacy of the CHIM study design • Justification of conducting the study in a low-income setting
2. Are the risks and burden of the research acceptable and can they be minimised?	• Risk and burden to individual participant • Risk and burden to community • Risk and burden to local infrastructure
3. What are the specific vulnerabilities of the target population, and should this vulnerable group be enrolled?	• Physiological vulnerability • Socio-economic vulnerability (e.g. financial hardship) • Logistical vulnerability (e.g. frequent medical appointments)
4. What is the perception from local community stakeholders and participants of controlled human infection models in the at-risk population?	• Perception of risks • Perception of benefits • Cultural factors

PLHIV remain at increased risk compared to HIV-uninfected individuals[16]. In addition, pneumococcal carriage is a precursor for transmission and PLHIV may be one of the drivers of ongoing transmission observed in Malawi following infant pneumococcal conjugate vaccine (PCV13) immunisation[7]. Pneumococcal carriage is also a precursor for emergence of antimicrobial resistance (AMR) and PLHIV could act as a reservoir of AMR[17].

There is currently no vaccination policy for PLHIV in sub-Saharan Africa. The pneumococcal polysaccharide vaccine (PPV23) was harmful in PLHIV in Uganda[18,19]. The 7-valent pneumococcal conjugate vaccine (PCV7) was safe and effective against vaccine-serotype disease in PLHIV in Malawi, however has limited serotype coverage and no evidence for effectiveness against carriage in PLHIV[20]. Further data on vaccine efficacy in PLHIV, immune correlates of protection from pneumococcal carriage, and dynamics of pneumococcal carriage in PLHIV are urgently required for an evidence-based vaccination strategy in sub-Saharan Africa and can be delivered by the EHPC CHIM in PLHIV.

Adequacy of study design: CHIMs allow researchers to control for factors which are often unknown in a community study including participant pre-exposure, microbiological and immunological status; dose, route, and strain of infectious inoculum; and environmental factors which may influence the pathogenesis of infection. Data exist on pneumococcal carriage in PLHIV, and how this differs from HIV-uninfected individuals, yet it is unclear whether this is a result of differences in immunity, or environmental and demographic factors[21]. In addition, CHIMs offer the unique opportunity for cost-effective vaccine evaluations, which require fewer participants and a shorter study-duration than a prospective community-based study. CHIMs can efficiently up- and down-select vaccine candidates, as described on the malaria CHIM[22].

Justification of study setting in a low-income country: Conducting CHIM studies requires good clinical services, microbiology, and governance structures to allow them to be conducted safely and to acceptable standards[12]. The World Health Organisation (WHO) released guidance highlighting the value of CHIMs for developing infrastructure and research capacity, where it meets local health priorities[23]. The setting in Malawi is essential to answer the pertinent questions on pneumococcal carriage and vaccine efficacy in PLHIV in sub-Saharan Africa. Distinct pneumococcal vaccine efficacy has been demonstrated between Malawi and the UK[8]. PLHIV in the UK can be expected to be different from Malawi or other low-income settings in terms of immune profile and vaccine response, as they are exposed to a higher force of infection than their UK counterparts and benefit from herd and direct immunity from PCV[24].

2. Are the risks and burden of the research acceptable and can they be minimised?

Participant safety is paramount when recruiting a potentially vulnerable group like PLHIV. This is important for study integrity, and participant and public trust in CHIMs. Binik (2020) advocates distinguishing study risks and burdens[13]. CHIM studies may demand significant burden on participants, such as isolation and frequent sampling, even if risk of serious harm is minimal[13]. CHIM studies must also consider risks and burdens to the local community and local infrastructure.

Risk and burden to individual participant – Individual risk may be evaluated by striving for a minimal risk study i.e. risk is no greater than those presented in daily life[13]. Pneumococcal carriage is ubiquitous in PLHIV in Malawi, and thus may be considered a risk presented in daily life for this population. At any one time, 26% to 52% of PLHIV will have natural pneumococcal carriage, and 99% of PLHIV will experience at least one pneumococcal carriage event over six to ten months[7,15,25]. Most of these events do not result in IPD and experimental carriage is expected to be a similar benign event[10]. However, it is prudent to consider experimental pneumococcal inoculation more than minimal risk to ensure comprehensive safety monitoring and risk mitigation is incorporated into the study design. This can include isolating or partially isolating participants in study accommodation, regular telephone or in-person contact with participants, careful participant selection, careful inoculum selection and preparation, and comprehensive safety information instruction.

The EHPC in Malawi has recruited only immune-reconstituted and virally-suppressed PLHIV, as risk of IPD closely correlates with CD4 T-cell count[10,26]. Selection of a relatively benign pneumococcal serotype (6B) which rarely causes disease and employing a slow dose-escalation also mitigates risk[27]. The EHPC model in Malawi houses inoculated participants in single-occupancy study accommodation and includes frequent telephone contact with participants between study-visits[10]. Paradoxically, many safety provisions increase participant burden as study accommodation may take participants away from earning and family responsibilities. Evaluating the burden of the research requires input from the volunteers themselves[14]. The EHPC in Liverpool and Malawi has been evaluated in terms of acceptability of sampling and study design to participants, but this must be an ongoing exercise for a CHIM in a vulnerable participant group[17,28–30].

Risk and burden to community – Risk of onward transmission exists and is particularly pertinent in PLHIV who exhibit more pneumococcal shedding than HIV-uninfected adults[17]. Mitigation of these risks mirror those for participants and includes participant selection to exclude those in contact with vulnerable patient groups, study accommodation to limit community contact, and study clinical care extending to household contacts of participants. However, considering the high natural carriage prevalence in PLHIV, it is unlikely that experimental carriage in PLHIV provides a risk to the community above and beyond natural carriage.

Risk and burden to local infrastructure – Risk to local infrastructure may include burden on health-care facilities with participants attending with inoculum-associated symptoms, and burden on local economy with participants not attending work or unable to fulfil family responsibilities. The EHPC in

Malawi provides a robust and experienced clinical team to manage any symptoms before the health-care system is burdened. Study follow-up visits have flexibility to allow participants to schedule visits around other commitments[10].

3. What are the specific vulnerabilities of the target population and should this vulnerable group be enrolled?

Vulnerabilities in PLHIV are physiological, socioeconomic and logistical. The EHPC in PLHIV in Malawi has been designed to provide PLHIV with population-specific information prior to participation, to account for differences in health-literacy and understanding of infection and disease[14]. PLHIV are under regular medical care and avoiding interference with this due to frequent study visits is essential, as well as mitigating against accidental serostatus disclosure in the study design. Although serious illness because of experimental pneumococcal challenge is unlikely, PLHIV may be living with undiagnosed complication which are unveiled during study recruitment and warrant further medical assessment which may not be easily accessible.

Furthermore, PLHIV in Malawi experience more financial hardship than the HIV-uninfected population which could lead to undue influence (by remuneration)[21]. Equally, selective non-recruitment of PLHIV because of financial hardship might be deemed unethical as financial discrimination. Financial reimbursement on the EHPC in Malawi has been determined by local guidelines on compensation, regardless of participants' serostatus or vulnerability[31]. Exclusion on the basis of perceived specific vulnerabilities may be considered paternalistic, and prevents PLHIV exercising their autonomy in the context of fully informed consent[13]. Key to this process is active consultation and engagement with the community advisory groups and the local ethics committees.

4. What is the perception from local community stakeholders and participants of controlled human infection models in the at-risk population?

Public and participant perception is a key consideration for CHIM studies, and community consultation and stakeholder engagement prior to, and during implementation is vital to permit CHIMs to be conducted and for enhancing the scientific and ethical quality of the studies. A step-wise approach to community consultation has been described in Kenya and Malawi[4,28,30]. PPIE provides a framework for CHIMs to implement safe, ethical, and acceptable studies. For example, the use of passive recruitment techniques in the EHPC in PLHIV was implemented as direct solicitation was identified by stakeholders to potentially risk unduly pressuring individuals to participate[10,30]. Although this approach also has potential to introduce bias, hence reducing the generalisability of the data.

The perception of CHIM in PLHIV from local community stakeholders and CHIM participants was explored in Malawi in two workshops in October 2022 and January 2023. A total of 37 attendees included PLHIV, healthcare providers, community leaders, community advisory groups, former pneumococcal CHIM participants, and ethical review board members. The perception of CHIM in PLHIV reported by attendees reflect the four ethical questions presented in our framework (Table 1). The scientific rationale or value of the research was framed in terms of reducing the burden of respiratory illness which would "reduce much workload on [the] health sector" and in terms of generating locally relevant data to inform local vaccine programmes:

"Why do we have to wait for results from studies done elsewhere? This is a welcome development"

Attendees at the workshop focused on individual risk and risk mitigation, rather than community or local infrastructure risk, and focused on risk rather than burden. Attendees largely supported acceptability of CHIM in PLHIV if risk to individual participants was mitigated, for example by recruiting participants who were considered stable and well:

"I agree that this research can be done in people who are infected with HIV but [they] must be stable"

"I will say two ways, yes and no. Yes, if the study will focus on PLHIV with good HIV control and no if the patient is severely sick"

Acceptability was also contingent on mitigating risk with robust safety procedures so "if a person gets sick, they can meet [the research team] easily" and "there should be a plan so that if there is any problem, the person can get help quickly". Attendees highlighted that these safety procedures should be clearly understood by participants:

"My opinion is that these people should be well protected and we should give them a chance to ask questions"

The need to maintain safety even when a participant withdraws consent was mentioned so *"if a person wants to quit they should quit safely"*. Although the risk and burden on local infrastructure and community was not directly raised by attendees, robust safety procedures necessary for individual participant safety was recognised as a mitigation against burdening local health infrastructure.

The specific vulnerabilities of PLHIV identified by attendees included differences in health literacy which would influence obtaining informed consent. The need to provide sufficient information to PLHIV participants was identified:

"Let's give full information so that if they want to join the study they know what it involves"

"Sit down with them and enlighten them thoroughly so that they understand"

Finally, the central role of community consultation for a successful CHIM in PLHIV was repeatedly mentioned by

attendees at the PPIE workshops in Malawi. Attendees highlighted the need to prevent unfounded myths and fears spreading in the community:

> *"If people are not told, they will not understand and we see them as afraid because they have not been taught [...]"*

> *"The study seems safe but there is need to involve the community throughout the study to clear out myths"*

The need to be sensitive to potential vaccine hesitancy was raised:

> *"…it is important is that people are educated well, because we already have challenges in the communities to convince them to have some of these vaccines"*

The workshop recommended continuous community engagement prior to, and during the study to clarify myths and build a community strategy for future challenge models.

Conclusions

The case for studying experimental pneumococcal carriage in PLHIV in Malawi is strong as there is a need to address the ongoing burden in PLHIV and the high post-vaccine residual pneumococcal carriage in Malawi. Like any human subject study, there must be a careful consideration of the potential benefits of the study, off set against the potential risks and burdens. Initial stakeholder consultation demonstrates support for CHIMs in PLHIV in Malawi as long as individual risk is mitigated against and community consultation and education is prioritised. The EHPC in PLHIV in Malawi demonstrates that this can be done safely and acceptably however ongoing community engagement and consultation is essential.

List of abbreviations

AMR = antimicrobial resistance

CHIM = Controlled Human Infection Model

EHPC = Experimental Human Pneumococcal Carriage model

IPD = Invasive pneumococcal disease

PCV7 = 7-valent pneumococcal conjugate vaccine

PCV13 = 13-valent pneumococcal conjugate vaccine

PPV23 = pneumococcal polysaccharide vaccine

PLHIV = people living with HIV

PPIE = patient and public involvement and engagement

Ethics and consent statement

Ethical approval was not required to conduct the stakeholder consultation meeting. This was part of community engagement conducted by the Malawi-Liverpool Wellcome programme and the MARVELS consortium. Verbal consent was sought to engage the PPIE participants and record the discussion.

Data availability

No data are associated with this article

Author contributions

KD, AC, SG, KJ, DF conceived the project. AC collected the stakeholder data. KD reviewed the literature and developed the framework. AC, SS, AK, EN, PL curated the data. AC and KD analysed the data and wrote the first draft of the manuscript. SG, KJ, DF, HM supervised the project. All authors reviewed and edited the final manuscript.

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We are grateful to all attendees at the PPIE workshops in Malawi.

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Open Peer Review

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Version 1

Reviewer Report 11 October 2025

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✓ **Andrew Gorringe**
UK Health Security Agency, London, UK

This letter describes an ethical framework for conducting a CHIM in a population living with HIV in Malawi. The letter describes the various areas that should be considered in appropriate detail.
I have had the opportunity to read the four previous reviews provided and agree with many of the points raised and see no reason to repeat these unnecessarily.
Specific comments

Abstract para 2 - "to better in order to" use one of these phrases. "...compared to populations with a greater..."

Section 1. para 2 The authors should make clear that reference 20 does not assess whether colonisation is affected by PCV7. A sentence that describes the affect of PCV vaccination on pneumococcal carriage should be added with evidence from natural infection and CHIM.
Risk and burden to the individual participant - "striving for a minimal risk study". I think "striving" is not a helpful word. What are the factors that would make a study of minimal risk for the PLHIV participants?

Section 3 para 1 - What are "undiagnosed complications". It would be helpful if this was more specific.

Section 4. Other reviewers have commented that the quotes from stakeholders are overwhelmingly positive, and it is difficult to get a sense of how the proposed study was received. Did any stakeholders think PLHIV individuals should not be used?

Is the rationale for the Open Letter provided in sufficient detail?
Yes

Does the article adequately reference differing views and opinions?
Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Partly

Is the Open Letter written in accessible language?
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Vaccine immunology (GBS, pertussis Neisseria), correlates of protection, CHIM studies

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.

Reviewer Report 07 October 2025

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Diane Gbesemete
University of Southampton, Southampton, UK

It is increasingly recognised that controlled human infection studies can, and should, be conducted within populations of relevance where possible. However, it is imperative that such studies are designed and conducted safely, ethically, transparently, and with a high level of scientific rigour. This is especially true when the population of relevance is particularly vulnerable, whether medically or socially. This letter provides a framework of ethical questions used to facilitate consideration of such a study, using the example of a pneumococcal CHIM in people living with HIV in Malawi. The scientific and ethical justifications for this study are discussed, with evidence of appropriate public consultation and stakeholder agreement. The framework provided can be adapted to facilitate the consideration of future CHIMs in other vulnerable populations, both in LMICs and HICs. The letter is therefore very relevant to the current direction of CHIM research and is well-written, I have just a few comments.

1. Scientific rationale - justification of the research question – the case for using CHIMs within vulnerable populations in general is explained well throughout the manuscript, and the importance of investigating pneumococcal carriage in this specific population is also explained well. However, given that natural pneumococcal carriage is reported to be so prevalent among PLHIV in Malawi, it is not fully explained why a CHIM is necessary to

answer the pertinent questions in this specific population, in comparison to epidemiological studies or field trials. I have therefore answered "partly" to Q2.

2. Adequacy of study design – this section repeats much of the argument regarding the importance of CHIMs and of investigating pneumococcal colonisation in PLHIV but does not discuss specific aspects of study design. While a full summary of a specific protocol is outside of the remit of this manuscript, some specific points demonstrating how the study design would ensure participant safety, data integrity and maximal scientific and social value would be useful in this section.
3. Risks and burdens – the discussion around potential risks and burdens is comprehensive and it is good that many non-medical risks have been considered as well as the more obvious medical ones. When considering clinical safety, it is clearly mentioned that participants will be closely monitored for occurrence of pneumococcal disease, but it is not explicitly mentioned how any concerns around possible disease would be assessed or managed, i.e. with antibiotic clearance or rescue therapy.
4. Community consultation – a large proportion of the manuscript describes the public consultation and quotes from stakeholders which highlights the importance of such consultation. The section is arranged to match the order of the framework which helps to reference different viewpoints back to the framework, although it this could be made more obvious e.g. with subheadings for the different areas of discussion. It is notable that the public views expressed are all very positive and in support of the study going ahead. Were there any negative viewpoints or concerns around risks or burdens expressed?

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Yes

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: CHIMs with respiratory bacteria in the UK and Mali, public consultation / PPIE for CHIMs

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 27 September 2025

https://doi.org/10.21956/wellcomeopenres.25656.r128819

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Stephen Lockhart
Hurst Grange Associates, Berkshire, UK

This letter presents a proposed framework of things to consider when planning a controlled human infection model (CHIM) in at-risk groups in sub-Saharan Africa. As an exemplar it describes the case for a pneumococcal controlled human infection model (CHIM) in people living with HIV (PLHIV) in Malawi, including presentation of outputs from stakeholder meetings.

The authors are very experienced in this field, with a prior pneumococcal conjugate vaccine (PCV) efficacy trial in Malawi showing efficacy against invasive pneumococcal disease (IPD) in a population largely PLHIV, and an established CHIM for vaccine efficacy in pneumococcal carriage in healthy adults in UK and Malawi.

The considerations are based upon two sets of ethical frameworks for CHIM studies, although I am unable to review these as they are both behind paywalls. Nonetheless the list of considerations in Table 1 appears reasonable. Most of this paper is entirely correct and reasonable so I am just commenting where there might be room for improvement.

1. Is the scientific rationale for a controlled human infection model in PLHIV justified, and does the research have translational value for the populations affected?

It is stated that there is no evidence of PCV7 preventing carriage based on reference 20, but for clarity that trial simply did not examine carriage; there is absence of evidence not evidence of absence. Most importantly that trial showed efficacy against vaccine type IPD, which in my opinion would do more to justify use of PCVs in PLHIV (now with more extended serotype coverage) than a CHIM carriage efficacy study. There is evidence of PCV10-HiD reducing carriage in HIV infected/exposed infants in South Africa.
(Madhi 2020 https://doi.org/10.1016/j.vaccine.2020.01.062)
However, I am not aware of a trial of PCV in prevention of natural carriage in adult PLHIV. Such a trial might fill a gap in information supporting policy discussions, but I agree that it would be more complex, take longer and probably be more expensive than a CHIM efficacy study.

It is stated that “Further data on vaccine efficacy in PLHIV, immune correlates of protection from pneumococcal carriage, and dynamics of pneumococcal carriage in PLHIV are urgently required for an evidence-based vaccination strategy in sub-Saharan Africa and can be delivered by the EHPC CHIM in PLHIV”. It would be very useful to describe how the CHIM data would contribute to policy decisions.

Adequacy of study design.
The study design is not presented, though I assume it would be similar to the study design of existing pneumococcal carriage CHIM studies. This might be a useful place to describe selection criteria which would be important in ensuring participant safety. It would also be of interest to understand a bit more about the reasons for selection of a challenge strain.

Justification of study setting in a low-income country.
It is stated that "Distinct pneumococcal vaccine efficacy has been demonstrated between Malawi and the UK". I assume that this means distinct differences. In the reference quoted CHIM efficacy in Malawi was 62%, (95% CI 28–80) compared to 78%, (95% CI 48–91), which is not remarkable given that these were in two separate populations and CIs are widely overlapping. Nonetheless, the evidence for a high force of infection does suggest that people in Malawi may experience more frequent exposure leading to a different immunological profile

2. Are the risks and burden of the research acceptable and can they be minimised?
All good, no comments

3. What are the specific vulnerabilities of the target population, and should this vulnerable group be enrolled?

All good, no comments

4. What is the perception from local community stakeholders and participants of controlled human infection models in the at-risk population?

The stakeholder meetings are important and there appears to be much useful feedback. Quantitative analysis is not really feasible, and it is reasonable to present results in the format used here. Use of anecdotal statements is subject to bias so it might be useful to have more information on who led the meeting discussions and who selected quotations from the outputs, or at least a comment on potential biases in reporting.

Is the rationale for the Open Letter provided in sufficient detail?
Partly

Does the article adequately reference differing views and opinions?
Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Yes

Is the Open Letter written in accessible language?
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Not applicable

Competing Interests: I was previously employed by Pfizer and have stocks in Pfizer.

Reviewer Expertise: Vaccine clinical trials and vaccine development

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 26 September 2025

https://doi.org/10.21956/wellcomeopenres.25656.r133435

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Paul Kaye
[1] Department of Biology and Hull York Medical School, Hull York Medical School, University of York, Heslington, York, YO10 5DD, UK
[2] Hull York Medical School (Ringgold ID: 12195), University of York, York, North Yorkshire, UK

As the breadth of CHIM studies expands, notably to LMIC settings, this is a timely case study-based framework for inclusion of participants from vulnerable groups (in this case PLHIV). The article is reasonable well written, nicely structured and easily accessible to experts and those entering the field of CHIM research. It covers some new ground and is a helpful addition to the literature. However, whilst posing many questions, the paper does not always provide the answers. For example, differences in the financial circumstances of PLHIV are noted, potentially at odds with the local recommendation for a standard reimbursement rate irrespective of vulnerabilities (Ref 31). How was this difference in views reconciled? The manuscript also suffers a little from poor editing, with numerous grammatical errors. These should be corrected for final indexing.

I have a few minor comments that the authors could also consider:

Introduction – was the “feedback” from PPIE sessions formalised through a qualitative research study design or just informal? Please specify.

Table 1
Q 1
Ethical– does “population affected” refer only to participants or also to the community, given PLHIV may be highly infectious? Please clarify and expand statement as necessary

Considerations – perhaps an additional point is “what alternate strategies to answer the question have been considered”?

Q2
Considerations – maybe a little off base, but "reputational risk to CHIM research" could also be considered here

Risk and burden to individual participants

- para 2 of this section indicates participants are “housed … in single-occupancy study accommodation”. This might be read as rather punitive without some further indication of duration of confinement, facilities available etc
- para 2 also mentions the benign nature of the 6B strain. To what extent does this undermine some of the objectives of the study? A comment on how well vaccine efficacy or ICP defined using 6B translate to more virulent strains causing IPD would be helpful.

Is the rationale for the Open Letter provided in sufficient detail?
Yes

Does the article adequately reference differing views and opinions?
Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Yes

Is the Open Letter written in accessible language?
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: CHIM, leishmaniasis, NTDs, immunology

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 06 Oct 2025

Klara Doherty

We thank Reviewer 3 for their positive assessment and useful suggestions. We have included many of the suggestions which improved the quality of the manuscript, and we hope we have improved the clarity of the manuscript. As the breadth of CHIM studies expands, notably to LMIC settings, this is a timely case study-based framework for inclusion

of participants from vulnerable groups (in this case PLHIV). The article is reasonable well written, nicely structured and easily accessible to experts and those entering the field of CHIM research. It covers some new ground and is a helpful addition to the literature. However, whilst posing many questions, the paper does not always provide the answers. For example, differences in the financial circumstances of PLHIV are noted, potentially at odds with the local recommendation for a standard reimbursement rate irrespective of vulnerabilities (Ref 31). How was this difference in views reconciled? The manuscript also suffers a little from poor editing, with numerous grammatical errors. These should be corrected for final indexing.

- ***Response: We thank the reviewer for raising this important point. We have amended the final sentence of the section on financial reimbursement to make clear that resolution of these conflicts relies on ongoing consultation with community advisory groups, ethics committees, and participants. Our intention is not to completely resolve inevitable ethical tensions inherent in conducting CHIMs, but to highlight areas requiring careful consideration and give an example of how it was addressed in the Malawi EHPC. The important step in ethical considerations is to identify, consider, and discuss these issues. We have also undertaken a careful edit of the manuscript to address grammatical issues prior to indexing,***

I have a few minor comments that the authors could also consider:

Introduction – was the "feedback" from PPIE sessions formalised through a qualitative research study design or just informal? Please specify.

- ***Response: We have clarified in Section 4 that meetings followed an unstructured format but were audio-recorded, transcribed, and analysed using thematic content analysis.***

Table 1

Q 1

Ethical– does "population affected" refer only to participants or also to the community, given PLHIV may be highly infectious? Please clarify and expand statement as necessary

- ***Response: Thank you. This question has been amended to: "1. Is the scientific rationale justified and does the research have translational value for the populations affected by the disease?"***

Considerations – perhaps an additional point is "what alternate strategies to answer the question have been considered"?

- ***Response: Thank you for the suggestion. This is a very useful additional point to consider and we have amended table 1 accordingly. We have also included a discussion of alternative strategies and limitations of CHIMs under "Adequacy of study design" subheading.***

Q2

Considerations – maybe a little off base, but "reputational risk to CHIM research" could also be considered here

- ***Response: Thank for this suggestion. We agree that reputational risk is a critical factor, particularly in Malawi and other similar contexts. We have made this more explicit in Section 4 by noting that stakeholder consultation is essential to preserve the reputation of CHIM research and maintain trust.***

Risk and burden to individual participants

- para 2 of this section indicates participants are “housed … in single-occupancy study accommodation”. This might be read as rather punitive without some further indication of duration of confinement, facilities available etc
- para 2 also mentions the benign nature of the 6B strain. To what extent does this undermine some of the objectives of the study? A comment on how well vaccine efficacy or ICP defined using 6B translate to more virulent strains causing IPD would be helpful.
- ***Response: Thank you for these comments. We have clarified that participants are housed for three days post-inoculation in study accommodation. We also expanded the discussion of limitations of using a single benign serotype (6B), while noting that immune mechanisms are largely conserved across serotypes.***

Competing Interests: No competing interests were disclosed.

Reviewer Report 05 September 2025

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Emmanuella Driciru
[1] Uganda Virus Research Institute, Entebbe, Uganda
[2] Vaccines theme, MRC/UVRI and LSHTM Uganda Research Unit (Ringgold ID: 47968), Entebbe, Uganda

This manuscript clearly articulates a wide range of critical considerations in regard to CHIMs, with sufficient attention to vulnerability of the target population in question, going further to tackle financial reimbursement considerations unique to the African LMIC setting. However, I have got just a few comments (and a question out of curiosity) for the authors.

1. The author does mention considerations that underscore such a study, safety being one of these. However, considering that the target population is one that is immunologically vulnerable (immune reconstitution based on CD4+ is plausible and the “gold standard” but does not equate to a fully competent immune repertoire thus participants still carry an immune disadvantage over the existing “healthy adult subjects” participant selection criteria for CHI studies). More so this being one of the first studies in a vulnerable population in this setting, the author surely ought to look into the immunological considerations in the article as well, to ensure a wholistic approach for a safe conduct of this model. “Frame 1” does mention physiological vulnerability in the article in regard to this and the author does give a brief section on HIV, ART and pneumococcal carriage. However, for a first time study in a vulnerable, again a more in depth discussion encompassing aspects of the physiological,

immunological risks, interplay and potential AEs in the context of HIV and ART will likely be met, either potential/expected and or from previous literature.

2. The response "partly" to question two above: “Pneumococcal carriage is ubiquitous in PLHIV in Malawi” points to alternative study designs and approaches could be used to answer the same research questions this CHI model wishes to address, that do not require the additional of risk of experimental pneumococcal carriage exposure of such a vulnerable group. Thus, discussing these in the manuscript as well would provide a more balanced discussion of the alternatives versus the preferred design (CHI model) presented here.
3. The response "partly" to question five above: measures to minimize risk of IPD such as strain of challenge agent are well discussed, however, despite stating the unlikely event of IPD occurring due to the preventive measures in place, I was expecting specific attention given to how IPD will be managed beyond the general mention of “robust and experienced clinical team to manage any symptoms before health-care system is burdened” in the manuscript. What extend of symptoms are/will be managed by the team and which ones will be referred to a hospital/medical facility outside the research clinical facility conducting the study?
4. In the first paragraph of the section titled “Risk and burden to individual participants”, the author presents two of the approaches for participant monitoring as “mutually exclusive” methods in the study design in the sense that one can replace the other. Yet regular telephone calls does not replace in-person contact and vice versa. The two approaches rather complement each other.
5. Out of curiosity regarding community perspective, among the PLHIV interviewed, was there a direct expression of willingness to participate in the study besides the views captured in this manuscript that highlight a general acknowledgement of the significance of implementing this CHI model among vulnerable populations. What was their response to a question along the lines of “would you consider participating/ be willing to participate in this study if you fit eligibility criteria?” (just in case such a question was posed to them during the time they were interviewed).

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Yes

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Immunology, NTDs, Schistosomiasis CHIMs and challenge agent production, molecular biology and clinical microbiology

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 06 Oct 2025

Klara Doherty

We are grateful to reviewer 2 for the thoughtful feedback. In response, we have expanded the discussion of the limitations of CHIMs and the alternatives to a CHIM and have improved the clarity of the manuscript in a number of sections. This manuscript clearly articulates a wide range of critical considerations in regard to CHIMs, with sufficient attention to vulnerability of the target population in question, going further to tackle financial reimbursement considerations unique to the African LMIC setting. However, I have got just a few comments (and a question out of curiosity) for the authors.

1. The author does mention considerations that underscore such a study, safety being one of these. However, considering that the target population is one that is immunologically vulnerable (immune reconstitution based on CD4+ is plausible and the “gold standard” but does not equate to a fully competent immune repertoire thus participants still carry an immune disadvantage over the existing “healthy adult subjects” participant selection criteria for CHI studies). More so this being one of the first studies in a vulnerable population in this setting, the author surely ought to look into the immunological considerations in the article as well, to ensure a wholistic approach for a safe conduct of this model. “Frame 1” does mention physiological vulnerability in the article in regard to this and the author does give a brief section on HIV, ART and pneumococcal carriage. However, for a first time study in a vulnerable, again a more in depth discussion encompassing aspects of the physiological, immunological risks, interplay and potential AEs in the context of HIV and ART will likely be met, either potential/expected and or from previous literature.
    - ***Response: This is a very important point. CD4 count alone does not fully capture immune reconstitution. Indeed, an objective of the EHPC in PLHIV is to explore the complex immune mechanisms underlying high pneumococcal carriage in this population and how this differs from HIV-uninfected adults. While this Open Letter focuses on ethical considerations rather than detailed inclusion/exclusion criteria, we now clarify that CD4 count was only one of several clinical criteria. The published study protocol (referenced) includes more detail on inclusion/exclusion criteria for example the exclusion of PLHIV with recent medical attendances or prior pneumococcal disease who despite a ‘good’ CD4 count may still be immunologically vulnerable. We have revised the manuscript to reflect this.***
2. The response "partly" to question two above: “Pneumococcal carriage is ubiquitous in PLHIV in Malawi” points to alternative study designs and approaches could be used to answer the same research questions this CHI model wishes to address, that do not require the additional of risk of experimental pneumococcal carriage exposure of

such a vulnerable group. Thus, discussing these in the manuscript as well would provide a more balanced discussion of the alternatives versus the preferred design (CHI model) presented here.
    - ***Response: We agree that it is important to acknowledge alternative study designs. We have expanded the section "Adequacy of study design" to include a discussion of CHIM limitations (e.g. single-serotype challenge) and to note that community trials could be considered, while outlining challenges in defining timing of exposure. We believe this helps place the CHIM model in a balanced context.***
3. The response "partly" to question five above: measures to minimize risk of IPD such as strain of challenge agent are well discussed, however, despite stating the unlikely event of IPD occurring due to the preventive measures in place, I was expecting specific attention given to how IPD will be managed beyond the general mention of "robust and experienced clinical team to manage any symptoms before health-care system is burdened" in the manuscript. What extend of symptoms are/will be managed by the team and which ones will be referred to a hospital/medical facility outside the research clinical facility conducting the study?
    - ***Response: We appreciate this request for detail. While the full management plan is specified in the EHPC study protocol, we have clarified in the manuscript that all adverse events were managed by the clinical team on site, with predefined agreements for referral to partner hospitals in Blantyre if needed. We emphasise that the manuscript's purpose is to highlight the ethical requirement to minimise burden on local health infrastructure, while the precise operational details are study specific***
4. In the first paragraph of the section titled "Risk and burden to individual participants", the author presents two of the approaches for participant monitoring as "mutually exclusive" methods in the study design in the sense that one can replace the other. Yet regular telephone calls does not replace in-person contact and vice versa. The two approaches rather complement each other.
    - ***Response: We agree that telephone and in-person follow-up are complementary rather than mutually exclusive. The wording has been corrected accordingly.***
5. Out of curiosity regarding community perspective, among the PLHIV interviewed, was there a direct expression of willingness to participate in the study besides the views captured in this manuscript that highlight a general acknowledgement of the significance of implementing this CHI model among vulnerable populations. What was their response to a question along the lines of "would you consider participating/ be willing to participate in this study if you fit eligibility criteria?" (just in case such a question was posed to them during the time they were interviewed).
    - ***Response: We agree this would have been a valuable addition. Unfortunately, willingness to personally participate was not directly asked in the workshops.***

Competing Interests: No competing interests were disclosed.

Reviewer Report 07 February 2025

https://doi.org/10.21956/wellcomeopenres.25656.r116886

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James D Kellner
University of Calgary, Calgary, Canada

This open letter is an interesting and well-conceived manuscript including recognized experts on the topic of controlled human infection models (CHIMs) in at-risk groups in Africa. I have just a few comments to offer, in response to the Peer Review Form questions and a careful reading of the article.

1. I responded “No” to the question about adequately referencing differing views and opinions. While the authors do present data from their two focus group workshops on perceptions about CHIMs, including risks and benefits, they do not present any information on the scientific limitations and alternative approaches to CHIMs to measure infectious disease pathogenesis and to evaluate vaccines in their population of interest.

2. The manuscript includes several statements made attendees at the focus group workshops regarding perceptions about CHIMs. However, the authors do not mention whether they conducted formal qualitative research methods and analysis, and whether the included statements reflect formal thematic analysis or informal review of the information obtained at the workshops. Either approach is acceptable, but it should be clarified.

3. In the discussion of risk and burden to individual participants and to the community, the authors justify their pneumococcal carriage model on the basis of a low risk of invasive pneumococcal disease (IPD) occurring after experimental carriage with a “relatively benign pneumococcal serotype (6B)” and on the basis of only including persons living with HIV (PLHIV) with a sufficiently high CD4 T-cell count. However, the authors will know that non-invasive pneumonia is by far the most common serious disease that occurs after pneumococcal carriage, and it is far more common than IPD. Yet there is no mention of pneumococcal pneumonia in the manuscript, either to estimate the incidence, or to acknowledge that this is the most important serious disease to consider.

4. Related to 3) above, there is no mention of whether precautions should be taken, at the time of inoculation with pneumococcus, in persons with acute respiratory tract infections, which may be caused by viruses e.g., influenza, respiratory syncytial virus, that may antecedent infections before secondary pneumococcal pneumonia. I expect these precautions are taken but they should be mentioned in the list of mitigations considered for the risk and burden to individuals and the community.

Is the rationale for the Open Letter provided in sufficient detail?
Yes

Does the article adequately reference differing views and opinions?
No

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Yes

Is the Open Letter written in accessible language?
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?
Yes

Competing Interests: I have been an investigator on projects funded by Pfizer Canada, and Merck Canada, related to pneumococcal infections and vaccines. All funds have been paid to my institute (University of Calgary), and I have not received any personal payments.

Reviewer Expertise: Pediatrics, infectious diseases, vaccine preventable infections (including Streptococcus pneumoniae), vaccines, clinical epidemiology, and vaccine clinical trials.

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 06 Oct 2025

Klara Doherty

We thank reviewer 1 for the constructive comments which have helped strengthen the manuscript. In particular, we have expanded the discussion of the limitations of CHIMs and the alternatives to a CHIM and have improved the clarity of the manuscript in a number of sections. This open letter is an interesting and well-conceived manuscript including recognized experts on the topic of controlled human infection models (CHIMs) in at-risk groups in Africa. I have just a few comments to offer, in response to the Peer Review Form questions and a careful reading of the article.

1. I responded “No” to the question about adequately referencing differing views and opinions. While the authors do present data from their two focus group workshops on perceptions about CHIMs, including risks and benefits, they do not present any information on the scientific limitations and alternative approaches to CHIMs to measure infectious disease pathogenesis and to evaluate vaccines in their population of interest.
    - ***Response: Thank you for this observation. We agree that the manuscript should more explicitly acknowledge scientific limitations and alternatives. We have added a discussion under “Adequacy of study design” describing the limitation of using a single-serotype model and noting that community trials may also be feasible given the ubiquity of pneumococcal carriage. Under***

"Risks and burden to individual participants," we now also discuss representativeness of CHIM participants. We hope this addition provides a more balanced perspective.

2. The manuscript includes several statements made attendees at the focus group workshops regarding perceptions about CHIMs. However, the authors do not mention whether they conducted formal qualitative research methods and analysis, and whether the included statements reflect formal thematic analysis or informal review of the information obtained at the workshops. Either approach is acceptable, but it should be clarified.
    - ***Response: Thank you for highlighting this need for clarity. We have revised Section 4 ("What is the perception…") to explicitly state that while the focus group workshops were not formal qualitative studies, we employed structured elements (recording, transcription, and thematic review) to analyse participant perspectives.***
3. In the discussion of risk and burden to individual participants and to the community, the authors justify their pneumococcal carriage model on the basis of a low risk of invasive pneumococcal disease (IPD) occurring after experimental carriage with a "relatively benign pneumococcal serotype (6B)" and on the basis of only including persons living with HIV (PLHIV) with a sufficiently high CD4 T-cell count. However, the authors will know that non-invasive pneumonia is by far the most common serious disease that occurs after pneumococcal carriage, and it is far more common than IPD. Yet there is no mention of pneumococcal pneumonia in the manuscript, either to estimate the incidence, or to acknowledge that this is the most important serious disease to consider.
    - ***Response: We agree that non-invasive pneumonia is the most common serious manifestation following carriage and that this required clearer discussion. We have amended the text to use the broader term "pneumococcal disease" rather than "IPD" as the associated reference does demonstrate CD4 count associated with pneumonia. We have also added a sentence under the section "Is the scientific rationale… justified?" to emphasise the importance of pneumonia in PLHIV.***
4. Related to 3) above, there is no mention of whether precautions should be taken, at the time of inoculation with pneumococcus, in persons with acute respiratory tract infections, which may be caused by viruses e.g., influenza, respiratory syncytial virus, that may antecedent infections before secondary pneumococcal pneumonia. I expect these precautions are taken but they should be mentioned in the list of mitigations considered for the risk and burden to individuals and the community.
    - ***Response: Participants with any symptom of upper respiratory tract infection were screened out of the study. We agree this precaution should be explicit. We have amended the section "Risk and burden to individual participants" to state that individuals with any symptoms of acute upper respiratory tract infection were excluded at the time of inoculation, to minimise the risk of secondary pneumococcal disease.***

Competing Interests: No competing interests were disclosed.