STUDY PROTOCOL

Exploring interrelationships between structural, social, and biological determinants of vaccine impact in Kenya and Uganda: VAnguard community mixed methods study protocol

[version 1; peer review: awaiting peer review]

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Abstract

Background

The key principle underlying the UN Sustainable Development Goals is to “leave no one behind”. However, following the COVID-19 pandemic, sub-optimal vaccine coverage is a continuing concern in low-and

middle-income countries (LMICs) and there is increasing evidence of impaired vaccine immunogenicity and efficacy in LMICs, compared to high-income countries (HICS) and in rural, compared to urban settings. It is documented that countries with the lowest vaccination coverage suffer the highest health inequalities. For vaccines to achieve their full health benefit, structural, social and biological determinants that impair vaccine impact must be concurrently addressed. This study aims to explore how structural, social and biological determinants interact to influence vaccine impact in vulnerable communities across Kenya and Uganda. By understanding these interactions, we can develop strategies to improve vaccine impact in vulnerable populations.

Methods

The study will utilise a cross-sectional mixed-methods design. It will be conducted in three counties in Kenya (Kilifi, Kwale and Kisumu) and three districts in Uganda (Kampala, Kikuube and Namayingo). We will conduct (i) in-depth interviews, (ii) focus group discussions (FGDs) with key community stakeholders, and (iii) a household-based quantitative survey where blood and stool samples of 1032 participants (172 in each community) will be collected. Samples will be used to measure proxy markers of reduced vaccine coverage and impaired vaccine immunogenicity.

Conclusions

The results of this study will identify potential determinants of vaccine impact that are modifiable. This evidence will be used in the development of a modelling framework to assess the likely impact of interventions targeting specific determinants of impact, both solely and concertedly, and how these might be tailored to different communities.

Plain Language Summary

This study explores why vaccines may not work well in some communities in Uganda and Kenya. The research aims to understand how social factors (like education and culture), structural challenges (such as poor infrastructure), and biological differences (like age or underlying infections) can affect how well vaccines protect people. The study will involve interviews, surveys, and laboratory tests on blood and stool samples from 1,032 participants across selected communities in both countries. By analyzing these factors, the study hopes to identify key barriers to effective vaccination, leading to better health outcomes for vulnerable communities.

Keywords
Vaccine impact, biological determinants, Social determinants, Structural determinants, Vaccine effectiveness, Kenya, Uganda, Health inequalities

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List of abbreviations

BCG: Bacillus Calmette–Guérin

COVID-19: Coronavirus disease 2019

FGDs: Focused Group Discussions

IRB: Institutional Review Board

KEMRI: Kenya Medical Research Institute

KWTRP: KEMRI Wellcome Trust Research Programme

LSHTM: London School of Hygiene & Tropical Medicine

NACOSTI: National Commission for Science, Technology & Innovation

NIHR: National Institute for Health and Care Research

REC: Research Ethics Committee

UNCST: Uganda National Council for Science and Technology

UVRI: Uganda Virus Research Institute

VAnguard: The NIHR Global Health Research Group on Vaccines for vulnerable people in Africa

WHO: World Health Organization

Introduction

The United Nations Sustainable Development Goals (SDGs) emphasize the principle of "leave no one behind"[1]. To achieve this health inequalities, particularly in low- and middle-income countries (LMICs) must be addressed. The World Health Organization (WHO) estimates that increasing global childhood vaccine coverage to 90% could prevent two million deaths among children under five years old[2]. However, following the COVID-19 pandemic, vaccine coverage remains suboptimal in LMICs. Countries with the lowest vaccination rates experience the highest inequalities[3], particularly in maternal and child health[4].

A Demographic and Health Survey conducted in 45 GAVI-supported countries (2005 – 2014) identified large vaccine coverage inequalities driven by social factors such as maternal and paternal education, as well as wealth indices[5]. Development assistance, improved maternal and paternal education, and good governance at the national level have been associated with reducing these disparities. These, and other, social and structural factors may impair vaccine impact by influencing attitudes, access, and uptake. For instance, parents of children aged 12–23 months have reported issues with accessing routine immunization services from their places of residence[6].

Moreover, being vaccinated does not always confer the expected health benefits in some populations. For example, Malawian adolescents have shown weaker immune responses to the BCG vaccine compared to their UK counterparts[7]. Similarly, variations in the efficacy of vaccines such as BCG for tuberculosis, and the oral polio vaccine, have been observed across populations, with lower efficacy in tropical regions[8,9]. These regions are often characterized by unique environmental exposures and infections, including environmental mycobacteria, malaria, and helminths, which can modulate immune responses. For instance, malaria has been shown to impair vaccine responses[10], while helminth infections polarize immune responses towards Th2 and regulatory T cells, potentially weakening vaccine effectiveness[11,12]. Nutritional factors, including body mass index, and micronutrient status, also associated with variation in immune response to vaccines[13]. Vitamin D in particular, plays a key role in immune function, although its specific impact on vaccine responses remains unclear[14]. In addition, iron plays a role in modulating immune responses, and iron deficiency has been linked to impaired vaccine responses[15,16]. Malnutrition, especially in children, leads to immunological changes that increase mortality and result in weaker responses to a range of vaccines[13,17]. Emerging research also highlights the role of microbiota in influencing vaccine responses, either locally at the gut for oral vaccines or systematically for parenteral vaccines[18].

To fully realize the health benefits of vaccines, it is essential to address the structural, social, and biological factors that impair vaccine impact. Although existing studies have examined these determinants individually, their combined effects and interrelationships remain under-investigated.

The broader VAnguard project is structured into three thematic work packages (WP) supported by four cross-cutting WPs[19]. This study is being led by on one of the cross cutting work packages (WP4). It aims to investigate how structural, social and biological determinants interact to influence vaccine impact in vulnerable communities across Uganda and Kenya. These communities will be selected based on varying levels of vulnerability regarding vaccine impact. Our goal is to inform strategies that optimise vaccine effectiveness in vulnerable populations, ultimately contributing to the reduction of health inequities in LMICs.

Conceptual framework

Our conceptual framework (Figure 1) illustrates the expected relationships between the structural, social and biological determinants that influence vaccine impact. It is further guided by the WHO Behavioral and Social Drivers of Vaccination (BeSD) framework[20], which identifies modifiable factors that can improve vaccine uptake. These drivers are grouped into four domains: thinking and feeling about vaccines, social processes that influence vaccination, motivation to seek vaccination and practical issues related to accessing vaccines. Vaccine impact in this study is conceptualized as a combination of vaccine uptake and the level of immune responses elicited by vaccination. To quantify vaccine impact, we will use multiplex serology to measure immune responses alongside vaccine uptake data as proxy indicators. This approach is necessary because direct measurement of disease incidence or prevalence is not feasible within the scope of this study.

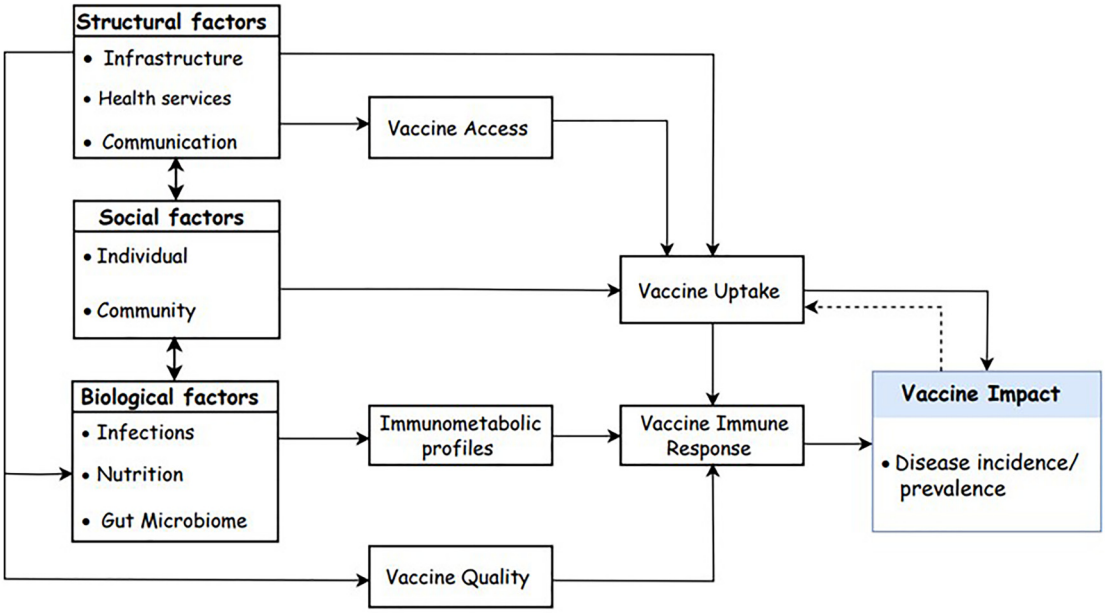

Figure 1. Conceptual framework illustrating the interrelationships between factors influencing vaccine impact.

Study aim and objectives

The overall aim of this study is to investigate structural, social and biological determinants that hinder vaccine impact in vulnerable communities in Uganda and Kenya. The specific objectives are to

1. Explore structural and social determinants that hinder vaccine impact in vulnerable communities.
2. Assess the effect of biological determinants on the proxy markers of vaccine impact in vulnerable communities
3. Explore the interrelationships between structural, social and biological determinants and their combined influence on proxy markers of vaccine impact in vulnerable communities

Methods

Patient and Public Involvement

A communication and engagement strategy has been developed to guide in the implementation of the study. Stakeholder mapping and engagement at district and community level will be done in the study communities, starting with visits for meetings with leaders. This will supplement the stakeholder mapping that was done during the preparatory phases of the project. To inform the development of this protocol, a consultative meeting was organised[19], to which representatives of national and community stakeholders were invited, and preliminary data shared.

Inception meetings will be conducted with national and local level stakeholders to ensure that they are informed and included in study plans. These engagement meetings will continue throughout the study period at the local and national levels. We will also utilize the research partnership's existing membership in relevant working/steering groups to engage and update stakeholders on the study.

Local stakeholders will be involved through local community meetings, which will be held at regular intervals. These meetings will comprise the host communities, the study partners, and local level leadership, and will be conducted to ensure uptake and understanding. We will also use local avenues such as the administrative meetings and any local gatherings to disseminate information about the study. We will share a newsletter regularly to keep stakeholders informed about the study's progress. We will also engage the public through the mainstream and social media channels and the VAnguard website.

Key communication output/activities are peer-reviewed publications, and knowledge translation products such as learning and policy briefs, which will summarize the study progress and findings. We will also participate in various fora such as workshops, conferences, webinars and community events related to vaccines and vulnerable communities.

Study design

This is a cross-sectional mixed-methods study that will use (i) in-depth interviews, (ii) focus group discussions (FGDs) with key community stakeholders, and (iii) a household-based quantitative survey where blood and stool samples of 1032 participants (172 in each community) will be collected. The planned study period is from July 2024 to May 2025.

Study sites

The study will be conducted in six communities, comprising three counties in Kenya and three districts in Uganda. In each country the study will aim to include urban and rural settings and to include settings with varying levels of vulnerability. Vulnerability, in this context is defined as the susceptibility or increased risk of certain communities to experiencing reduced or sub-optimal vaccine outcomes. This could be due to high prevalence of hypothesized structural, social, biological determinants that may impede optimal vaccine impact such as remote location, poverty, lack of education, undernutrition and infections.

To inform the selection of communities for inclusion in our study, we utilized the community vaccine impact vulnerability index (CVIVI), described in detail in our earlier work published Manuscript[21]. The index integrates data for 16 indicators across three domains: structural factors (e.g. distance to the health facility, access to postnatal care), social factors (e.g. household wealth, maternal education) and biological factors (e.g. nutritional status, malaria prevalence), to assess possible community vulnerability to impaired vaccine impact. The percentile rank methodology was used to compute both domain specific and overall vulnerability indices. Subsequently, the domain specific indices were aggregated into an unweighted overall vulnerability index that quantifies the relative degree and magnitude of community vulnerability to suboptimal vaccine impact. Findings were used to select study communities across vulnerability categories to allow us to capture a range of community settings, providing a holistic view of vaccine related vulnerabilities. In addition to the vulnerability indices related to vaccine impact, there were practical considerations for instance feasibility of conducting research in each community, and cost implications associated with survey activities.

The vulnerability index has been developed iteratively, evolving to reflect the availability and scope of data. In Uganda, study districts were selected based on an earlier version of the index than the published one. The earlier version incorporated a limited number of indicators, primarily focusing on malaria, stunting, socio-economic status and minimal structural factors. The initial index classified districts into five categories, ranging from least to most vulnerable. Based on this classification, three districts were selected in Uganda: Kampala (categorised as less vulnerable and urban), Namayingo (more vulnerable and rural) and Kikuube (most vulnerable and rural) as shown in Figure 2. The vulnerability classification of all Ugandan districts based on this initial index is shown in Figure 2. Subsequently, a refined index (Figure 3) was developed, which includes a more comprehensive set of indicators, particularly on structural factors, while excluding vaccine coverage in the computation of the index. A comparison of the two versions showed minimal differences in the overall vulnerability patterns across districts, indicating that the initial index provided a reliable basis for study site selection in Uganda.

In Kenya, community selection was informed by the current version of the index Manuscript[21]. Using this updated index, the selected countries were Kisumu (considered less vulnerable and urban), and Kwale and Kilifi (categorised as more vulnerable and rural) as depicted in Figure 4. The full

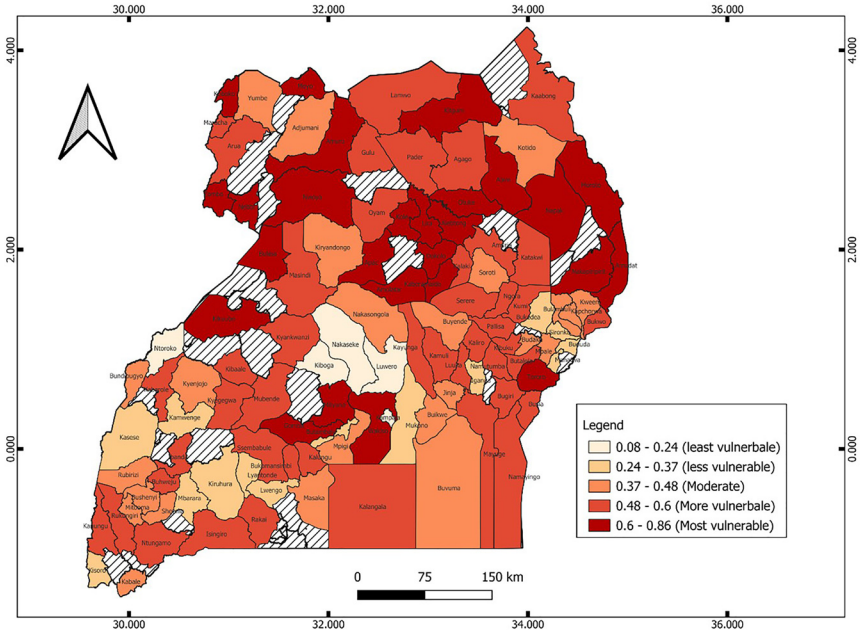

Figure 2. Vulnerability classification of Ugandan districts based on the initial index, from least (lightest) to most vulnerable (darkest).

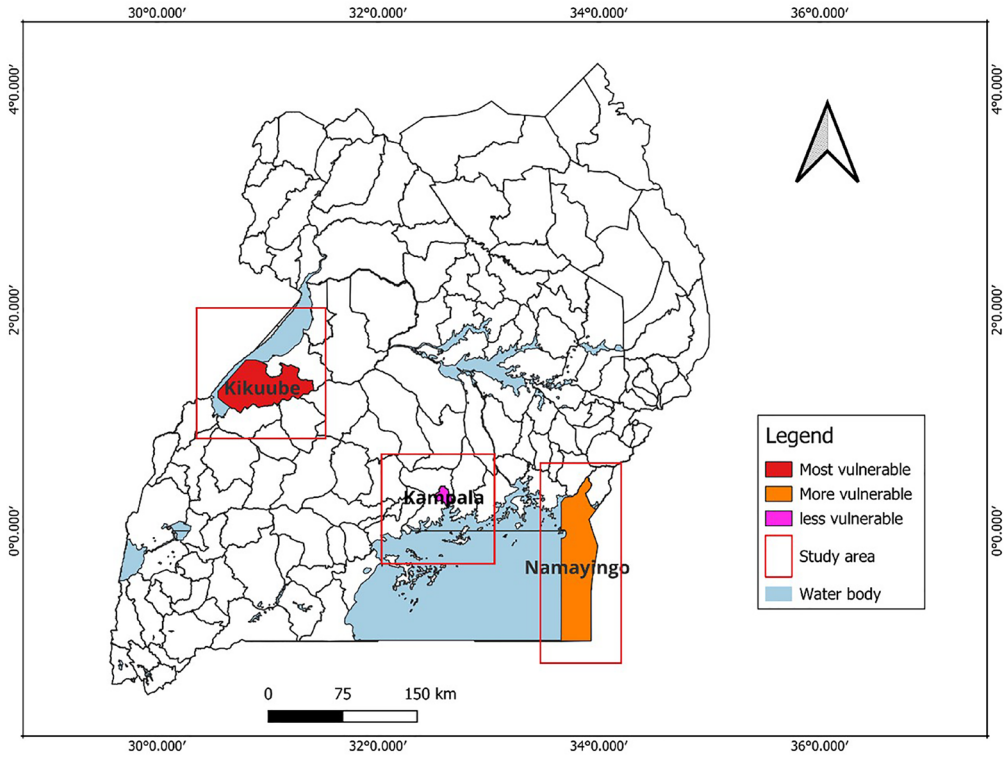

Figure 3. **Vulnerable and less vulnerable selected study districts in Uganda as per the refined vulnerability index.**

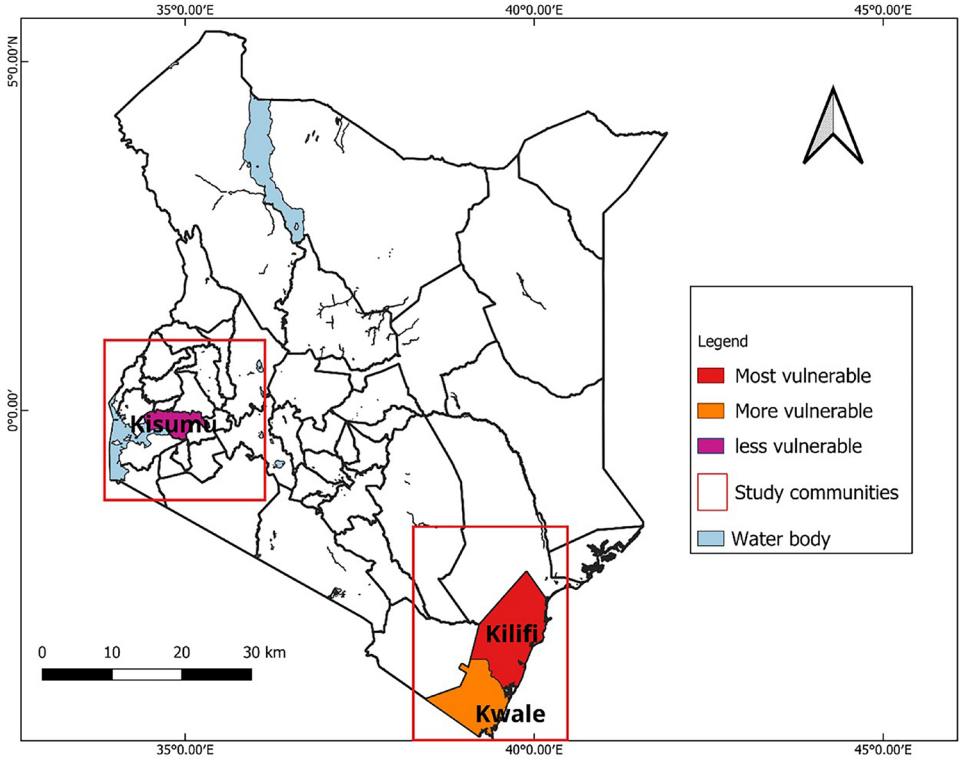

Figure 4. **Vulnerable and less vulnerable selected study counties in Kenya.**

classification of the all the counties in Kenya is shown in another related publication[21].

Study population

The qualitative component of the study will draw on key vaccine-related stakeholders at the county/district and village levels. This will include individuals at the county/district departments of health overseeing immunization programmes, health facility managers and staff overseeing the implementation of the vaccine programmes and groups of community health volunteers/village health teams who participate in health promotion and mobilizing the community for health activities such as vaccinations. At the community level, the study will draw on community members, community and religious leaders and other stakeholders deemed important in helping us understand more about access and uptake of vaccines at the community level.

The quantitative component of the study will draw participants from randomly selected households in the chosen counties/districts. The following eligibility criteria will be followed for inclusion in the community study:

1. Available within the households at the time of conducting the study
2. Resident in the community for at least the past year
3. Age greater than or equal to 1 (one) year
4. Provide written informed consent and assent as applicable (adults aged 18 years or above, consent; children <18 years consent of parent or guardian plus child's assent if older than 8 years in Uganda, 12 years in Kenya)

Exclusion criteria:

1. Individuals who report a history of current moderate or severe acute illness will be excluded.

Sample size determination and sampling procedures

Qualitative component of the study

The participants will be drawn from the selected communities and will be purposively selected to maximize the range and diversity of views obtained. The selection will ensure maximum variation on key characteristics relevant to this study, including, sex, age, socio-economic status, education, people/families affected by disability, proximity to health facility, pregnancy status and vaccine uptake. Across the different categories of participants, we will conduct approximately 10–15 interviews and 4–6 focus group discussions with around 50–60 participants per county/district making an overall number of 200–240 participants per country. The proposed sample size for the qualitative component is indicative and may change based on the attainment of saturation as the research progresses[22].

Quantitative component of the study

Selecting the households and participants

Using locally available maps and district-level data, we will work with district or county leadership to select a specific area (e.g., village or local council) for the study. The selection will be based on characteristics aligned with our district-level vulnerability index.

Each selected area will be sub divided into enumeration areas by overlaying a grid on the map to create enumeration areas of uniform size and shape. The midpoint of each enumeration area will be identified by its coordinates using a geographic information system (GIS) device. This will be used as the starting point for sampling households and the nearest house will be selected for inclusion. Houses will then be sequentially selected, the next house to be sampled being the nearest to the previous house. If a household is found empty or declines to participate, the next one will be approached until the sample size for the area is achieved.

In the selected households, permission will be sought from the household head or another adult in the household if the household head is absent. Household residents will be enumerated and a single participant in each household will be randomly selected for inclusion in the survey. This approach is designed to recruit a sample of participants with age and sex representative of the community, since these demographic characteristics are expected to contribute to the overall community vulnerability to reduced vaccine impact.

Sample size calculation: We propose to enrol 172 participants per community totalling to 1,032 (of appropriate ages, see above) giving 80% power to detect differences (odds ratios ≥2) in exposure prevalence between vulnerable and less vulnerable communities for exposures with prevalence ≥20% and greater power for more common exposures (Table 1)[19]. Assuming that the standard deviation of continuous outcome measures (e.g., antibody responses) will lie between 0.2 and 0.6 $\log_{10}$, with responses in vulnerable settings 0.1 to 0.2 $\log_{10}$ lower than in less vulnerable settings and allowing for ~10% of participants not giving blood samples, 172 participants from each community will give >80% power to compare antibody responses between vulnerable and less vulnerable communities in each setting.

Table 1. Sample sizes required for 80% power to detect various odds ratios by exposure prevalence (1:1 ratio)[19].

Prevalence of exposure in vulnerable	Number of participants required					
	Odds ratio 2		Odds ratio 2.5		Odds ratio 3	
	Vulnerable		Vulnerability		Vulnerability	
	High	Low	High	Low	High	Low
10%	283	283	151	151	100	100
20%	172	172	95	95	64	64
30%	141	141	80	80	55	55
40%	133	133	77	77	54	54
50%	137	137	81	81	58	58

Shaded areas indicate prevalence and odds ratios that VAnguard Community Study would have power to detect.

Data collection

Qualitative data

In-depth interviews and FGDs will be conducted with community stakeholders, including community members, leaders, healthcare workers, and other relevant actors. The purpose is to explore perceptions of vaccine access, uptake, and barriers to vaccination.

Quantitative data

Household level data: A structured researcher-administered questionnaire will be used to collect quantitative data on key social and structural factors from participants in the selected communities[19]. Social factors to be assessed include demographic information, vaccination history, household attributes (such as income and household structure), perceptions and altitudes toward vaccines and sources of vaccine-related information. Structural factors influencing access such as mode of transport, place of immunisation, distance to the nearest health facilities, will also be captured. Furthermore, blood and stool samples will be collected to assess proxy markers of vaccine impact, including immune responses.

Health facility-level data: A brief questionnaire will be administered at health facilities providing immunisation services within the selected communities. These facilities will be identified with the assistance of village or district leaders. The questionnaire will capture additional structural factors, including the frequency of the immunisation sessions, vaccine supply availability, staff capacity, and other relevant variables. Additionally, vaccine coverage data from the past six months will be extracted from the immunisation records at these facilities.

Collection of biological samples. The survey will include the collection of samples (blood, and stool)[19]. The blood samples will be used tomeasure immune responses to vaccines and exposure to infectionsand stored as plasma, serum and cells, The blood volume to be collected will vary with age. The blood volume will follow guidelines from Harvard Medical School and the Massachusetts General Hospital, which recommend that a maximum of 3ml/kg body weight is taken at a time point (http://www.drgreene.com/21_1616.html). The maximum volume of blood at any given study visit will be 20ml for any one participant. Blood sample collection will be done by well trained staff and all samples will be sealed, labelled and transported in proper sample courier boxes, accompanied by their respective chain of custody forms. Results from the samples identified to have clinical relevance to the participants will be returned and they will be advised and referred appropriately.

Multiplex immunoassays will be conducted using plasma or serum samples to assess infection-specific and vaccine-specific antibody response to the routinely administered Expanded Programme on Immunisations (EPI) vaccines. These vaccines include BCG, polio, hepatitis B, yellow fever, measles, rubella, diphtheria, pertussis, tetanus, HPV, and SARS-CoV-2. The analysis will be conducted on samples collected from participants in both Uganda and Kenya. These immunoassays will measure proxy markers indicative of potential impairments in vaccine immunogenicity and efficacy such as antibodies. Furthermore, the results will contribute to establishing a proxy biological profile of vaccine impact in the study populations. Peripheral blood mononuclear cells (PBMCs) will be stored for a subset of participants and used for further exploration of cellular immune responses such as cytokine responses. Part of the plasma or serum samples will be used for micronutrient assays.

The stool sample collected will be examined for helminth infections such as *Schistosoma mansoni, Strongyloides stercoralis* and *Necator americanus* using multiplex real-time PCR. All assays will be conducted in laboratories in Uganda and Kenya where possible.

Data analysis

Qualitative component of the study

All interview and FGD data will be audio recorded, transcribed and translated into English, if conducted in a different language, to facilitate cross-site analysis. Observational data will be documented as field notes and then digitized. The qualitative data will be managed using NVIVO 14 software (QSR International, www.qsrinternational.com/nvivo) and analysed using a framework analysis approach, a type of thematic analysis recommended for multidisciplinary research teams[23].

Codes will be iteratively developed from the data, initially based on our conceptual framework and informed by findings from the case studies and scoping review, using the structural violence framework. This framework will help analyse how institutionalized inequities and power imbalances embedded within social, economic and political systems perpetuate vulnerabilities, limit access to essential health services and undermine vaccine impact[24]. The analysis will combine inductive and deductive approaches, with codes developed and reviewed by team members.

The initial codes will be organized into categories and further refined into themes, creating a codebook that captures the analytical framework. Data will be charted to identify patterns for each country, followed by a comparative analysis between Uganda and Kenya. While recognising contextual differences, we expect to find both similarity and variations in the identified themes and their specific content.

The findings will include structural, social and biological themes that shape decision-making, and limit access, uptake, and responses to vaccines. These themes will then be further examined to identify and explain relevant intersections using the intersectionality lens[25].

All qualitative data will be stored in password protected computers at the KWTRP in Kenya and at the MRC/UVRI & LSHTM Uganda Research Unit head offices in Entebbe, Uganda. Access to the data will be restricted to the study investigators and authorized personnel such as field workers and data

entry clerks. To ensure participant confidentiality, all personal identifiers will be removed from the data and replaced with anonymized codes. Following transcription and quality assurance checks, the original audio recordings will be securely deleted.

Quantitative component of the study

The study data collecting tools will be designed and uploaded into a Research Electronic Data Capture system (REDCap), and data collection will be done using encrypted mobile devices. Quantitative information will include that from the main survey questionnaire and biological sample results. Data will be transmitted daily to an online secure server for storage. All data collected will be reviewed for completeness. Consistency checks will be routinely run by the data manager. Descriptive analysis will be conducted by analysing means and percentages for variables such as demographic indicators e.g., sex, age, income, marital status, and educational status, and other variables of interest such as parasite exposure. Regarding proxy measures of vaccine impact, we will first look at antibody responses to individual vaccines and compare them between the communities. Then we shall investigate how antibody responses individually relate to specific exposures. Further exploration will be done on how the antibody responses correlate with each other and whether we can use data reduction approaches such as Principal Component Analysis (PCA) to characterise the overall vaccine responsiveness in different communities. Vaccine coverage will be compared across study groups using binomial regression with an identity link to estimate differences in proportions. To assess vaccine impact, as defined in our conceptual framework, linear regression will be used to compare outcomes between groups of participants.

Clustering by compound will be adjusted for using generalised estimating equations with robust standard errors. In planned subgroup analysis, antibody responses will be disaggregated by age and sex.

Discussion

The findings from this study are expected to have significant implications for public health strategies aimed at improving vaccine coverage and effectiveness in LMICs. By identifying both modifiable barriers to vaccine access and immunogenicity, the results will guide evidence-based policy changes and targeted interventions for vulnerable populations.

Specifically, the study will highlight the critical role of social determinants, including poverty and education, in shaping vaccine outcomes and will provide insights into how infections, malnutrition, and other biological factors influence immune responses to vaccines. Furthermore, the findings will shed light on the complex interplay between structural, social and biological determinants. For example, poor healthcare infrastructure may exacerbate the effects of poverty and malnutrition on vaccine outcomes, while policy frameworks can either mitigate or amplify these vulnerabilities by influencing access to immunization services. This integrated understanding of the interconnected factors shaping vaccine impact will provide a holistic foundation for designing and implementing more effective and equitable vaccination programmes.

Equality, diversity and inclusion

The survey has been designed to ensure representation across diverse geographical locations, including urban, peri-urban, and rural settings, to address regional disparities in vaccine delivery and uptake. Efforts will be made to include participants of different genders, age groups, and individuals with disabilities, recognizing the importance of diverse perspectives in identifying barriers to effective vaccine delivery. This approach aims to achieve equitable representation of experiences and challenges within the study communities. By fostering inclusivity, the study will strengthen the validity of its findings and inform the development of targeted strategies to improve vaccine access and equity in low- and middle-income countries.

Study status

Ethics approvals have been secured in both countries. In Uganda, participant recruitment and data collection began in July 2024. In Kenya, recruitment and data collection began in December 2024 and is on-going.

Conclusions

The VAnguard community study will generate critical insights into the factors limiting vaccine effectiveness in vulnerable populations in Kenya and Uganda, offering a robust evidence base to inform interventions. By focusing on the interrelationship between structural, social, and biological determinants, this research moves beyond isolated perspectives to provide a comprehensive understanding of vaccine related challenges in these communities. The study findings will not only identify modifiable barriers to vaccine coverage, uptake and immune response but also offer actionable strategies tailored to the unique needs of different populations.

These insights are expected to inform more equitable and effective vaccine delivery systems, supporting public health policies aimed at reducing health disparities in LMICs. Ultimately, the study will contribute to global efforts to optimize vaccine impact, particularly in resource-limited settings, where the burden of vaccine-preventable diseases remains disproportionately high.

Ethical approval and consent to participate

This study has received ethical and regulatory approvals from multiple bodies. In Kenya, approval was granted by the KEMRI Scientific & Ethics Review Unit (KEMRI/RD/22) on [02 July 2024], and the National Commission for Science, Technology & Innovation (NACOSTI/P/24/38566) on [02 September 2024]. In Uganda, approval was obtained from the Uganda Virus Research Institute Research and Ethics Committee (GC/127/994) on [19 December 2023] and the Uganda National Council for Science and Technology (SS2309ES) on [12 June 2024]. Additionally, ethical approval was obtained from the London School of Hygiene and Tropical Medicine Ethics Committee (Ref: 30944) on [04 July 2024].

All study activities will be conducted in accordance with the ethical guidelines set by these bodies and will adhere to the principles outlined in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) on ethical principles for medical research involving human participants.

Written informed consent will be obtained from all study participants, or from parents/guardians in the case of minors. Assent will also be sought from children over the age of 8 years in Uganda and 12 years in Kenya, as per local regulatory requirements. Participants will be informed about the study's objectives, procedures, risks, and benefits, and will be given the option to withdraw from the study at any time without consequence. No waiver of consent has been granted by the ethics committees, and no verbal consent will be used in this study. All participants will provide written informed consent, which has been reviewed and approved by the ethical committees overseeing the study.

Data availability statement

Underlying data

No data are associated with this article.

Extended data

OSF: Exploring interrelationships between structural, social, and biological determinants of vaccine impact in Kenya and Uganda: VAnguard community mixed methods study protocol. Doi: https://doi.org/10.17605/OSF.IO/CX4AT[26]

- This project contains the following extended data: **Study main questionnaires (child and adult):** Used to collect data from participants.
- **Interview guides:** Structured questions for qualitative interviews.
- VAnS HH Observation Guide_Final.pdf
- VAnS Info + assent English v2 Clean.pdf
- **Participant information and consent forms:** Details provided to participants before enrollment.

Software availability statement

The primary software used for qualitative data analysis is NVivo 12 (QSR International). As an alternative, ATLAS.ti (https://atlasti.com) offers open-access qualitative analysis tools that can perform equivalent functions.

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References

1. Zhongming Z, Linong L, Xiaona Y, *et al.*: **A new global partnership: eradicate poverty and transform economies through sustainable development.** 2013.
Reference Source

2. Davey S: **State of the world's vaccines and immunization.** World Health Organization, 2009.
Reference Source

3. Ikilezi G, Augusto OJ, Sbarra A, *et al.*: **Determinants of geographical inequalities for DTP3 vaccine coverage in sub-Saharan Africa.** *Vaccine.* 2020; **38**(18): 3447–54.
PubMed Abstract | Publisher Full Text

4. Fadnes LT, Jackson D, Engebretsen IMS, *et al.*: **Vaccination coverage and timeliness in three South African areas: a prospective study.** *BMC Public Health.* 2011; **11**(1): 404.
PubMed Abstract | Publisher Full Text | Free Full Text

5. Arsenault C, Harper S, Nandi A, *et al.*: **Monitoring equity in vaccination coverage: a systematic analysis of demographic and health surveys from 45 Gavi-supported countries.** *Vaccine.* 2017; **35**(6): 951–9.
PubMed Abstract | Publisher Full Text

6. Francis MR, Nuorti JP, Lumme-Sandt K, *et al.*: **Vaccination coverage and the factors influencing routine childhood vaccination uptake among communities experiencing disadvantage in Vellore, Southern India: a mixed-methods study.** *BMC Public Health.* 2021; **21**(1): 1807.
PubMed Abstract | Publisher Full Text | Free Full Text

7. Lalor MK, Ben-Smith A, Gorak-Stolinska P, *et al.*: **Population differences in immune responses to Bacille Calmette-Guerin vaccination in infancy.** *J Infect Dis.* 2009; **199**(6): 795–800.
PubMed Abstract | Publisher Full Text | Free Full Text

8. Fine PE: **Variation in protection by BCG: implications of and for heterologous immunity.** *Lancet.* 1995; **346**(8986): 1339–45.
PubMed Abstract | Publisher Full Text

9. Serazin AC, Shackelton LA, Wilson C, *et al.*: **Improving the performance of enteric vaccines in the developing world.** *Nat Immunol.* 2010; **11**(9): 769–73.
PubMed Abstract | **Publisher Full Text**

10. Cunnington AJ, Riley EM: **Suppression of vaccine responses by malaria: insignificant or overlooked?** *Expert Rev Vaccines.* 2010; **9**(4): 409–29.
PubMed Abstract | **Publisher Full Text**

11. Maizels RM, Yazdanbakhsh M: **Immune regulation by helminth parasites: cellular and molecular mechanisms.** *Nat Rev Immunol.* 2003; **3**(9): 733–44.
PubMed Abstract | **Publisher Full Text**

12. Wammes LJ, Mpairwe H, Elliott AM, *et al.*: **Helminth therapy or elimination: epidemiological, immunological, and clinical considerations.** *Lancet Infect Dis.* 2014; **14**(11): 1150–62.
PubMed Abstract | **Publisher Full Text**

13. Zimmermann P, Curtis N: **Factors that influence the immune response to vaccination.** *Clin Microbiol Rev.* 2019; **32**(2): e00084–18.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

14. Sadarangani SP, Whitaker JA, Poland GA: **"Let there be light": the role of vitamin D in the immune response to vaccines.** *Expert Rev Vaccines.* 2015; **14**(11): 1427–40.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

15. Jiang Y, Li C, Wu Q, *et al.*: **Iron-dependent histone 3 lysine 9 demethylation controls B cell proliferation and humoral immune responses.** *Nat Commun.* 2019; **10**(1): 2935.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

16. Stoffel NU, Uyoga MA, Mutuku FM, *et al.*: **Iron deficiency anemia at time of vaccination predicts decreased vaccine response and iron supplementation at time of vaccination increases humoral vaccine response: a birth cohort study and a randomized trial follow-up study in Kenyan infants.** *Front Immunol.* 2020; **11**: 1313.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

17. Rytter MJH, Kolte L, Briend A, *et al.*: **The immune system in children with malnutrition—a systematic review.** *PLoS One.* 2014; **9**(8): e105017.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

18. de Jong SE, Olin A, Pulendran B: **The impact of the microbiome on immunity to vaccination in humans.** *Cell Host Microbe.* 2020; **28**(2): 169–79.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

19. Zirimenya L, Zalwango F, Owino EA, *et al.*: **NIHR Global Health Research Group on Vaccines for vulnerable people in Africa (VAnguard): concept and launch event report [version 1; peer review: 2 approved with reservations].** *NIHR Open Res.* 2024; **3**: 35.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

20. WHO: **Behavioural and social drivers of vaccination: tools and practical guidance for achieving high uptake.** Geneva: World Health Organization, 2022.
Reference Source

21. Nalwanga R, Natukunda A, Zirimenya L, *et al.*: **Assessing community vulnerability to reduced vaccine impact in Uganda and Kenya: a spatial data analysis [version 1; peer review: 1 approved with reservations].** *NIHR Open Res.* 2025; **5**: 24.
Publisher Full Text

22. Guest G, Bunce A, Johnson L: **How many interviews are enough? An experiment with data saturation and variability.** *Field Methods.* 2006; **18**(1): 59–82.
Publisher Full Text

23. Gale NK, Heath G, Cameron E, *et al.*: **Using the framework method for the analysis of qualitative data in multi-disciplinary health research.** *BMC Med Res Methodol.* 2013; **13**: 117.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

24. Galtung J: **Violence, peace, and peace research.** *J Peace Res.* 1969; **6**(3): 167–91.
Publisher Full Text

25. Shannon GD, Motta A, Cáceres CF, *et al.*: **¿Somos iguales? Using a structural violence framework to understand gender and health inequities from an intersectional perspective in the Peruvian Amazon.** *Glob Health Action.* 2017; **10**(sup2): 1330458.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

26. Zirimenya LD: **Exploring interrelationships between structural, social, and biological determinants of vaccine impact in Kenya and Uganda: VAnguard community mixed methods study protocol.** OSF. 2025.
http://osf.io/cx4at