STUDY PROTOCOL | Article in Press

Integrating Malaria Vaccine with Seasonal Malaria Chemoprevention in West Africa (IMVACS): study protocol for a cluster-randomized trial

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Abstract

Background Despite wide-scale implementation of malaria prevention strategies, including seasonal malaria chemoprevention (SMC), a substantial disease burden persists. The R21/Matrix-M (R21/MM) malaria vaccine, recommended by the World Health Organization in 2023, is expected to substantially reduce this burden in children. However, the optimal delivery strategy in highly seasonal transmission settings remains uncertain. Integrating vaccine delivery with SMC campaigns may improve access, timeliness, and coverage, especially for the fourth dose. This trial will evaluate whether integrated delivery of R21/MM through SMC campaigns will provide non-inferior protection against malaria compared with routine Essential Program on Immunization (EPI)-based delivery or routine pre-seasonal delivery before SMC campaigns. Feasibility, acceptability, and cost-effectiveness will also be assessed.

Methods This trial is a multi-site, phase IV, open-label, two-arm, cluster-randomized, non-inferiority trial conducted in the rural health districts of Boussé (Burkina Faso) and Dioila (Mali). Clusters, defined as peripheral health centers catchment areas, will be randomized separately within each country (1:1) and stratified by cluster size, with 20 clusters in Burkina Faso and 16 in Mali. Following written informed consent, trained study staff will enroll eligible children. Children aged 3–59 months living in intervention clusters and those aged 5–36 months living in control clusters will be eligible for vaccination. Children with previous malaria vaccination or conditions compromising participation will be excluded. Vaccination will be delivered through integrated SMC campaigns in the intervention arm and through year-round EPI-based delivery in Burkina Faso or pre-seasonal delivery before SMC campaigns followed by year-round EPI-based delivery in Mali. Power calculations will assume a non-inferiority margin of 0.10. The primary outcome will be the incidence of clinical malaria among children aged 5–36 months over 12 months after the first dose. Secondary outcomes will include adverse events following

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immunization, adverse events of special interest, serious adverse events, vaccine coverage, dropout rates, barriers and facilitators to implementation, stakeholder perceptions, and cost per disability-adjusted life year averted.

Discussion Beyond effectiveness and safety, the study will provide evidence to support integrated R21/MM delivery with SMC in highly seasonal transmission settings. The findings are expected to inform national and global malaria vaccine policies.

Trial registration ClinicalTrials.gov, NCT06860178. Registered on 20 January 2025.

Keywords R21/Matrix-M · Seasonal malaria chemoprevention · Malaria · EPI · Burkina Faso · Mali

Abbreviations

AE	Adverse event
AESI	Special Interest Adverse Event
AEFI	Adverse event following immunization
CI	Confidence interval
DALY	Disability-adjusted life years
DSMB	Data and Safety Monitoring Board
eCRF	Electronic case report form
EPI	Essential Program on Immunization
ICC	Intraclass correlation coefficient
LLIN	Long-lasting insecticide-treated mosquito net
MIS	Malaria indicator survey
QLS	Qualitative longitudinal study
R21/MM	R21/Matrix M malaria vaccine
RDT	Rapid diagnostic test
SAE	Serious adverse event
SMC	Seasonal Malaria Chemoprevention
TSC	Trial Steering Committee
SOP	Standard Operating Procedure
WHO	World Health Organization

Background

Malaria continues to be a leading cause of morbidity and mortality in sub-Saharan Africa, with the greatest burden reported among young children. In 2023, an estimated 263 million cases and 597,000 deaths (95% confidence interval (CI), 548,000–723,000) occurred globally, of which 95% were from Africa [1]. Burkina Faso alone reported around 10.5 million cases and 3396 deaths that year, while Mali recorded nearly 3.4 million cases and 1305 deaths, placing both countries among the ten most affected settings worldwide [1]. These two countries are located in the Sahel region, where malaria transmission is highly seasonal, with most cases occurring within a 4- to 5-month window during and immediately after the rainy season [2]. This epidemiological pattern has shaped prevention strategies, including seasonal malaria chemoprevention (SMC) to prevent malaria in children under 5 years of age [3]. The latter, consisting of monthly administration of sulfadoxine–pyrimethamine (SP) and amodiaquine (AQ), has contributed to reducing the malaria burden, along with long-lasting insecticide-treated nets and indoor residual spraying [4]. Yet despite these successes, malaria burden remains extremely high.

The recent development and adoption of malaria vaccines, RTS,S/AS01 and R21/Matrix-M (R21/MM), offer a new opportunity to reinforce control efforts in high-burden areas [5, 6]. Specifically, the R21/MM vaccine, prequalified and recommended by the World Health Organization (WHO) in October 2023, demonstrated 77% (95% CI, 67–84) protective efficacy against clinical malaria over 12 months when administered before the transmission

season in Burkina Faso [7, 8]. A large multi-country Phase III trial confirmed high efficacy of 75% (95% CI, 71–79) when the primary series and booster doses were administered seasonally, prior to the peak season in Burkina Faso and Mali [9]. With adequate coverage, modeling studies suggest that malaria vaccines could avert 181,825 (range, 38,815–333,491) clinical cases and 629 (range, 250–646) deaths per 100,000 fully vaccinated children in perennial transmission settings over a 15-year period. In seasonal transmission settings, the estimated impact increases to approximately 202,017 (range, 29,868–405,702) clinical cases and 653 (range, 204–723) deaths per 100,000 fully vaccinated children [10].

However, a key question for national malaria control programs is: what is the most efficient strategy to deliver these vaccines at large scale? [11]. The current four-dose schedule, which includes a booster dose given approximately 1 year after the first dose, requires multiple service contacts and precise timing. Experience from RTS,S/AS01 pilot introductions showed significant drop-offs between primary doses and the booster, threatening the long-term effectiveness [12]. Additionally, in highly seasonal malaria transmission settings, age-based routine delivery throughout the year through the Essential Program on Immunization (EPI) approach may further limit effectiveness, as vaccination is not aligned with malaria risk period [13].

Evidence from a previous trial conducted in Burkina Faso and Mali showed that the combination of SMC plus a temporally targeted approach to RTS,S/AS01 vaccination (primary series and annual boosters delivered just prior to the rainy season) reduced malaria incidence and severe malaria by 60–70% compared to either intervention given alone [14]. However, this approach, now adopted by Mali with a target age of 5–36 months, requires eight service contacts (four for vaccination and four for SMC), making it costly and operationally demanding. Modeling studies have further shown that a seasonal vaccination approach would prevent more cases and be more cost-effective than the standard age-based EPI approach, in settings with strong seasonality [10].

SMC campaigns are already designed to reach large numbers of children through door-to-door or fixed-point strategies, consistently achieving administrative coverage rates above 90% in most Sahelian countries [3]. These campaigns are carefully timed to coincide with peak transmission months, and thereby, offering a potentially optimal platform for seasonal malaria vaccination. Integrating R21/MM delivery into SMC campaigns could therefore improve access, timeliness, and adherence, particularly for the critical booster dose, while enhancing efficiency through shared logistics, transport, and community mobilization. The SMC platform also makes it possible to reach older children who are not part of the EPI program, even though they are at high risk of malaria.

The Integrating Malaria Vaccine with SMC in West Africa (IMVACS) trial was therefore designed to generate pragmatic evidence on the optimal delivery strategy for malaria vaccination in highly seasonal transmission settings, in Burkina Faso and Mali.

Objectives

The primary objective of the trial is to evaluate whether, compared to routine EPI vaccination, integrated SMC vaccination has a non-inferior effectiveness, defined as the incidence of malaria among vaccinated children aged 5–36 months over a period of 12 months after the first dose.

The secondary objectives are:

(1) To evaluate the impact of integrated SMC vaccination compared to routine EPI vaccination on the incidence of clinical malaria among children aged 5–36 months over 24 and 36 months, and among children aged 3–59 months over 12, 24, and 36 months after the first dose;
(2) To evaluate the impact of integrated SMC vaccination compared to routine EPI vaccination on the prevalence of malaria infection at the end of the peak transmission in November 2025 and 2026;
(3) To compare R21/MM vaccine coverage (total doses, dropout rates from dose 1 to 3 and 3 to 4), reasons for non-vaccination, bednet usage, and SMC and EPI coverage between study arms;
(4) To describe the post-licensure safety profile of R21/MM; and

(5) To assess the acceptability, feasibility, and cost-effectiveness of both vaccination strategies.

Methods

This study protocol is reported in compliance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [15].

Trial design and settings

The IMVACS trial is a multisite, multidisciplinary, phase IV, two-arm, open-label, cluster-randomized, noninferiority trial in Burkina Faso and Mali to evaluate the effectiveness and real-life impact of a novel integrated delivery strategy of the R21 malaria vaccine alongside SMC among children in areas with highly seasonal malaria transmission (ClinicalTrials.gov, NCT06860178).

In this trial, a cluster is defined as the catchment area of a primary health center named "Centre de Santé et de Promotion Sociale (CSPS)" in Burkina Faso and "Centre de Santé Communautaire (CSCOM)" in Mali. The study clusters will be randomized at a 1:1 ratio to receive either year-round age-based routine EPI vaccination for children beginning at age of 5 months ("routine EPI vaccination") in Burkina Faso or an annual campaign of the 3-dose primary series in children 5–36 months prior to the malaria season and SMC campaign ("routine pre-SMC vaccination") in Mali versus an annual campaign of the 3- dose primary series aligned with SMC delivery in children aged 3–59 months ("integrated SMC vaccination") in each country. For the purpose of this study, all children aged 5–36 months in the control arm in Burkina Faso will be eligible to receive the Routine EPI Vaccination, similar to that in the control arm in Mali ("routine pre-SMC vaccination"). Both routine and intervention strategies were co-developed with national EPI and malaria programs of Burkina Faso and Mali.

The trial will be implemented in two rural health districts: the Boussé Health District in Burkina Faso and the Dioila Health District in Mali. The Boussé Health District covers 1595 km^2 and includes 86 villages. It comprises 34 CSPS, one medical center, and one referral hospital located in Boussé, serving approximately 200,000 inhabitants in 2024 (Fig. 1) [16]. The Dioila Health District includes 36 CSCOM and one referral health center, with an estimated population of 418,780 in 2024, including about 20,819 children under 5 years of age (Fig. 2) [17].

In both districts, malaria transmission is highly seasonal, with most cases occurring between July and October. SMC is delivered through four monthly rounds (July to October) targeting children aged 3–59 months and achieves high administrative coverage, estimated in 2024 at 100% in Boussé [16] and Dioila [18].

Study population and eligibility criteria

The study population comprises children in the target SMC age range (3–59 months) living in the catchment areas of the health centers selected for the study in the two countries. These children represent the populations most at risk of malaria.

Inclusion criteria similar in both study arms are as follows: (1) children aged 3 to 59 months; (2) residence in the catchment area of a health center assigned to either the control or intervention arm; (3) willingness of parents or caregivers to comply with study procedures; and (4) provision of written informed consent by a parent or caregiver. However, the eligibility for vaccination differs between arms regarding the age: (i) in the intervention clusters, children aged 3 to 59 months, the same target age as SMC, will be eligible to receive the R21/MM vaccine; (ii) in the control clusters, eligible children for vaccination are those aged 5 to 36 months as per WHO recommendation. Children in the control clusters outside the vaccination age range (i.e., aged 3–4 months and 37–59 months) will also be enrolled to enable evaluation of the impact of the integrated malaria vaccination with SMC on the incidence and prevalence of malaria in these non-vaccinated age groups.

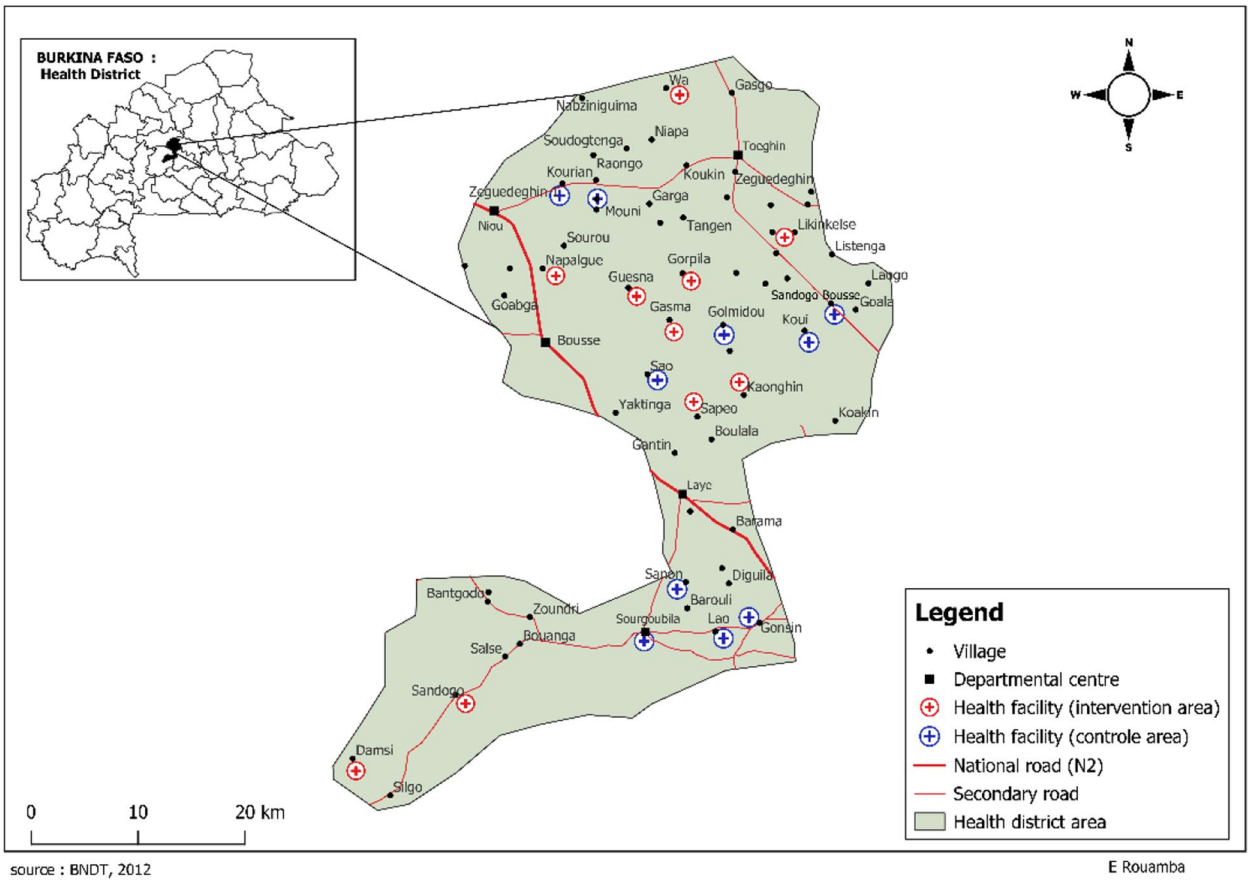

Fig. 1 Map of Boussé Health District in Burkina Faso with the 20 study clusters

For both arms, exclusion criteria include the following: (1) a history of allergic disease or hypersensitivity likely to be exacerbated by any component of the vaccine; (2) any history of anaphylaxis in relation to vaccination; (3) any significant disease, chronic illness, disorder, or condition which, in the opinion of the investigator, may place the participant at risk because of participation, influence trial outcomes, or compromise participation; and (4) a history of previous malaria vaccination.

Recruitment of trial subjects

Before initiating the participants' enrollment, a community engagement phase will be conducted in each study district. Meetings will be organized with local administrative and health authorities, traditional and religious leaders, and community health workers to present the study objectives, procedures, and potential benefits, and to obtain community support for implementation. The aim of these engagements will be to build trust, address concerns, and ensure that local populations are well informed about the study's purpose and timeline.

Following the engagement phase, a baseline census will be conducted across all clusters to enumerate households and identify children under 5 years of age. The census will serve as a foundation for age verification, eligibility screening, and planning of vaccination and SMC activities (Fig. 3). Age and sex will be collected before randomization during the census and subsequently verified during participant enrollment. Additional baseline characteristics, including cluster of residence, vaccination modality (door-to-door vs. fixed-site delivery), and contraindications to vaccination, will be collected during enrollment.

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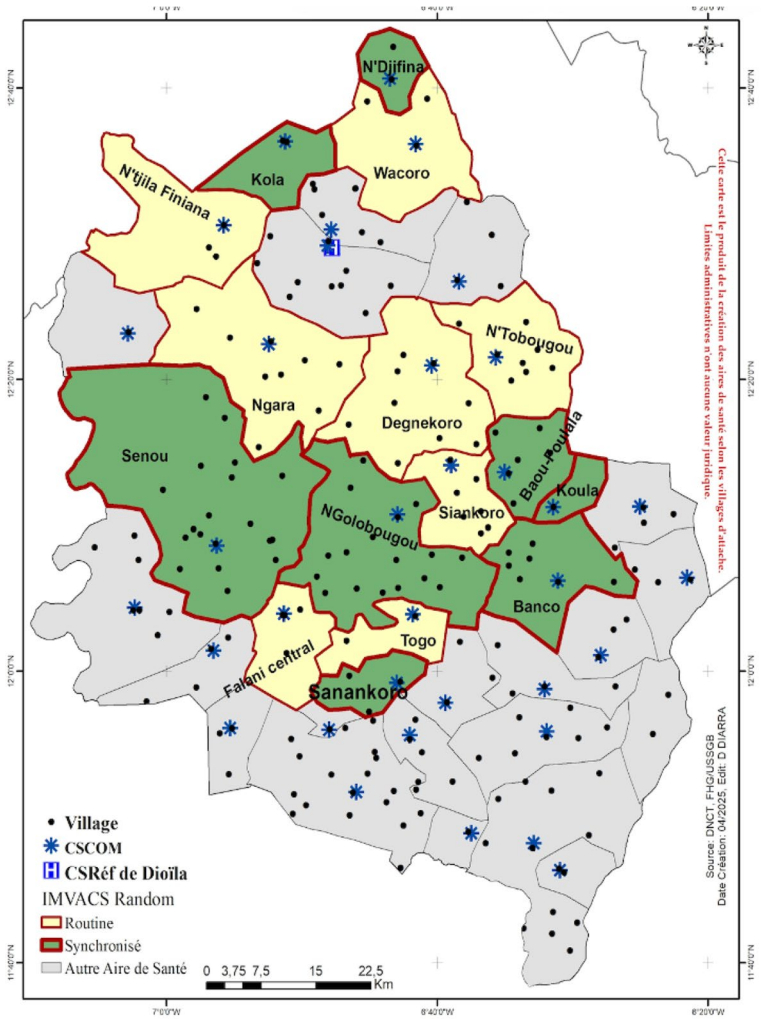

Fig. 2 Map of Dioila Health District in Mali with the 16 study clusters

Informed consent procedures in the intervention arm will be conducted approximately 1 month before the first SMC campaign in July 2025 to streamline implementation during campaign days. Parents or caregivers of eligible children will be approached at home by trained study staff, informed about the study, and invited to provide written consent. Children who will become newly eligible, either by reaching the required age or by moving into the study area, will also be consented and enrolled at the time of SMC distribution.

In the control arm, recruitment will take place at health centers during routine EPI vaccination in Burkina Faso or routine pre-SMC vaccination in Mali. Study staff trained on the protocol and study procedures will identify eligible children, inform parents or caregivers about the study, and obtain written consent before inclusion and vaccination.

Vaccination strategy

Vaccination in the control arm in Burkina Faso

In the control arm in Burkina Faso, R21/MM will be delivered through the routine EPI Vaccination. The 3-dose primary series of R21/MM, 4 weeks apart, will be administered year-round according to standard EPI programming (Fig. 4) Vaccination will be administered to children aged 5–36 months, the age range recommended for

	TRIAL PERIOD					
	Enrollment	Post-randomization				Close-out
TIMEPOINT	*-30 days* to 0	*Dose 1*	*Dose 2*	*Dose 3*	*Dose 4 (Booster)*	36 months after Dose 1
ENROLLMENT:						
Eligibility screen	X					
Informed consent	X					
Baseline demographics	X					
Cluster randomization	X					
INTERVENTION/ COMPARATOR:						
Intervention: R21/MM vaccination with SMC delivery [a]		X	X	X	X	
Comparator: Routine EPI (Burkina Faso) / Pre-SMC + routine EPI (Mali) [b]		X	X	X	X	
ASSESSMENTS:						
Adverse events following immunization (AEFI) [c]		X	X	X	X	
Adverse events of special interest (AESI) [c]		X	X	X	X	
Serious adverse event (SAE) [d]		X →	→	→	→	→ X
Clinical malaria surveillance [e]		X →	→	→	→	→ X

Fig. 3 Schedule of enrollment, interventions, and assessments of study participants. [a] In the intervention arm, children aged 3–59 months will receive the three-dose primary series of the R21/Matrix-M (R21/MM) malaria vaccine during the first three monthly rounds of the Seasonal Malaria Chemoprevention (SMC) campaign in 2025, with the fourth SMC round reserved for catch-up vaccinations for children who missed one or more doses. The booster dose will be delivered during the first SMC round in July 2026. [b] In the control arm, children aged 5–36 months will receive vaccination as per national Essential Program on Immunization (EPI) guidelines in each country: year-round EPI delivery in Burkina Faso, pre-seasonal vaccination prior to the SMC campaign followed by year-round EPI-based delivery in Mali. [c] Adverse events following immunization (AEFIs) and adverse events of special interest (AESIs) will be actively monitored for 15 min post-vaccination and passively up to 7 days after each vaccine dose. [d] Serious adverse events (SAE) will be monitored continuously throughout the study period. [e] Clinical malaria surveillance will be conducted continuously using routine surveillance for case detection

R21/MM, any time throughout the year, as soon as the child in the age range attends the EPI services. The booster dose will be administered 8 months after the third dose, as per national guidelines. Vaccination will be administered at the peripheral health centers in the control clusters by trained study staff and routine EPI health workers.

Vaccination in the control arm in Mali

In the control arm in Mali, R21/MM will be delivered through vaccination campaigns at health facilities. The 3-dose primary series of R21/MM will be administered at 4-week intervals to children aged 5–36 months, prior to the annual SMC campaign, as recommended by the ministry of health (Fig. 5). For children not captured during the pre-SMC mass vaccination campaigns, the vaccine will be available throughout the year at health facilities. The booster dose will be administered 12 months after the third dose, prior to the first SMC round in 2026 as per national implementation guidelines. A national communication and sensitization campaign will accompany the

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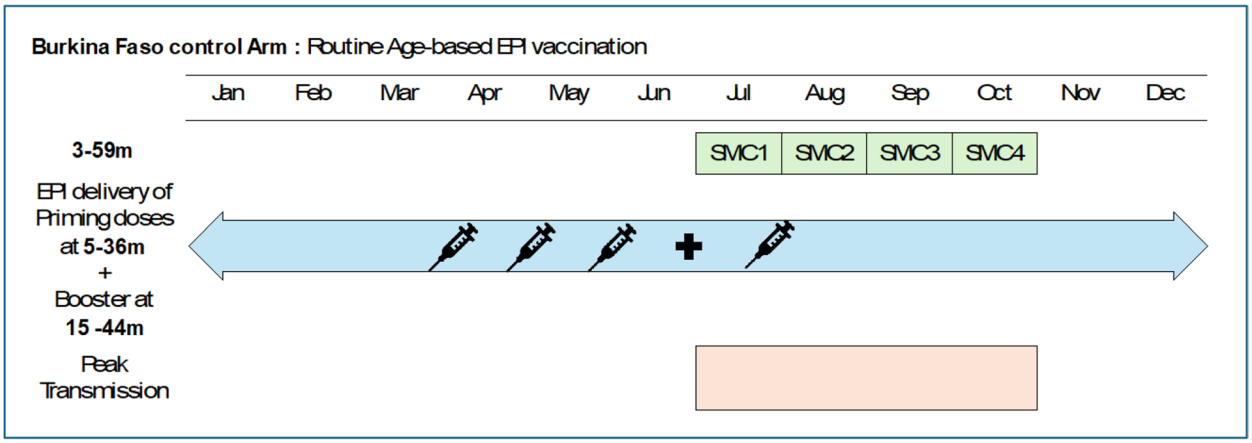

Fig. 4 Schematic representation of the vaccination schedule in the control arm in Burkina Faso ("routine EPI vaccination")

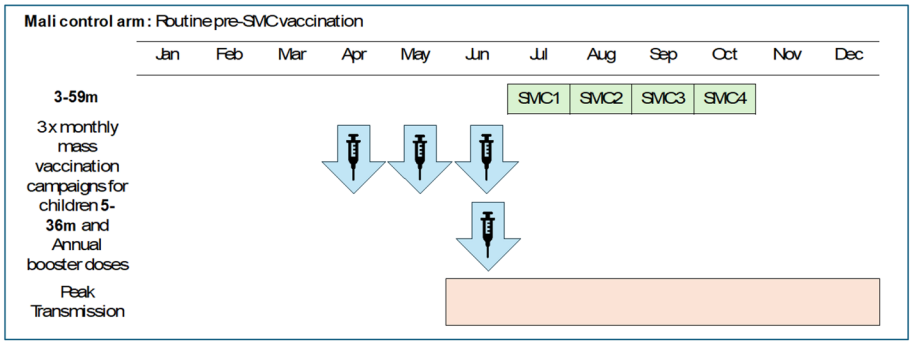

Fig. 5 Schematic representation of the vaccination schedule in the control arm in Mali ("routine pre-SMC vaccination")

vaccine introduction, focusing on timing of malaria vaccination relative to EPI schedules, management of mild side effects, and the complementarity between malaria vaccination and existing malaria control interventions. The vaccine will be administered by qualified EPI-trained health workers in accordance with national immunization protocols.

Vaccination in the intervention arms in Burkina Faso and Mali

In the integrated SMC vaccination arms in both countries, the 3-dose primary series will be administered together with monthly SMC distributions to all children in the SMC age group (3–59 months). The administration of the priming doses will target the first three SMC rounds in 2025. The fourth SMC round will be reserved for catch-up vaccinations for children who missed one or more doses. Children unable to complete the primary series during the SMC campaign will be invited to receive their remaining doses through the routine EPI services. The booster dose will be administered during the first SMC round of the 2026 transmission season (Fig. 6). Vaccination in the intervention arm will adhere to the SMC campaign strategy in each country: door-to-door administration in Burkina Faso and fixed-site administration in Mali. A similar profile of vaccinators used for EPI vaccines' administrations in Burkina Faso and Mali will be in charge of R21/MM administration during the SMC campaigns.

The expected demographic characteristics of the study participants are presented in Table 1.

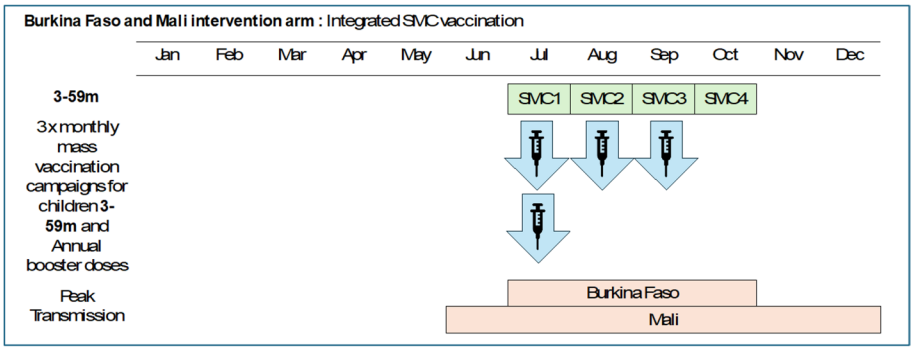

Fig. 6 Schematic representation of the vaccination schedule in the intervention arm in both Burkina Faso and Mali ("intervention SMC vaccination")

Table 1 Expected demographic characteristics of the participants in the IMVACS trial

Characteristic	Expected characteristics
Age	Children aged 3–59 months, the target age for SMC
Sex	Male and female
Gender	Gender will not be assessed because the study population consists of young children
Race, ethnicity and ancestry	Participants will include children from multiple ethnic groups residing in the study areas in Burkina Faso and Mali. No eligibility criteria will be based on ethnicity or ancestry
Socioeconomic status	Socioeconomic status is not an eligibility criterion and participants from a broad range of socioeconomic backgrounds will be included. Household-level indicators will be collected during cross-sectional surveys
Geographic location	Participants will be recruited from communities served by health facilities in the rural health districts of Boussé in Burkina Faso and Dioila in Mali, where malaria is seasonal

Vaccine administration

The vaccine will be administered intramuscularly under aseptic conditions, following national recommendations. For children aged 3 to 24 months, the anterolateral thigh will be the preferred injection site, whereas for those over 24 months of age, the deltoid muscle will be used in case of sufficient muscle mass. However, the vaccine will be administered in the anterolateral thigh in children over 24 months of age if the deltoid has insufficient muscular mass. All eligible children, regardless of age, will receive the same vaccine dose of 0.5 ml containing 5 µg of R21 with 50 µg of MM. The dose for each of the 3 doses in the primary series and the booster dose are identical. After vaccination, each child will remain under observation for 15 min to monitor the occurrence of any immediate adverse reactions.

Vaccination will be temporarily deferred in the presence of any of the following conditions:

- Moderate or severe acute illness including malaria episode at the time of vaccination. However, the vaccine will be administered to individuals suffering from minor illness such as diarrhea, mild upper respiratory tract infection with or without low-grade febrile illness, i.e., axillary temperature < 38.0 °C (with a negative malaria diagnostic test).
- Axillary temperature ≥ 38.0 °C at time of vaccination.

Once these conditions resolve, vaccination will proceed as planned. Of note, EPI vaccines can be co-administered with R21/MM, as per national guidelines.

Vaccine storage and handling

The R21/MM vaccine will be stored in accordance with national EPI cold-chain standards and the manufacturer's recommendations. Vaccines will be maintained at 2–8 °C throughout the supply chain, from central depots to the participating health facilities. Each study site will ensure that refrigerators, cold boxes, and temperature monitoring devices are available and functioning.

Refrigerators' temperature will be recorded twice a day, and any deviation outside the 2–8 °C range will be documented and reported to the study sponsor and the vaccine provider (Serum Institute of India, Pune, India). Transportation of vaccines from the central storage to the peripheral health facilities and during integrated SMC campaigns will be conducted using cold boxes equipped with temperature monitors.

Pharmacovigilance and safety monitoring

R21/MM was recommended by WHO for widespread use in October 2023, and was prequalified in December 2023 [4, 5]. Because R21/MM is newly prequalified and not yet implemented at scale, this study will integrate a post-licensure pharmacovigilance component to assess its safety and tolerability in real-world settings. Data on adverse events (AEs) following immunization (AEFIs) and adverse events of special interest (AESIs), as defined by WHO, and for this study defined as febrile convulsions occurring within 7 days of vaccination, will be collected throughout the study using complementary active and passive surveillance strategies: (1) immediate active monitoring of AEFIs within 15 min post-vaccination at all vaccination sites, (2) short-term active monitoring of AEFIs and AESIs during the 7 days following vaccination, (3) reinforced passive surveillance of AEFIs, AESIs and serious adverse events (SAEs) in health facilities during the entire study period.

Dedicated study personnel at each health center will collect and document AEFI and AESI data and report them through the respective national pharmacovigilance systems. All events will be assessed for frequency, severity, and causality using the Division of AIDS (DAIDS) table for Grading the Severity of Adverse Events (v2.1, July 2017) [19].

Pharmacovigilance training sessions will be held before study initiation for vaccinators, nurses, and clinicians to strengthen their ability to identify, manage, and report AEFIs, AESIs, and SAEs. A study-specific pharmacovigilance database will be created, and periodic pharmacovigilance reports will be sent to an independent Data and Safety Monitoring Board (DSMB), composed of three members with expertise relevant to the trial.

Cross-sectional surveys

Two cross-sectional surveys will be conducted in each country to assess malaria infection prevalence, R21/MM vaccine coverage, and uptake of other malaria interventions. The surveys will take place at the end of each malaria transmission season (November 2025 and November 2026) following SMC and vaccination activities. A simple random sampling design will be applied. All eligible children aged 3–59 months at the time of first vaccination and residing during the survey period will be invited to participate and consent obtained prior to study procedures. The first survey recall period will start when vaccination began and end on the date of the survey. The second survey recall period will cover the period between the first survey and the second.

During each survey, information will be collected on vaccination status (R21/MM doses received), SMC uptake, ownership and use of long-lasting insecticide-treated nets (LLINs), and uptake of other EPI vaccines. Blood samples will be collected by finger prick for malaria parasite microscopy and for the preparation of dried blood spots (DBS) for molecular analysis. Children presenting with fever or history of fever during the past 24 h will be screened for malaria using rapid diagnostic test (RDT) and will be treated if positive according to national guidelines.

Feasibility and acceptability studies

Qualitative longitudinal study (QLS) research methods will be used to evaluate the feasibility and acceptability of the two vaccination strategies (routine and integrated with SMC) among study participants' parents/caregivers, community leaders, health workers and policymakers [20, 21]. The qualitative study will cover a full, 2-year R21/MM delivery cycle with data collection in both control and intervention arms at two time points: (1) shortly after the completion of the primary vaccination series, and (2) shortly after administration of the booster dose.

An ecological framework approach will be applied with emphasis on the interplay and interdependency between individual, interpersonal, organizational, and policy levels. Qualitative data will be collected through non-participant observations, in-depth interviews, group interviews and focus group discussions to explore factors in service delivery, household, and broader social environments that will lead to R21/MM adoption and adherence. A core module of questions will be asked to all participants in the longitudinal panel at each round of data collection, facilitating continuity of data and enabling comparison across cases and through time. At the same time, flexible modules of questions will be incorporated into each round of data collection, building inductively on insights emerging from earlier rounds, and enabling new themes to be explored as they emerge. We will also assess the impact of the new vaccine on ITN use and care-seeking practices for malaria, and on the uptake of other childhood vaccine-preventable diseases.

Data will be analyzed thematically to identify behavioral, organizational, and contextual determinants that facilitate or hinder successful integration. The findings will inform the refinement of implementation strategies and communication approaches in future maternal and child vaccines.

Health economics study

The health economics study will evaluate the incremental cost-effectiveness of integrated SMC vaccination versus routine EPI vaccination (Burkina Faso) and routine Pre-SMC vaccination (Mali). Costs and outcomes will be measured from the societal perspective, and outcomes will be expressed in cost per case and, separately, cost per disability adjusted life years (DALYs) averted. Costs associated with the different vaccination strategies will be estimated by collecting data on direct and indirect costs to health systems and opportunity costs to vaccinees and their caregivers (beneficiaries). Beneficiary costs will be collected during the household coverage and prevalence survey, via case report forms developed to collect data on direct costs (transport, food, medication) and indirect costs (time and income loss) incurred by their household related to each intervention arm. Provider costs will be collected using custom-built spreadsheets structured to comprehensively capture the resources used for all intervention delivery related activities (excluding research activities) by cost category (person time, equipment, consumables including vaccines, storage, transport, overheads and other costs) by arm. Health economic focal persons in each country will be supported to gather, collate and analyze these data using local unit costs which will be converted to US dollars for analysis.

Malaria incidence estimates (primary clinical outcome) will be used to calculate malaria cases and DALYs averted by arm, adjusted for intervention coverage (using the coverage survey data). DALYs will be calculated based on the standard method used by the 2010 Global Burden of Disease Study. Parameter uncertainty will be assessed using deterministic and Monte Carlo probabilistic sensitivity analyses. The incremental cost-effectiveness ratio (ICER) of the intervention relative to the control will be calculated using the standard formula (i.e., change in cost/change in effect) and presented for interpretation on the cost-effectiveness plane against a range of willingness-to-pay thresholds as well as on the cost-effectiveness acceptability curve (CEAC). The CEAC plots the intervention's probability of being cost-effective against a range of threshold values, enabling policy makers to make their informed decisions by considering how sure they want to be about the decision in deciding whether the interventions are worth implementing. Appropriate economic evaluation modeling techniques will allow comparisons between the two trial arms, and beyond, i.e., by using secondary data on costs and outcomes

from other malaria vaccine economic evaluations in a comprehensive modeling exercise. A full health economics protocol detailing base case and sensitivity analyses will be published prior to full health economic analysis.

Outcomes

The primary outcome is the incidence of malaria, expressed as the proportion of children aged 5–36 months at the time of the first dose who present at least one malaria episode within 12 months after the first dose, comparing the integrated SMC vaccination strategy to routine EPI vaccination (Burkina Faso) or pre-SMC vaccination (Mali). Malaria cases will be collected by dedicated study staff based at each health center through passive case detection (PCD) during the study period. Malaria cases will be defined as fever or history of fever in the preceding 48 h, confirmed by a positive rapid diagnostic test (RDT).

Secondary outcomes include:

1) Malaria incidence, expressed as the proportion of children presenting at least one episode of malaria among children aged 5–36 months within 24 and 36 months after first vaccine dose, and among children aged 3–59 months within 12, 24, and 36 months post-first dose, using routine surveillance activities for case detection;
2) Malaria prevalence, expressed as the proportion of children with malaria infection at the end of the peak transmission period in November 2025 and 2026, assessed through annual cross-sectional surveys combining microscopy and molecular testing;
3) Vaccination coverage indicators, measured as the proportion of eligible children who completed the three-dose primary series and the booster dose, received only one or two doses, or did not receive the booster dose. Dropout rates (from dose 1 to 3 and from dose 3 to 4), reasons for non-vaccination, SMC coverage (including the proportion of participants having received all four SMC rounds), EPI coverage (defined as the completion of routine EPI vaccinations), and use of long-lasting insecticide-treated net (LLIN, proportion of participants having used a LLIN during the preceding night) will also be assessed during the cross-sectional surveys;
4) Safety outcomes, measured as the occurrence and frequency of AEs, AEFIs, AESIs, and SAEs following R21/MM vaccination, assessed through active and passive pharmacovigilance;
5) Qualitative study outcomes, namely the acceptability and feasibility of the vaccination strategies, assessed through in-depth interviews and focus group discussions conducted among policymakers, health managers, health providers, and caregivers;
6) Health economics study outcomes, measured as the incremental cost per child vaccinated, the incremental cost per malaria case averted, and the incremental cost per DALY averted.

Additional details regarding outcome definitions, analytical methods, and assessment procedures are provided in the statistical analysis plan (Appendix 1).

Data collection and management

All field data will be collected by trained study personnel using tablets equipped with the REDCap mobile application and following detailed standard operating procedures (SOPs). Standardized electronic case report forms (eCRFs) will be developed to ensure data quality and consistency. Data will be captured offline in the field and synchronized regularly to the server hosted by the trial sponsor.

Each enrolled child will be assigned a unique study identifier to maintain confidentiality and enable longitudinal tracking. Data will be collected on key study outcomes, including vaccination and SMC administration, adverse events, and confirmed malaria episodes.

A dedicated data management team will be responsible for performing routine data quality checks, including completeness, consistency, and accuracy, and will issue electronic queries to field teams for correction when

needed. During monitoring visits, data will be reviewed against source documents to verify accuracy, assess protocol compliance, and ensure timely resolution of discrepancies.

Power calculations

The number of clusters in each country was determined based on operational considerations and census data collected in the study districts. Power calculations rather than conventional sample-size calculations were performed. Because malaria incidence and the control groups differ between Burkina Faso and Mali, calculations were conducted separately for each country.

In Burkina Faso, malaria incidence among children under five was approximately 1997 per 1000 person-years in 2021 despite full SMC coverage [16]. Assuming a 70% vaccine efficacy for R21/MM, the expected lowest malaria incidence in the control arm is estimated at 600 per 1000 person-years, and 500 per 1000 person-years in the intervention arm. In Mali, where baseline incidence is lower (1590 per 1000 person-year in children under 11 months, and 1110 per 1000 person-year in children aged 1–4 years) [22], expected incidence values are 400 and 300 per 1000 person-years in the control and intervention arms, respectively.

Assuming 20 clusters in Burkina Faso and 16 in Mali, randomized in a 1:1 ratio, an average of children aged 5–36 months varying from 200 to 500 vaccinated children in each cluster in Burkina Faso and from 500 to 1000 in Mali (because clusters cover a larger population), a one-sided alpha of 0.025, and a non-inferiority margin of 0.1, several power calculation scenarios were explored for each country. These scenarios assessed the power to demonstrate the non-inferiority of the intervention arm compared with the control arm in malaria incidence (expressed as a proportion) by varying a range of parameters such as the intraclass correlation coefficient (ICC) and expected malaria incidence. The ICC assumptions were based on data from the Burkina Faso [23] and Mali [24] Malaria Indicator Surveys (MIS). The estimated national ICCs derived from malaria RDT positivity data were 0.0423 for Burkina Faso and 0.0397 for Mali. Based on these estimates, an ICC value of 0.04 was selected for the simulations. To account for potentially greater between-cluster variability, an ICC value of 0.08 was also considered in the power calculations. Power calculations were performed using PASS 2023 [25]. The corresponding contingency power tables are presented in Appendix 2.

An absolute non-inferiority margin of 0.1 is more stringent than the 20% relative value used in the literature if incidences are higher than 0.5 [12]. The non-inferiority margin is the larger reduction in efficacy that we would be willing to accept, or consider unimportant, between intervention and control, to still conclude that the intervention is non-inferior. An absolute increase in malaria incidence of 100 per 1000 person years seems acceptable in light of the potential other advantages of integrating R21 vaccination into SMC campaigns.

The randomization list will be prepared by the study statistician independently from the trials' sites. Stratification by the size of clusters will be performed to limit the imbalance in numbers of eligible children between arms. Stratification will use country-specific thresholds based on the 75th percentile of the cluster-size distribution according to the number of children eligible for vaccination identified during the census. Clusters above the threshold will be classified as high-size clusters, whereas those below the threshold will be classified as low-size clusters. The thresholds were set at 1000 children in Burkina Faso and 2500 children in Mali. Allocation will be implemented centrally and will not be disclosed to field teams until cluster assignment is finalized.

Statistical analysis

All analyses will be conducted in accordance with the SAP (Appendix 1).

In general, unless otherwise specified, analyses will be done at the individual level, accounting for clustering effect when data are collected individually, and at the cluster level as appropriate for aggregated data (for example data obtained from DHIS2). Statistical analyses for the assessment of the non-inferiority will be performed at the individual level.

The analysis populations will be objective-dependent and are described in detail in the SAP. The primary analysis will be conducted using a modified intention-to-treat (mITT) population including all eligible children aged 5–36 months at the time of the first vaccination who received at least one dose of vaccine. The analysis will be repeated in the per-protocol (PP) population, including all children from the mITT having received the full 3 doses of primary vaccine series. Separate populations will be defined for the secondary objectives, the cross-sectional surveys and the safety analyses. The criteria for inclusion in and exclusion from each analysis population are described in the SAP.

In general, missing data will be considered missing at random, and no imputation will be made. If the assumption of missing at random is not tenable, the extent and patterns of missing data will be explored across clusters within the same group and sensitivity analyses will be conducted, notably by excluding cluster(s) with extreme patterns.

Participant demographics and baseline characteristics will include age (3–4, 5–17, 18–36, and 37–59 months), sex, and vaccination modality (door-to-door or fixed-site delivery). Cluster-level characteristics will include the number of clusters, the mean cluster size, the number of villages, the total population, and the number of households in each cluster. All quantitative variables will be summarized as number of participants, number of missing data points, mean, and standard deviation. Categorical variables will be summarized as number of participants, number of missing data and percentage.

The study endpoints will be compared between groups using a two-sided significance level (α) of 5%, except for noninferiority comparisons, which will use a one-sided significance level of 2.5%. For the primary endpoint, superiority will be assessed only if noninferiority has first been demonstrated and no adjustment for multiplicity will be applied. For the primary analysis of noninferiority of the primary outcome, malaria incidence will be expressed as the proportion of children with at least one episode of malaria between the first vaccination and 1 year following this first dose and estimated using a generalized estimating equations (GEE) approach. Noninferiority will first be assessed separately for each country. Subsequently, data from the two countries will be pooled using an individual participant data meta-analysis approach, after assessing heterogeneity between countries and applying either fixed or random effect model, depending on the level of heterogeneity.

Additional adjusted analyses will also be performed as secondary analysis, including covariates such as the stratification factor used during randomization (size of the catchment area), age, sex, the number of vaccine doses received, the number of SMC rounds received, and other relevant baseline characteristics showing substantial imbalance between groups. Estimation of vaccine coverages will be performed for each dose, for the full 3-dose vaccination, and with the booster during the second survey, at the individual level, controlling for clustering effects. Comparisons on vaccine coverages between groups will be performed only in the age group of 5–36 months.

Safety analyses will include all vaccinated participants. Adverse events, including AESIs, AEFIs, and SAEs, will be summarized as frequencies and percentages, by country, group and overall.

All statistical analyses will be performed using Stata version 19 or later [26] and all estimates will be reported with their 95% CIs. The results of the analyses will be reported in accordance with the CONSORT 2025 reporting guidelines [27].

Trial oversight

An independent Trial Steering Committee (TSC) comprising three independent members and the leads of the IMVACS work packages will be established before the start of study. The general task of the committee will be to provide independent advice and expertise on the design and conduct of the study, and to ensure its smooth execution. The committee will meet prior to the start of the study and at regular intervals to review progress, consider recommendations from the DSMB and relevant ethics committees, and agree on communications relating to the study.

Discussion

To the best of our knowledge, IMVACS is the first phase IV trial evaluating the effectiveness of the integrated delivery of R21/MM with SMC for children living in highly seasonal transmission settings. The study focuses on the operational question of whether integrating R21/MM vaccination into SMC campaigns can reduce malaria burden in children under 5 years as compared to the routine EPI vaccination in Burkina Faso or the routine Pre-SMC vaccination in Mali.

The IMVACS trial combines effectiveness, pharmacovigilance, and implementation evaluations, including the acceptability, the feasibility and the cost-effectiveness of the integrated delivery of the R21/MM malaria vaccine alongside SMC under real-world conditions. This integrated approach allows evaluation of vaccine delivery beyond the constraints of routine EPI schedules, extending protection to older children who remain at high risk of malaria but are not eligible under age-based EPI strategies. In addition, annual vaccination aligned with the malaria season may provide improved protection toward the end of peak transmission periods. The cluster-randomized approach, use of routine delivery platforms, and inclusion of economic and qualitative components are expected to generate comprehensive evidence to guide national and regional malaria control policies.

The trial will also provide insights into the operational realities of introducing a new vaccine in complex field settings. In Mali, the three-dose vaccination series in the control arm was planned as a campaign from April to June, before the onset of malaria transmission. However, delays in national vaccine deployment resulted in vaccinations starting in June, closer to the rainy season. Additionally, due to reductions in global financing for SMC in 2025, Mali transitioned from the standard door-to-door SMC delivery model to fixed-site SMC distribution within villages. In contrast, Burkina Faso maintained the door-to-door SMC delivery approach. These differences provide an opportunity to compare the performance and feasibility of two delivery modalities within the same regional and epidemiological contexts.

Integrating R21/MM vaccination into SMC campaigns could enhance program reach and timeliness by aligning vaccination with the malaria season, while leveraging established SMC campaign logistics, community mobilization, and supervision networks [28]. Importantly, this approach could contribute to improving adherence to the fourth booster dose by maintaining annual contact with parents/caregivers through the existing SMC platform. If successful, such an integration approach could support sustained protection across multiple transmission seasons while reducing missed opportunities and inequities for vaccination and optimizing resource use.

Some limitations must be acknowledged. As a community-based intervention, local variations in implementation and population mobility may affect comparability between clusters [29, 30]. Moreover, while the study settings are representative of Sahelian malaria transmission, they may not capture the full diversity of operational contexts across the region. A study currently underway in Chad (COSAV-R21; ClinicalTrials.gov NCT07038837) is assessing a similar integrated delivery strategy and will help contextualize and strengthen the generalizability of IMVACS findings. Importantly, these sources of variability reflect real-world conditions and align with the pragmatic objectives of the trial.

Ultimately, IMVACS is expected to generate evidence to inform national and global policies on whether integrating malaria vaccination into SMC campaigns represents a viable and more cost-effective strategy compared to current routine vaccine delivery through the EPI. The results will inform how to optimize the deployment of R21/MM in seasonal transmission settings and strengthen integrated approaches for malaria prevention in Africa.

Trial status

The trial is currently ongoing under protocol version 1.3 (1 April 2025). Recruitment in the control arm started in June 2025 in both countries. Recruitment in the intervention arm is aligned with the SMC schedule in both countries, with 4 rounds from July to October. Booster doses are planned to be held in July 2026 in the intervention

arm. Recruitment is expected to end in January 2026. Cross-sectional surveys, cost-effectiveness and acceptability and feasibility studies started in November 2025.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1186/s13063-026-09970-3.

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Dissemination policy Trial findings will be disseminated to participants, communities, healthcare professionals, and policymakers, and the wider scientific community through stakeholder meetings, conference presentations, and publication in open-access peer-reviewed journals. Authorship will follow the ICMJE criteria.

Authors' contributions HT conceived the study. HT, HMN, KK, VB, MC, JH, EW, SO and DS developed the study design. HMN drafted the protocol. EB designed the statistical analysis plan for the study and conducted the sample size calculations. EB, GM, MD, SG and LAD contributed to the refinement of the protocol. HMN, SO and HT wrote the draft of the manuscript. All authors read and approved the final manuscript.

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Data availability The full study protocol and code will be available from the IMVACS consortium through the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate The study protocol, informed consent documents, and patient information sheets have been reviewed and approved in Burkina Faso by the "Comité d'Ethique pour la Recherche en Santé (CERS, ref. number 2025-01-09)" and the "Agence Nationale de Régulation Pharmaceutique (ANRP, ref. number: 2025-1502)" of the Ministry of Health. In Mali, the study was approved by the institutional ethics committee of the University of Science, Technology and Technology of Bamako (USTTB, ref number: 2025/82) and the Ministry of Health (ref. number: 2025-000449). The study was also approved in France by the ethics committee of Médecins Sans Frontières (MSF-ERB, ref. number: ERB 2515), which is the parent organization of EPICENTRE, the sponsor of the trial, and in the UK by the ethics committee of Liverpool School of Tropical Medicine (ref. number: 25-005). Any protocol amendments will be communicated to the ethics committees.

Trained study staff will obtain written informed from parents/caregivers of all study participants prior to any study procedures.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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