Study Protocol

Determining whether mass campaigns with fractional dose PCV10 would accelerate herd protection against pneumococcal transmission in Sub-Saharan Africa

Primary Sponsor	Rebecca F. Grais
Sponsor's Investigator	Matthew E. Coldiron
Co-investigators	Ousmane Guindo Issaka Soumana Aitana Juan-Giner Rabiou Dare Hassan Abdoul Nasser Katherine Gallagher Wangeci Kagucia John Ojal Eric Adehossi Anthony Scott Angela Karani Souleymane Brah
Manufacturer	Serum Institute of India Pvt. Ltd., Pune, India
Registration	Clinicaltrials.gov NCT05175014 PACTR Number: PACTR20211257448484

Declaration of Confidentiality

The information contained herein is confidential and therefore are provided in confidence as a potential examiner or investigator.

It is understood that this information will not be disclosed to others without the written permission of the Sponsor, except to the extent necessary to achieve the consent of those who can participate in the study.

General Information

Type of study	Clinical trial
Registration of Study	Clinicaltrials.gov NCT05175014 PACTR Number: PACTR20211257448484
Study product	PCV10 vaccine (Pneumosil®)
Sponsor and Sponsor representative	Epicentre, Rebecca F. Grais
Sponsor's Investigator	Matthew E. Coldiron, Epicentre
Manufacturer	Serum Institute of India Pvt Ltd., Pune, India
Funding	EDCTP
Principal Investigator	Matthew E. Coldiron, Epicentre
Co-Investigators	Ousmane Guindo, Epicentre Issaka Soumana, Epicentre Aitana Juan-Giner, Epicentre Rabiou Dare, Niger Ministry of Public Health Hassan Adboul Nasser, National Immunization Program Katherine Gallagher, KWTRP and LSHTM Wangeci Kagucia, KWTRP John Ojal, KWTRP and LSHTM Eric Adehossi, Université Abdou Moumouni Anthony Scott, KWTRP and LSHTM Angela Karani, KWTRP Souleymane Brah, Université Abdou Moumouni
Site of Study	Madarounfa District, Niger
Consortium of partners	Epicentre Paris and Niger London School of Hygiene and Tropical Medicine, UK African Research Collaboration for Health Limited (KWTRP), Kenya Université Abdou Moumouni, Niger
Data Monitoring Committee	DSMB

1 Signature page

By my signature below, I hereby confirm that I will conduct the study described in this protocol in compliance with ICH/GCP and the version of such protocol agreed to by the applicable regulatory authorities and approved by all Institutional Review Board and Ethical Committees.

Sponsor, Rebecca F. Grais

_____ 13 December 2021

Signature Date

Principal Investigator, Matthew E. Coldiron

13 December 2021

_____ _____

Signature Date

Please note that study responsibilities are documented in the Trial Master and Investigator Site Files.

2 Trial Registration Information

Primary Registry and Trial Identifying Number

ClinicalTrials.gov NCT05175014

Date of Registration in Primary Registry

13th December 2021

Secondary Identifying Numbers

PACTR20211257448484

Sources of Monetary and Material Support

EDCTP

Sponsor

Epicentre

Primary Sponsor contact

Rebecca F. Grais, 14-34 Avenue Jean Jaurès, 75019 Paris, rebecca.grais@epicentre.msf.org

Contacts for Queries

The following individuals will provide responses to general queries including information about current recruitment status:

Matthew Coldiron, Epicentre: matthew.coldiron@epicentre.msf.org

Issaka Soumana, Epicentre, Maradi, Niger: Issaka.soumana@epicentre.msf.org

Public Title

Mass campaigns with fractional dose pneumococcal vaccines in sub-Saharan Africa

Scientific Title

Determining whether mass campaigns with fractional dose PCV10 would accelerate herd protection against pneumococcal transmission in Sub-Saharan Africa

Site of Recruitment

Madarounfa District of Niger

Health Condition(s) or Problem(s) Studied

Pneumococcal carriage

Intervention

Mass vaccination campaign with one single dose PCV10 vaccine administered as a full dose or fractional dose

Key Inclusion and Exclusion Criteria

For participation in pneumococcal carriage surveys

Inclusion criteria:

(1) Aged 1-9 years
(2) Residing in the villages included in the study
(3) Parent or caretaker provides informed consent for the child to participate in the study

Exclusion criteria:

(1) Head or facial injuries that contraindicate nasopharyngeal swabbing
(2) Any condition or criteria, including acute or chronic clinically significant abnormality that in the opinion of the investigator might compromise the wellbeing of the participant or interfere with the outcome of the study

For participation in mass vaccination campaigns (with full or fractional dose PCV10)

Inclusion criteria:

(1) Aged 1-9 years
(2) Residing in the villages included in the study and allocated to vaccination
(3) Head of the household or main caretaker provides consent for the child to be vaccinated

Exclusion criteria:

(1) Hypersensitivity to any component of the vaccine, including diphtheria toxoid
(2) Vaccination with a PCV vaccine within the previous 4 weeks, as there should be a minimum of 4 weeks between doses
(3) Moderate or severe febrile illness (temperature ≥39°C) is a temporal contraindication and the child should not be vaccinated until improvement
(4) Any condition or criteria, including acute or chronic clinically significant abnormality that in the opinion of the clinical staff might compromise the wellbeing of the volunteer

Study Type

Phase IV cluster-randomized controlled trial

Date of First Enrolment

November 2021

Target Sample Size

63 clusters with a total population between 500 and 4000 will be randomized in a 3:3:1 ratio to receive either (1) mass campaigns targeting children aged 1-9 years with a single full dose of PCV10, (2) mass campaigns targeting children aged 1-9 years with a single fractional (1/5) dose of PCV10, or (3) no mass campaigns (control arm). It is estimated that approximately 32 000 children will be targeted by the campaigns.

Cross-sectional surveys conducted at baseline prior to the vaccination campaign, and approximately 6 months after the vaccination campaign, will collect nasopharyngeal swabs from children aged 1-9 years. Simple random sampling will be used to select 36 households from each of the 63 clusters. One child aged 1-9 will be randomly selected from each household to participate. A total of 2268 children will be targeted in each survey.

Recruitment Status

Not yet recruiting

Primary Objective

To evaluate whether a mass vaccination campaign targeting children approximately 1-9 years of age with a full dose of PCV is superior to the absence of vaccine in reduction of VT carriage prevalence at 6 months post-campaign, and subsequently to evaluate if a single 20% dose of PCV is non-inferior to a full dose.

Secondary Objectives

- To measure the age-stratified prevalence of NP carriage of *S. pneumoniae* in children 1-9 years of age in the study area.
- To determine the effect of a mass vaccination campaign with one full dose of PCV in children 1 to 9 years of age on VT pneumococci carriage 6 months after vaccination
- To assess the occurrence of adverse events (AE) during 7 days and serious adverse events (SAE) during 28 days after administration of fractional and full doses of PCV.
- To model the potential effect of fractional dose PCV campaigns in other contexts using the results of the clinical trial.
- To develop recommendations on how a potential future fractional dose PCV mass campaign could be successfully planned, communicated, delivered and integrated into national immunization programmes using qualitative analysis.

Data Safety and Monitoring Board

To be named

3 Abbreviations

AE	Adverse Event
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
EC	Institutional Ethical Committee
ERC	Ethics Review Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ISF	Investigator site file
LMIC	Low and middle-income countries
MOH	Ministry of Health
MSF	Doctors Without Borders
NP	Nasopharyngeal
NRA	National regulatory authority
PI	Principal Investigator
PIS	Patient information sheet
SAE	Serious Adverse Event
SII	Serum Institute of India Pvt. Ltd
SSL	Secure Sockets Layer
SOP	Standard operating procedures
SUSAR	Suspected unexpected serious adverse reaction
VT	Vaccine-type
WHO	World Health Organization

4 Background

In 2015, there were an estimated 8.9 million cases (uncertainty range 7.7-10.6 million) of clinical pneumococcal pneumonia globally, with 2.4 million cases estimated in Africa alone (uncertainty range 2.1-3.1 million) (1). These figures represent a global reduction of 37% from 14.2 million cases (12.3 million–16.9 million) in 2000. However, pneumococcal disease continues to be a leading cause of severe disease and death representing 10% of all death in children under 5 years of age (1). These deaths occur disproportionally in low- and middle-income countries (LMICs), with approximately 50% of global pneumococcal deaths estimated to occur in 4 countries: India, Nigeria, Pakistan and the Democratic Republic of Congo (1).

Streptococcus pneumoniae is part of the normal bacterial flora in the nasopharynx (NP) (2). Colonization with *S. pneumoniae* is generally asymptomatic, but in some cases it spreads and causes disease, including sinusitis, otitis media, bacteraemia and meningitis, referred to as invasive pneumococcal disease (IPD) (3). It has been estimated that approximately 75% of cases of IPD, and 83% of cases of pneumococcal meningitis, occur in children <2 years, although these estimates may vary by country, study method and socio-economic status within countries (4). There are over 90 known pneumococcal serotypes identified throughout the world, but a small number are responsible for most severe disease (4). The pneumococci are easily transmitted from person to person, generally within families, from older to younger siblings and between households within communities (2). NP colonization generally occurs early in life (2), with some studies reporting a peak in children younger than 2 years of age (5). Studies have estimated NP carriage prevalence >70% among children <5 years in Kenya (6), The Gambia (7) and Uganda (8) in the period before introduction of pneumococcal conjugate vaccines (PCV).

PCVs were introduced in Africa from 2011 onwards with support from Gavi, the Vaccine Alliance. At present there are three PCVs that are WHO-prequalified: Synflorix™, a 10-valent vaccine (PCV10); Prevenar®, a 13-valent vaccine (PCV13); and the most recently prequalified PCV10, Pneumosil®. The vaccines contain different serotypes, though each includes serotypes most frequently responsible for severe disease, and are considered effective against pneumococcal disease (4,9). Vaccination with PCV has a direct effect reducing carriage amongst those vaccinated, but also has the capacity to reduce carriage amongst unimmunized populations by interrupting transmission (10). This indirect effect of vaccines that goes beyond individual protection is linked to the reduced exposure to *S pneumonia*e vaccine serotypes (VT) in communities where a large proportion of the population have been vaccinated (10), i.e., herd protection.

To date, the majority of countries have introduced PCV into routine immunization programs (11). Following WHO recommendations, most LMICs have introduced the vaccine in a 3 dose schedule, starting at 6 weeks of age and with vaccine doses separated by 4 weeks (4). In settings with high disease burden and mortality, catch-up vaccination at the time of vaccine introduction has also been recommended to accelerate the impact of vaccination. Catch-up vaccination should ideally target children 1 to 5 years of age and should prioritize children <2 years of age (4). The WHO Framework for vaccination in humanitarian emergencies also recommends PCV mass campaigns following assessment of local epidemiology and other risk factors (12). In humanitarian emergencies, mass campaigns could rapidly establish direct and indirect protection when vulnerability is highest and routine health services are disrupted (13).

Coverage of PCV vaccination through routine immunization has been heterogenous. Some countries achieved >80% coverage quickly after introduction of the vaccines and have been able to sustain this over time. Other countries, however, have difficulties and continue to have low coverage (<50%) years after vaccine introduction (14). Carriage studies conducted in LMICs with high vaccination coverage have shown some level of residual VT carriage. For instance, in Malawi, 7 years after the introduction of PCV13, VT carriage is reported at 16.6% VT amongst 3-5 years old vaccinated children (15). In a study conducted in Kilifi, Kenya, 5 years after PCV10 introduction, VT pneumococci is identified in 6% of children aged less than 5 years and 8% of infants(16). However, it has been considered that current vaccination strategies are unlikely to reduce this further (17). Further complicating this, although decreasing VT colonization with PCV decreases subsequent IPD, the exact nature of the relationship is not well-described, and a target threshold necessary to establish her protection has not been established. Regardless, in countries with low vaccination coverage, the beneficial effects of PCVs have yet to be fully realised. Mass campaigns as a strategy to boost herd protection in areas of low routine vaccination coverage, could have a role in these different settings.

However, a barrier to PCV vaccination strategies is their cost. From 2001 to 2017, the cost to fully immunize a child in LMICs has increased from USD 1.00 to approximately USD 32.00[1], with vaccines against rotavirus and pneumococcal disease accounting for three quarters of the total cost of vaccinating a child (11). These high costs also impact considerations of PCV for mass vaccination campaigns (13).

5 Rationale

Vaccination campaigns targeting children up to 5 years of age, in addition to routine vaccination in infancy, have been shown to have an effect in the reduction of VT carriage and disease (18,19). However, the benefits of catch-up campaigns are reduced if they delay or affect coverage of routine vaccination activities, and if those in the catch-up age cohort have only moderate vaccine serotype carriage and disease (4). Moreover, there is limited evidence on the optimal deployment strategies for mass campaigns (4,13). Some programs, for instance, have used a single dose while others have considered that two PCV doses are needed for children 12-23 months of age (4). The target age group for mass vaccination has also varied. WHO recommendations for catch-up vaccination target children <5 years of age. However, this target has been questioned as there is no clear rationale for this limit (13). Whilst it has been considered that children <5 years of age usually bear the heaviest burden of pneumococcal pneumonia, this is not necessarily the case in all settings. In crisis situations or in settings with high prevalence of malnutrition, the high pneumococcal carriage prevalence is likely to extend to older age groups and vaccination of a larger age group might be needed to control VT circulation (13). Consequently, the inclusion of older children in campaigns might be beneficial in particular settings where older children contribute substantially to the transmission of pneumococci (18).

Niger introduced PCV13 into the routine vaccination program in 2014, with doses given at 6, 10, and 14 weeks of age, without catch-up campaigns. Administrative coverage with 3 doses was estimated to be 81% in 2019, however, coverage estimated directly in the Maradi region is considered to be

[1] Excluding HPV vaccine.

around 48%[2], suggesting a heterogeneity in the reach of the program. Currently, for Gavi-supported countries, such as Niger, PCV13 vaccine has a cost of US$3 per dose. The most recently WHO prequalified PCV vaccine (Pneumosil®) has, however, the lowest price at US$2 per dose. The vaccine cost is also far below current market prices offered by the other manufacturers for uses outside Gavi support (20). Consequently, as the overall cost to health systems is lower, this provides more opportunities to countries and organizations supporting countries on the choice of how to use the vaccine. Pneumosil® is a PCV10 manufactured by Serum Institute of India Ltd (SIIL), tailored specifically to African, Asian, and Latin American countries by including serotypes 6A and 19A, two serotypes available in PCV13 but not in the Synflorix™ PCV10 (21). Although Pneumosil® is a PCV10, which has fewer serotypes than PCV13, there is currently insufficient evidence to show any difference in impact between PCV10 and other PCV vaccines (4,9). Moreover, although product switching, in this case from PCV13 to PCV10, has not been recommended (4), a mass campaign would be directed to children older than the routine vaccination target group (infants), and for many this would be done years after they received their primary schedule.

Although a relatively low cost PCV (Pneumosil®) is currently available, mass campaigns targeting large age groups with a full dose of vaccine would require a large quantity of vaccine and might not be sustainable over time. Fractional dosing of licensed vaccines have been considered for situations of high vaccine costs and/or supply chain shortages (22). Fractional doses administered through the intradermal route have been assessed for several vaccines including influenza, rabies, hepatitis B, inactivated polio vaccine (IPV) (23) and through the standard subcutaneous route for yellow fever vaccine (24). Following available evidence, fractional doses of IPV, rabies and yellow fever vaccines are recommended by WHO and used routinely in several countries and for outbreak response (25,26). Data from the original dose-finding studies for a pentavalent PCV indicate that a dose as low as 1/4th of the current dose in PCV10 could elicit adequate immunogenicity (27). A non-inferiority trial of fractional doses of PCV10 and PCV13 is currently underway in Kenya (ClinicalTrials.gov Identifier: NCT03489018; PI Anthony Scott). Following this, fractional doses of PCV could be a solution to overcome the high PCV costs, increase vaccine access and expand vaccination benefits through alternative strategies.

This study aims to assess the impact of a mass campaign with a single, fractional dose of Pneumosil®, a PCV10, on VT carriage. A 20% fractional dose (1/5th) will be used as a practical formulation to prepare and administer. This study will assess whether the impact of a single fractional dose mass campaign on carriage is non-inferior to a single full dose mass campaign in a cluster randomized trial in a low coverage setting in Niger. The results would provide evidence of the population-level direct and indirect impact of fractional dose in older children which will be completed by mathematical modelling, to inform the policy debate regarding PCV dosing schedules in different contexts. This trial and the modelling exercises that follow, would allow for larger scale evaluation of fractional dose PCV strategies in multiple contexts.

[2] Administrative coverage from UNICEF Immunization data https://data.unicef.org/topic/child-health/immunization/
Actual coverage from MSF-Epicentre data.

6 Study Objectives

Primary objective

To evaluate whether a mass vaccination campaign targeting children approximately 1-9 years of age with a full dose of PCV is superior to the absence of vaccine in reduction of VT carriage prevalence at 6 months post-campaign, and subsequently to evaluate if a single 20% dose of PCV is non-inferior to a full dose.

Secondary objectives

- To measure the age-stratified prevalence of NP carriage of *S. pneumoniae* in children 1-9 years of age in the study area.
- To determine the effect of a mass vaccination campaign with one full dose of PCV in children 1 to 9 years of age on VT pneumococci carriage 6 months after vaccination
- To assess the occurrence of adverse events (AE) during 7 days and serious adverse events (SAE) during 28 days after administration of fractional and full doses of PCV.
- To model the potential effect of fractional dose PCV campaigns in other contexts using the results of the clinical trial.
- In the setting of a qualitative study, to develop recommendations on how a potential future fractional dose PCV mass campaign could be successfully planned, communicated, delivered and integrated into national immunization programmes using qualitative analysis.

6.1 Definition of outcomes

Effect of PCV10 campaign

The effect of a single dose PCV10 campaign in the reduction of VT carriage will be assessed by: first, assessing the superiority of a campaign using full doses of PCV10 compared to control group without vaccination; and second, by establishing the non-inferiority of a campaign using fractional doses of PCV10 compared to a campaign using full doses.

NP carriage will be measured in the 3 study arms (full dose arm, fractional dose arm and control arm) in a baseline survey implemented prior to the vaccination campaign and in a post-vaccination survey conducted 6 months post-vaccination campaign.

The NP carriage of VT *S. pneumoniae* will be measured as the proportion of participants that are colonized with any of the 10 serotypes covered by PCV10 at each time point. The reduction in NP carriage will be calculated by comparing the proportion of children carrying VT pneumococci 6 months post-vaccination to baseline, at the time of vaccination. Prevalence of colonization of non-VT serotypes will also be described at both timepoints.

Vaccine safety

Vaccine safety will be monitored up to 28 days after vaccination and all AEs and SAEs will be recorded.

Cost-effectiveness and modelling study

An age-structured, dynamic, deterministic model of pneumococcal transmission will be constructed to estimate the impact of mass fractional dose PCV campaigns on VT carriage. The model will use the

data on social interactions between age groups and PCV coverage estimates collected during the baseline survey as well as the results of the VT carriage from the baseline survey.

Based on the modelled epidemiological impact of PCV10 mass campaigns, with both full and fractional doses, a cost-effectiveness analysis will be performed to estimate the incremental cost-effectiveness ratio of routine PCV10 mass campaigns.

The modelled epidemiological impact and cost-effectiveness of a fractional dose mass campaign will be used to inform ongoing discussions of dose-sparing strategies and the use of single-dose fractional PCV in acute humanitarian emergencies.

Facilitators and barriers to implementing mass campaigns of fractional dose PCV

A qualitative study will be conducted among parents, healthcare workers, national and international stakeholders to develop insights and recommendations on how a potential future fractional dose PCV mass campaign could be successfully planned, communicated, delivered and integrated into national immunization programmes.

7 Methodology

7.1 Overall study design

A Phase IV, 3-arm, observer-blinded, cluster-randomized controlled trial will be implemented in rural villages of the Madarounfa District of Niger. A schematic representation of the trial is presented in

After results of the baseline survey are known, clusters will be randomized to full dose, fractional dose or control arm in 3:3:1 allocation ratio. The trial will be conducted in 63 clusters, with 27 randomized to full dose arm, 27 randomized to fractional dose arm and 9 randomized to a control arm. Clusters will be composed of a village or group of closely-neighbouring villages that share a school or market, and will be limited to a population of between 500 and 4000 persons. Stratified randomization will be used to account for proximity to the nearest health centre (<5 km vs ≥5 km). In the event of significant imbalance in carriage of VT pneumococci between clusters in the baseline survey, randomization will also be stratified by baseline prevalence. Vaccination will target all children aged 1 to 9 years of age residing in the selected villages. (If baseline survey data unexpectedly shows very low prevalence of carriage at the extremes of this age range, the target age group may be adjusted upon recommendation of the trial steering committee.) We estimate that children eligible for the vaccination campaigns will represent 30% of the total population. With an estimated average of 2000 people per cluster, vaccination will target 600 children 1-9 years of age in each cluster receiving vaccine. In total, in the 54 clusters receiving vaccine, the mass vaccination campaign with single full- or fractional-dose PCV will target approximately 32,400 children 1-9 years of age.

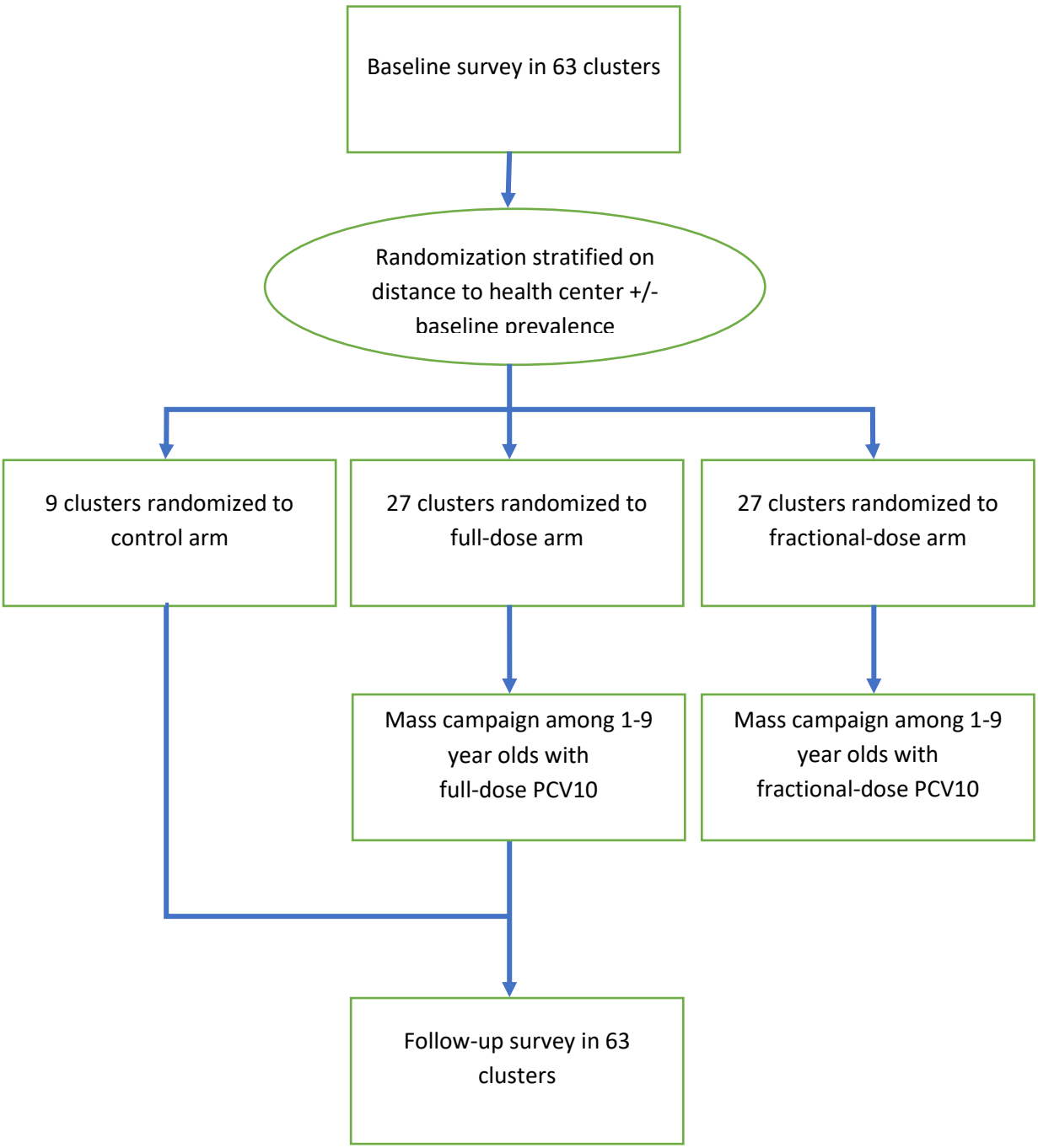
Prior to the mass vaccination campaign, a cross-sectional survey will be implemented to estimate community-level carriage of VT pneumococci, as well as to collect data on household composition, social interactions and PCV vaccination coverage in the routine EPI. A total of 36 households in each cluster will be invited to participate in the cross-sectional survey. This sample size may be re-evaluated based on the results of the baseline survey.

Selection of households will be based on probability sampling. The required number of households in each cluster will be randomly selected using simple random sampling based on an exhaustive list of heads of household in the cluster. Six months after the mass vaccination campaign, the post-

vaccination cross-sectional survey will be implemented. This will be used to estimate community-level carriage of VT pneumococcus after a single-dose PCV delivered as full or fractional dose as well as carriage in the clusters that received no vaccination. The survey will target the same number of children as the baseline survey and will follow the same methodology with the households selected by simple random sampling from the sampling frame.

For the qualitative component of the study, focus groups discussions and key informant interviews will be conducted with immunisation stakeholders, community members and healthcare workers.

Figure 1: Schematic representation of cluster-randomized trial



7.2 Description of the investigational product

In this study we will use Pneumosil®, the PCV10 vaccine manufactured by SII. Pneumosil® is a WHO-PQ vaccine licensed for use in infants and toddlers from 6 weeks up to 2 years of age.

Each dose of PCV10 (Pneumosil®; SIIL) contains 2mcg of saccharide for each serotype 1, 5, 9V, 14, 19A, 19F, 23F, 7F and 6A; and 4 mcg of saccharide for serotype 6B.

Vials containing 5 full doses will be used. Following manufacturer's instructions, each full dose has a volume of 0.5ml and is administered by intramuscular injection.

A fractional dose of 1/5 of a dose will be defined as 0.1ml and will be administered via intramuscular injection using a graduated syringe. For the fractional dose PCV dose arm, each vial will contain approximately 25 fractional doses.

7.2.1 Summary of vaccine safety

The most frequently reported adverse reactions include fever, irritability, injection site reactions including pain, erythema, swelling or induration, decreased appetite, drowsiness and diarrhoea. Serious reactions are rare.

Extending the use of the 5-dose multi-dose vial to provide 25 administrations may increase the risk of injection site reactions e.g. swelling and localised inflammation due to contamination. The preservative contained in the vial should minimise this risk.

7.2.2 Storage and handling

Following manufacturer's recommendations, vaccines will be stored at a temperature ranging between +2°C and +8°C. A fine white deposit with clear colourless supernatant may be observed upon storage of the vial. This does not constitute a sign of deterioration.

Because Pneumosil is a suspension containing an adjuvant, vaccinators will vigorously shake vials immediately prior to use to obtain a homogenous, whitish turbid liquid in the vaccine container.

Once opened, multi-dose vials will be kept between +2ºC and +8ºC. Following the conditions stated on the WHO policy statement on handling of multi-dose vials after opening (WHO/IVB/14.7), opened multi-dose vials may be used up to a maximum of 28 days.

7.3 Site selection

The study will take place in the Madarounfa Health District, situated in the Maradi Region of south-central Niger along the Nigerian border. Madarounfa District had an approximate population of 540,000 inhabitants and covers a rural area of 4700 km^2 largely representative of the Sahel region of Niger and sub-Saharan Africa. The main economic activity is subsistence agriculture, and the region is generally peaceful without any underlying political or social tension. The Madarounfa Health District has one district hospital and 25 health centres, of which 2 are led by full-time doctors, and 23 of which are led by nursing staff. Each of the health centres is the first-level care facility for a Health Area, which is usually composed of 10-20 villages.

The villages to be included in the study will be purposefully selected from different health areas of the Madarounfa Health District. Health areas will be selected based on access and security. To avoid contamination of the different interventions, a minimum radius of 2 km will be kept between clusters. In some cases, two or more closely neighbouring villages sharing a school or market may be

combined to form a single cluster. Clusters will be limited in size to a total population of between 500 and 4000 persons.

Epicentre has been conducting research studies in the Maradi region, and the Madarounfa District specifically, since 2008. Main themes have included childhood malnutrition, meningitis, malaria, and rotavirus, and antimicrobial resistance among many other subjects. Clinical, laboratory and logistical staff, as well as a dedicated community engagement team, are present.

7.4 Obtaining informed consent

Informed consent will be obtained from parent or guardian before any study specific procedures are undertaken. Separate consent will be sought for the cross-sectional surveys, the vaccination campaign and the qualitative interviews. Informed consent will be taken by study personnel specially trained for the informed consent process. It will be made clear from the outset that refusal to participate will not jeopardize any of the other health services or care participants and families receive.

An information notice will be used to present the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part in the study. It will be clearly stated that participation is voluntary and that the participant or their parent/guardian is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. The information notice will be available in French and Hausa.

The potential participant or representative will be allowed as much time as necessary to consider the information and to take the opportunity to question the person taking the informed consent and to decide whether they will allow their charge to participate in the study.

Written informed consent will be needed for the participation in the different components of the study. This will be obtained by means of the participant's or participant's representative dated signature or thumb print (if unable to write), and the consent form must be signed and dated by a literate witness and dated signature of the person who presented and obtained the informed consent.

Different informed consent documents will be used:

1. Consent form for the head of the village to provide consent for the village to participate in the cluster randomized trial
2. Consent form for overall participation in the surveys and for nasopharyngeal sampling of a randomly selected household member aged 1-9 years
3. Consent form for the head of the household for vaccination of children of the target age group living in the household
4. Consent form for participants in qualitative study

Other considerations regarding informed consent are detailed below in section 9.9 "Informed Consent".

7.5 Cross sectional survey procedures

Households selected at random will be invited to participate in the cross-sectional surveys. Sampling will be independent between the two surveys, and there will be no longitudinal follow-up. Survey procedures will be conducted at a single visit to each household, unless the members are absent, in which case there will be a second attempt to reach the potential participants. There will be no follow-up after this visit.

For the purposes of this study, a household is defined as a group of people living under the authority of a head of household, sleeping under the same roof, and sharing at least one meal per day, for at least two weeks, independent of any family ties.

7.5.1 Inclusion and exclusion criteria

Households containing at least one member aged 1-9 years whose head of the household or main caretaker provides consent to participate will be eligible to participate.

To participate in the carriage surveys, children meeting the following inclusion criteria are eligible for enrolment:

(4) Aged 1-9 years
(5) Residing in the villages included in the study
(6) Parent or caretaker provides informed consent for the child to participate in the study

Exclusion criteria for participating in the carriage survey will include the following:

(3) Head or facial injuries that contraindicate nasopharyngeal swabbing
(4) Any condition or criteria, including acute or chronic clinically significant abnormality that in the opinion of the investigator might compromise the wellbeing of the participant or interfere with the outcome of the study

7.5.2 Screening procedures and enrolment

The baseline and 6-months post-vaccination surveys will follow similar screening and enrolment procedures. Survey teams will visit randomly selected households and will go through the informed consent process with the head of the household (see sections 7.4 and 9.9).

In the pre-vaccination survey we will:

1) Administer a household questionnaire to the head of the household to collect information on the number of members who live in the household, their age and sex, school or other day care attendance of the children living in the household, PCV vaccination status of children living in the household, exposure to solid fuel smoke, and smoking habits.
2) Select a household member at random (using a simple lottery system) to collect information on the number of contacts with people of different age groups in the last 24h. This information will be collected using the social interactions questionnaire. If this person is absent from the household, a second attempt at a pre-scheduled time will be arranged. If the person is still unreachable after a second attempt the social contact questionnaire will not be completed.

3) Select a child aged 1 to 9 years of age at random (using a simple lottery system) for nasopharyngeal sampling. A short questionnaire will be used to collect the child's recent symptoms of an upper respiratory tract infection, including receiving any antimicrobials in the previous two weeks. If the selected child is temporarily absent from the household, a second attempt of inclusion will be made at another agreed upon time. In the rare event that the child is not eligible to participate another member will be randomly selected from the list. In the unlikely event that no child in the household is eligible to participate in the survey, the household will not be replaced.

In the post-vaccination survey we will:

1) Administer a household questionnaire to the head of the household to collect information on the number of members who live in the household, their age and sex, school or other day care attendance of the children living in the household, PCV vaccination status of children living in the household in the EPI, exposure to solid fuel smoke, smoking habits, and PCV vaccination during the study campaign from all children of the target age group.

2) Select a child of the target age group for vaccination at random for nasopharyngeal swab. A short questionnaire will be used to collect the child's recent symptoms of an upper respiratory tract infection, including receiving any antimicrobials in the previous two weeks. If the selected child is absent from the household, a second attempt of inclusion will be made at another agreed upon time. In the rare event that the child is not eligible to participate another member will be randomly selected from the list. In the unlikely event that no child in the household is eligible to participate in the survey, the household will not be replaced.

7.5.3 NP carriage sampling and analysis

The NP swab will be taken by trained study nurses following the WHO standard method described by Satzke et al (31) for detecting upper respiratory carriage of *S. pneumoniae*. Briefly, a study team member trained in standard procedures for nasopharyngeal sample collection will sample the nasopharynx of participants using a flocked swab. The sample will be immersed in skim milk, tryptone, glucose, glycerol (STGG) media prior to being transported to the lab.

Samples will be processed, aliquoted and temporarily stored at ultra-low temperature (≤-70°C) until shipment to African Research Collaboration for Health Limited (KWTRP), Kilifi, Kenya.

Culture and serotyping of NP samples will be done at the KWTRP laboratory in Kenya. At the KWTRP laboratory, samples will be cultured on gentamicin-blood agar and *S pneumoniae* identified by optochin susceptibility testing. Serotyping will be done by latex agglutination and the Quellung reaction. Confirmatory pathogen and serotype testing will be done on 10% of culture positive samples by PCR.

To assure the quality of sample collection, culture positivity data will be stratified by various characteristics such as study staff performing sample collection, date of collection, date of shipping and age category to assess the quality of samples to identify any unexpected patterns that may indicate low quality of sample collection. To support transfer of skills and capacity in laboratory evaluations for pneumococcus, staff from Epicentre Niger and Université Abdou Moumouni, Niger will participate in an in-service training program led by peers at KWTRP, Kenya.

7.6 Vaccination

Vaccination activities will occur at village level following implementation of community awareness activities and liaison with village leaders. Vaccination will take place on a pre-scheduled day. All children of the target age group for vaccination, for instance aged 1-9 years of age, residing in the study villages allocated to full or fractional dose arm will be targeted for vaccination. Vaccination will occur at fixed sites in each participating village.

Vaccination activities will be timed to happen in the same geographical area at the same time and will be scheduled as to not interfere with other planned vaccination activities.

7.6.1 Eligibility criteria for mass vaccination campaigns

Children meeting the following inclusion criteria are eligible for vaccination:

(4) Aged 1-9 years
(5) Residing in the villages included in the study and allocated to vaccination
(6) Head of the household or main caretaker provides consent for the child to be vaccinated

Exclusion criteria for vaccination will include the following:

(5) Hypersensitivity to any component of the vaccine, including diphtheria toxoid
(6) Vaccination with a PCV vaccine within the previous 4 weeks, as there should be a minimum of 4 weeks between doses
(7) Moderate or severe febrile illness (temperature ≥39°C) is a temporal contraindication and the child should not be vaccinated until improvement.
(8) Any condition or criteria, including acute or chronic clinically significant abnormality that in the opinion of the clinical staff might compromise the wellbeing of the volunteer

A SOP will be used to assess eligibility in accordance with the inclusion and exclusion criteria for vaccination listed above.

7.6.2 Community mobilization and eligibility screening

Prior to the mass vaccination campaigns, community information sessions will occur in each village to discuss the vaccination campaign, and the design, objectives and methods of the overall trial. During these sessions, study staff will stress the importance of vaccination in this context, but also underscore that parents of children are free to choose whether to have their child vaccinated. Prior to vaccination activities, the study team will ensure that each head of the household or main caretaker goes through the informed consent process and provides consent for the children of the target age group living in the household to participate in the study. The head of the household or main caretaker will be asked to accompany the children of the target age group for vaccination at the scheduled day.

On the vaccination day, a nurse will screen each child for contraindications for vaccination and will ensure that the inclusion criteria, including written informed consent, are fulfilled.

7.6.3 Administration of vaccine

PCV vaccine will be administered intramuscularly following the manufacturer recommendations. The vaccine will be administered in the deltoid region of either arm avoiding broken skin or injuries. It is recommended, but not required, that the injection be administered into the non-dominant arm.

The necessary equipment will be in place to manage eventual hypersensitivity reactions.

Vaccine preparation and administration as well as management of hypersensitivity reactions will be detailed in a study specific SOP.

The number of doses of vaccine administered at each site will be noted on tally sheets.

7.6.4 Dose modifications

There are no anticipated dose modifications following enrolment since the intervention consists of a single dose.

7.6.5 Labelling

Study vaccines will be labelled specifically for the study.

7.7 Qualitative study

A literature search and desk review of available reports from countries and/or NGOs that have introduced government-sponsored mass vaccination campaigns children under the age of 15 years will be conducted.

Data gaps related to Niger and pneumococcal vaccination campaigns in particular will be filled through key informant interviews and focus group discussions, either in-country or by telephone.

For the qualitative data collection on the feasibility, acceptability, and community needs regarding a mass PCV vaccination campaign, an exercise to map the relevant stakeholders will take place in the first month of the project.

International and national stakeholders who are/would be involved in the planning, implementation, and/or evaluation of a mass vaccination campaign with PCV will be invited to participate in key informant interviews and/or focus group discussions. This will include healthcare workers who take an active role in vaccination campaigns (e.g., doctors, nurses, nurse aides, and any others e.g., community health volunteers) and community members (mothers or fathers) with children between 1-9 years of age. The University Abdoul Moumouni of Niamey will be the lead partner for the implementation of this qualitative study.

7.7.1 Recruitment, inclusion criteria and exclusion criteria

Four groups will be targeted for qualitative data collection:

1) Parents/ caregivers local to the area in which the trial is being implemented will be invited to focus group discussions on the perceived acceptability, feasibility and communication needs when delivering a (hypothetical) mass PCV campaign to 1–9-year-old children. Individuals will be identified during house-to-house visits in a mix of communities across the trial area.

Inclusion criteria for parents/caregivers:

- A parent/caregiver to a child under the age of 15 years
- A community member from the general population in the catchment area of a selected health facility

- An adult able to give informed consent

Exclusion criteria for parents/caregivers:

- A community member not resident in the catchment area
- An adult unable to give informed consent
- An adult with obvious signs/symptoms of COVID-19 on the day of interview

2) Healthcare workers local to the area in which the trial is being implemented will be invited to Focus Group Discussions on the perceived acceptability and feasibility of delivering a mass campaign of fractional dose PCV e.g., the requirements that would be needed for planning, delivery, monitoring & evaluation. Individuals will be identified through visits to a mix of government health facilities in the trial area.

Inclusion criteria for healthcare workers in focus group discussions are:

- Healthcare worker working in immunisation or in a leadership/coordination position within the health centre
- Able to give informed consent

Exclusion criteria for health care workers:

- Healthcare worker working in a different service at the health facility
- Healthcare worker with obvious signs or symptoms of COVID-19 on the day of the interview
- Unable/ unwilling to give informed consent

3) Immunisation programme managers and stakeholders at the regional and national level will be invited to key informant interviews on the feasibility, cost, and sustainability of using mass campaigns of fractional dose PCV in older children to enhance herd protection. Interviewees may be members of the Ministry of Health or other implementing partner organisations (e.g., non-governmental organizations or research institutes).

Inclusion criteria for healthcare workers in focus group discussions are:

- Able to give informed consent

Exclusion criteria for health care workers:

- Unable/ unwilling to give informed consent

4) Stakeholders at Gavi, the Bill & Melinda Gates Foundation and WHO will be invited to key informant interviews on the perceived facilitators and barriers to implementing a mass PCV campaign both in countries with established routine immunisation programmes and in fragile or

crisis-affected states. Individuals will be identified from relevant documents and websites and informal collaborators at the international level within WHO, Gavi and BMGF.

Inclusion criteria for external stakeholders in focus group discussions are:

- Able to give informed consent

Exclusion criteria for external stakeholders:

- Unable/ unwilling to give informed consent

7.7.2 Sample size

Dependent on the number and availability of key informants, we will aim to conduct:

- 4-10 focus group discussions with parents/ caregivers (maximum 6 participants each)
- 4-10 focus group discussions with healthcare workers (maximum 6 participants each)
- 4-10 key informant interviews with national immunization programme stakeholders
- 4-10 key informant interviews with international level immunization stakeholders

7.7.3 Interview procedures

Focus groups with healthcare workers and parents/caregivers

If a healthcare worker or parent/caregiver agrees to participate in a focus group discussion and meets the inclusion and none of the exclusion criteria above, they will be given a time, date and place for discussion. At the beginning of the discussion the purpose will be described clearly again. Confidentiality and anonymity will be assured. Once the participant has understood the information, informed consent and permission to record the interview will be obtained. The informed consent form will describe the purpose of the study, the procedure to be followed (interview or focus group discussion), and the extent that the information obtained will be used.

Participants will be given the participant information sheet and consent form to read (or will have the information sheet read out to them) and they will be asked to sign stating that they consent to taking part. If the volunteer is illiterate or unable to fully understand the written information in the consent form an independent witness will be invited to accompany the volunteer and sign the consent form, the participants will be asked to put their thumb print on the consent form. Adequate time for each potential participant to ask questions will be allowed.

Focus group discussions with parents/caregivers and healthcare workers will be carried out by a trained interviewer and facilitator using topic guides.

During the focus group discussion each member of the group will be given a placard with a number on it, they will be asked to say that number before inputting into the discussion, for the purpose of the recording.

Key informant interviews with national and international stakeholders

Key informants will be approached by phone or email. Once they agree to the interview, the interviewer will explain the purpose of the interview and will identify a private area in which to conduct the interview at the interview site or ask the participant over the phone to ensure they are in a private area to ensure confidentiality. Signed written informed consent and permission to record the interview will be obtained either in person or this will be organized prior to the phone interview by email.

Each participant will be assigned a unique identification number which will be used throughout the interview in recordings and written records. The identity of interviewees will be confidential and will remain non-identifiable in project outputs released into the public domain. Participants will be able to opt-in or opt-out of being anonymously quoted. All interviews will be recorded, if the participant consents. If the participant consents to interview but declines to have the interview recorded, handwritten notes will be taken at the time of interview by the interviewer and typed up in full immediately afterwards. All relevant information in the interview recordings/ notes will be transcribed and entered into the data extraction template.

Interviews with national and international immunization stakeholders will be conducted by telephone or in-person using the interview topic guides. The topic guide will be piloted prior to the start of data collection. As far as possible, an informal interview style will be used, including open ended questions, in order to gain as much information as possible.

The topic guide will include relevant questions on the following topics: questions will be selected based on the gaps in the literature specific to Niger and/or pneumococcal vaccine campaigns:

- The decision to conduct a campaign
- The planning, implementation, and timing of the social mobilization
- Training and preparation of implementing staff
- Vaccine management and cold chain capacity
- Delivery strategy
- Effectiveness data
- Vaccine coverage
- Funding for vaccine supply and implementation
- Integration of the campaign with other health services/ the impact on routine health service provision

7.8 Early withdrawal from study

In accordance with the principles of the current revision of the Declaration of Helsinki[1] and any other regulations, a participant has the right to withdraw from any part of the study at any time and for any reason and is not obliged to give their reasons for doing so.

The mass vaccination consists of a single dose while outcomes are at the community level measured through two cross-sectional surveys. However, individual participants (in surveys or the qualitative

study) may withdraw their consent and in that case their data will not be included in the data analysis.

7.9 Concomitant interventions

Any interventions required to treat a disease or condition in an enrolled participant will be allowed.

7.10 Provision of medical care

Immediate reactions post-vaccination will be treated free of charge on-site by trained clinical staff. Free referrals to the nearest health center will be provided for any participants presenting to vaccination campaign sites with acute medical conditions necessitating clinical evaluation. Likewise, during the two cross-sectional surveys, household members with acute illness who need medical attention will be provided free referrals to the nearest health center.

7.11 Randomization and blinding procedures

Following the results of the baseline survey, clusters will be randomized in a 3:3:1 ratio, with 27 clusters randomized to receive a campaign with the full dose, 27 clusters randomized to receive a campaign with the fractional dose and 9 clusters randomized to the control arm. Randomization will be stratified by proximity to nearest health center (<5 km vs. ≥5km). In the event of significant imbalance in carriage of VT pneumococci between clusters in the baseline survey, randomization will also be stratified by baseline prevalence. An equal or proportional number of clusters will be randomized to each study arm from each stratum.

The randomization list will be generated by an independent statistician with no other contact with trial participants.

Study implementation will be blinded to the extent possible. Vaccination nurses will not be blinded to the vaccine they are giving, but they will not communicate vaccine allocation to other members of the team or to participating villages. Villages randomized to the control arm will not receive any "dummy" intervention, so will not be blinded to their group allocation. The trial will be observer-blind in that personnel at KWTRP will be blinded to group allocation until after the completion of culture and serotyping in each survey.

7.12 Sample size for surveys

The sample size has been calculated to respond to the objective of determining whether community-level prevalence of VT pneumococci after a fractional dose PCV mass campaign among children aged 1-9 years is non-inferior to that seen after a mass campaign among children aged 1-9 years using full-dose PCV as well as determining the superiority of a full dose PCV mass campaign compared to no vaccination.

Based on NP carriage studies conducted in Sub-Saharan Africa settings (7,28–30) and considering an estimated coverage of 3 doses of PCV in children <12 months of age of 48% in the study area, we estimate the prevalence of VT carriage, among 1-9 year olds, to be between 25 and 35% and take the middle value, 30%, as an initial estimate. We assume a 50% reduction in PCV10 VT carriage after vaccination with a full dose and consider the prevalence of VT carriage amongst vaccinated children with a full dose 6 months after the vaccination campaign to be 15%.

Based on a previous cluster randomized trial assessing meningococcal carriage in the same study area, we consider an intra-cluster correlation coefficient of 0.02(20).

To test the non-inferiority of a mass campaign using fractional doses compared to a mass campaign using full doses, we have chosen a non-inferiority margin of 7.5% to ensure that a campaign with fractional doses provide at least half of the benefits provided by a campaign using full doses. We consider a 2.5% level of significance for a one-sided test and 90% power. With these assumptions, 27 clusters with 36 households sampled per cluster would provide a power of at least 90% (1944 individuals, with 972 in the full dose and 972 in the fractional dose arm). Non-inferiority will be achieved if the lower limit of the 95% confidence interval (CI) around the difference in the proportion of children with VT carriage (full dose group – fractional dose group) is >-7.5%.

Given the sample size of the full-dose arm to test non-inferiority as described above, to test the superiority of a mass campaign to the control (non-vaccinated) arm, and considering a 5% level of significance for a two-sided test and 90%, we would need to sample 9 clusters with 30 households apiece in both the full-dose and control arms. Since the non-inferiority evaluation requires a larger sample size, the control arm will include the larger number of participants per cluster (36), which will lead to >90% power to detect superiority.

For the NP carriage survey, one participant will be sampled from each household. We consider that most households will have a child aged 1 to 9 years of age, but account for 20% refusal to participate and/or absences and increase the number of households to be invited to participate by 20%. All selected households, even if they do not have a child of the target age group, will be invited to participate in the social contacts survey. Table 1 summarizes the number of cluster and households to be included in each survey.

Table 1. Initial estimates of clusters and households to be invited to participate in each survey

Allocation	N° clusters	N° households	Total participants
Control arm	9	36	324
Full dose arm*	27	36	972
Fractional dose arm	27	36	972
Total	63	108	2268

*Adjustment for multiplicity will be done at the analysis phase if necessary

In order to adjust the initial estimates, sample size will be recalculated with VT carriage data obtained from the baseline survey.

The sample size calculations were performed using PASS 14 (Power Analysis and Sample Size Software (2015). NCSS, LLC. Kaysville, Utah, USA).

7.13 Expected Results

The overall project will present results for each of the primary and secondary objectives. For the main trial, results of prevalence of vaccine-serotype pneumococcus will be presented and compared. The results of the qualitative study will be presented in the form of a report. All results will be communicated as described below in section 13.6.

8 Safety reporting for Adverse Events and Serious Adverse Event

Data on Adverse Events (AEs) will be collected in a passive surveillance system for 7 days following vaccination. Data on Serious Adverse Events (SAEs) will be collected in a passive surveillance system for 28 days following vaccination.

A health professional from the study team will be based in the nearest health centre to the vaccinated villages for 28 days after vaccination activities, and will be the key notifiers of AEs and SAEs to the study team. Moreover, the community health workers from the vaccinated villages will be asked to act as a focal point and communicate to the study team any events that occur during the follow-up period. During the vaccination activities, caretakers will be informed about vaccine safety and will be asked to contact the community health worker or to attend the nearest health centre in case of a health problem.

Following, the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice, an adverse event (AE) is defined as any untoward medical occurrence in a clinical trial subject to whom a vaccine has been administered; it does not necessarily have a causal relationship with the vaccine/vaccination.

Definitions of AEs and grading will be specified in an SOP. In this trial, the recording of AEs will be limited to the evaluation of injection-site reactions (pain, tenderness, induration, infection, etc).

A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death.
- Is life threatening: if the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Results in persistent or significant disability/incapacity: if the event results in a substantial disruption of the participant's ability to carry out normal life functions.
- Requires in-patient hospitalization or prolongation of existing hospitalization: In general, hospitalization signifies that the participant has been detained (usually involving at least 24h stay) at the hospital or emergency ward for treatment that would not have been appropriate in an outpatient setting.
- Is a congenital anomaly/birth defect in the offspring of a study participant.
- Is an important medical event that may jeopardize the participant or may require intervention to prevent one of the other outcomes listed above.

Hospitalization for either elective surgery related to a pre-existing condition, which did not increase in severity, or frequency following initiation of the study, or for routine clinical procedures (including hospitalization for "social" reasons) are not considered as SAEs. When in doubt as to whether hospitalization occurred or was necessary, the AE will be considered serious.

The definition of a routine clinical procedure is a procedure, which may take place during the study period and should not interfere with the study vaccine administration or any of the on-going protocol specific procedures. If anything untoward occurs during an elective procedure and satisfies any of the criteria for SAE, this will be documented and reported.

8.1 Causality Assessment

If an event meets the criteria to be determined "serious" (see definition of SAE); it will be examined by the investigator (and DSMB) to determine all contributing factors applicable to each SAE. These contributing factors will be documented and reported appropriately. Every effort will be made by the investigator to explain each SAE and assess its causal relationship, if any, to administration of the study vaccine.

In case of concomitant administration of multiple drugs, it will not be possible to determine the causal relationship of SAEs to the individual drugs administered. The investigator will, therefore, assess whether the SAE could be causally related to vaccination rather than to the individual drugs.

The degree of certainty with which an SAE can be attributed to administration of the intervention (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of one or more of the following:

- Reaction of similar nature having previously been observed with Pneumosil or other PCV.
- The event having often been reported in literature for similar interventions.
- The event being temporally associated with Pneumosil vaccination.

The Investigator will assess the causality of all SAEs, using the following question: “Is there a reasonable possibility that the SAE may have been caused by vaccine administration?” After assessment of causality, the investigator will classify the SAE as related or unrelated, as defined below:

- Related: there is suspicion that there is a relationship between vaccine and SAE (without determining the extent of probability); there is a reasonable possibility that the vaccine contributed to the SAE.
- Unrelated: there is no suspicion that there is a relationship between vaccine and SAE, there are other more likely causes and administration of the study vaccine is not suspected to have contributed to the SAE.

8.2 Procedure for recording Serious Adverse Events

8.2.1 General information about SAEs

The investigator will document all SAEs according to the detailed guidelines set out below. All participants will be instructed to contact the investigator immediately, either directly or via the community representative should the participant show any signs or symptoms perceived as serious during the period extending from enrolment to the study to the study end. Whenever possible, SAEs will be documented in terms of a diagnosis or syndrome rather than multiple symptoms that are clearly manifestations of the same diagnosis/syndrome. In case the participant reports signs and symptoms, the investigator will obtain a medical diagnosis. If a diagnosis cannot be obtained, then enter each sign or symptoms as separate events. Pre-existing conditions or signs and/or symptoms (including any which are not recognized at study entry but are recognized during the study period) present in a participant prior to enrolment will be recorded in the medical history in the participant's CRF.

8.2.2 Recording SAEs

Information regarding SAEs will be collected through an SAE CRF as soon as the investigator is made aware of an SAE. SAEs will be followed up to resolution, and cessation of treatment or end of study, irrespective of severity or whether they are considered vaccination-related.

The diagnosis, date and time (where appropriate) of onset, outcome, severity and relationship to vaccination will be established. Details of any treatment (all concomitant interventions) given will be recorded appropriately. Where applicable, information from relevant hospital case records and autopsy reports will be obtained.

SAEs will be coded following MedRA coding conventions.

8.2.3 Management of SAEs

SAE will be managed in line with current Good Medical Practice. Management of any SAE will be recorded in the CRF. Participants will be referred to an approved health clinic and will be treated according to national and/or MSF standards.

SAEs will be followed to their conclusions. Possible conclusions of an SAE will include followed up to resolution (participant's health has returned to baseline status); followed up to stabilization (no further improvement or worsening of the event is expected) or the event is otherwise explained.

8.3 Expectedness

SAEs will be considered as unexpected if the nature, seriousness, severity or outcome of the event is not consistent with the current information available for the vaccine as documented in the Reference Safety Information.

8.4 Reporting of SAEs

8.4.1 Initial Reporting

Any SAE (whether or not considered to be related to the study vaccine) will be reported to the Sponsor (or designee) by telephone or in writing or by email within 24 hours (1 calendar day) of becoming aware of the event. If the SAE is fatal or life threatening, the Sponsor (or designee) will be informed immediately by telephone, in addition to the duly completed form. The PI (or designee) will ensure that the information provided on the form, is legible, does not have abbreviations or personal and institutional identifiers, and is as complete as possible.

The following is the minimum information required for the initial SAE report:

- Description of the event
- Date of vaccination
- Reporter information
- Preliminary causality assessment
- Severity

8.4.2 Follow Up Reporting

A more detailed record of the Serious Adverse Event must follow the initial SAE within 5 days after receipt of the new information.

A follow-up report will contain new, updated or corrected information. The follow-up report will describe whether the event has resolved or continues, if and how it was treated including documentation of all supportive actions taken.

8.5 SAE Reporting to relevant bodies

The Sponsor (or designee) will coordinate the safety monitoring and reporting in the study. SAEs will be reported to local ERBs following local laws and requirements. SAEs will be reported to the Data Safety and Monitoring Board (DSMB) according to the schedule and transmission flow set forth in the DSMB charter. Notification of SAE to concerned National Regulatory Authorities will follow national law requirements. Table 2 summarizes SAE reporting timelines.

Table 2. SAE reporting timelines.

Reported To	Reported By	Timeline
Sponsor (or designee)	PI (or designee)	Within 24 hours for all SAEs
Local IRB and MSF-ERB	PI (or designee)	Within the delay established by local procedures/laws
DSMB	Sponsor (or designee)	Within 24 hours for fatal and life threatening events or SUSARs, and within 7 days for other SAEs (according to DSMB charter)

9 Ethical and regulatory aspects

9.1 Ethical considerations particular to cluster randomized trials

The design and implementation of cluster randomized trials raises a variety of ethical questions. These include who is considered a research subject; from whom, how and when informed consent should be obtained; whether clinical equipoise exists; the determination of risks and benefits; the protection of vulnerable groups; and the roles and responsibilities of “gatekeepers” (32). In response, a series of recommendations for the ethical design and conduct of cluster randomized trials were developed by a consensus group in 2012, referred to as the Ottawa Statement (33).

Two general types of cluster-randomized trials have been described (34). The first is a “cluster-cluster” trial, where the intervention necessarily takes place at the cluster level (such as treatment of a community well). The second is an “individual-cluster”, where the intervention takes places at the individual or household level. The proposed cluster randomized trial can be classified as an “individual-cluster” trial, as the intervention, i.e. vaccination, is delivered at the individual level but the outcome measurement will be reported at the cluster level. In “individual-cluster” trials, as the intervention occurs at the individual level, the individual can provide consent to receiving that intervention (34). However, consent necessitates the special consideration of the role of political and administrative authorities as gatekeepers, as well as the nature of individual consent for participation.

The following sections will address some of the important ethical considerations of the proposed trial design, taking into account the guidance of the Ottawa Statement and other important documents from the medical/ethical literature on the subject of cluster-randomized trials.

9.2 Definition of research participants and identification of gatekeepers

Given that the primary outcome of interest is the effect of a single-dose mass campaigns on NP carriage in the different arms, and knowing that vaccination has a direct effect amongst those vaccinated as well as an indirect effect, all residents of randomized villages should be considered as research participants (32,35). Following the principles stated in the Ottawa Statement, permission for the villages to take part in the study will be sought from "gatekeepers". This will include health and political/administrative leaders. For the purposes of this study, the gatekeepers who will be asked for permission will be the village chief and his/her deputies for the villages eligible for inclusion.

9.3 Community engagement

Appropriate engagement with the communities in the study area is crucial. We will follow use guidelines developed by UNAIDS for clinical trial research, Good Participatory Practices to ensure participation and mutual respect of values and actions. Open meetings will be routinely held with community representatives to discuss this research project. Moreover, the existing Community Advisory Boards in Niger will be convened to facilitate open communication between targeted communities and study personnel and inform adaptations to procedures and communication around the trial.

Community representatives will be asked for advice before, during and after trial, ensuring a transparent and meaningful participatory process.

9.4 Summary of known and potential risks

This study is considered to be of minimal risk to participants. The main three risks are related to vaccination, sample collection and confidentiality.

The study product vaccine is an already approved and pre-qualified by WHO. There have not been any safety concerns regarding PCV10 and is considered safe (20). In a study assessing lower doses of a pentavalent PCV, doses close to what will be used in this study were not associated with increased frequency of local reactions (27). Administration of fractional doses will result, however, in an increased number of piercings of vial stoppers compared with what they are validated for. Possible stopper failures could include loss of self-sealing capacity, increasing the risk of contamination or leakage, and fragmentation of the stopper material, which could increase the risk of syringe blockage or injection of particles (36). However, a study assessing different vials stoppers found that all stoppers maintained their self-sealing capacity even after 100 punctures (36). Considering this and the presence of a preservative in the vaccine, the risk of multiple piercings is minimal. However, vaccination will be performed following a study specific SOP and vaccinated children will be followed-up to monitor and treat any reactions to the vaccine. A pharmacovigilance officer is permanently in place at the Epicentre Niger research center and with the Sponsor.

If one dose of PCV has an effect in the reduction of VT carriage, serotype replacement could eventually occur. However, the serotypes included in the PCV10 vaccine used in this study are the most common cause of IPD. Consequently, VT carriage is likely to be replaced by non-VT pathogenic serotypes, preventing cases of IPD.

All clinical procedures, including administration of the vaccine and collection of the NP swab, will be performed by adequately trained and experienced personnel under regular supervision to minimize any risk or discomfort to participants.

Data management and confidentiality will all be conducted according to the EU General Data Protection Regulations (GDPR).

9.5 Risk minimization and benefits

The introduction of the swab through a nostril might be particularly uncomfortable to young children. The procedure will be carefully explained to the parent/guardian and if the age of the child allows it will also be explained to the child in an adapted language. The procedure will be carried out by medical study personnel specifically trained to perform this procedure and following a study SOP. Should the COVID-19 pandemic be circulating in the region at the time of the study, a SOP will be in place to ensure proper use of personal protection equipment (PPE), which will be provided, as well as alignment with all public health regulations issued by the Nigerien government and as recommended by international regulators.

At the individual level, children will benefit from immunization with a booster dose of PCV. Increased vaccine coverage will contribute to reduction of pneumococcal associated disease.

At the population-level, the increase in PCV vaccination might have a positive effect on the uptake of other vaccines increase the overall protection against vaccine-preventable diseases. If PCV mass campaigns have an effect in reduction of VT carriage, this will be a benefit for the entire community. The data obtained from this study will be used to inform mass campaigns targeting a large age group in different settings, including emergency situations.

WHO policy regarding handling of multi-dose vaccine vials (WHO/IVB/14.07) will be followed and used to minimize any risk from injections during vaccine campaigns.

Relying on passive surveillance of AEs and SAEs may lead to underreporting, but this will be mitigated by having study staff dedicated to safety follow-up in health centers in the study area.

9.6 Expenses and reimbursements

Participants will not receive any direct financial benefit from participating in the study.

Clinic and treatment costs due to serious adverse events will be covered by the study for all participants during a period of 28 days post-vaccination.

It is not anticipated that participants will travel for any study visits, as they will be home visits. However, if they should occur, reasonable travel expenses for any visits additional to normal care will be reimbursed or a mileage allowance provided as appropriate.

Households participating in the surveys will be offered two bars of soap as a gesture of thanks and to compensate for time taken to participate, a practice that has been commonly accepted in the study area.

9.7 Ethics review and approvals

9.7.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

9.7.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) E6(R2) 2016.

9.7.3 Approvals

The protocol, informed consent form, and participant information sheet will be submitted for ethical review to the MSF Ethical Review Board, the Kenya Medical Research Institute Scientific Ethics Review Unit, and the *Comité National d'Ethique pour la Récherche en Santé* in Niger.

The Investigators will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

Study authorization will be obtained by the Ministry of Public Health in Niger, and from the drug and pharmacy regulatory authorities "*Autorité Nationale de Réglementation des Médicaments*" in Niger for approval of the importation of the product.

9.8 Study registration

Before study start, the study will be registered on clinicaltrials.gov and PACTR.

9.9 Informed consent

9.9.1 Community consent

The community engagement process will map the willingness and requirements of the community for involvement in the study, to ensure participation and mutual respect of values and actions. A study team will visit the selected villages to discuss community consent with gatekeepers as defined above.

Before study activities, villages will be visited, and information sessions will be held to inform about study activities and assignment of villages to the different study arms. During these sessions, information will be given on the study vaccine, and it will be explained that the vaccination campaign is part of a larger study and that some individuals will be selected to participate in pre and post-vaccination surveys.

Information sessions will be planned to reach the highest number of household's representatives. The involvement of community leaders will be key in assessing the reach of the information sessions. During these sessions the Information notice will be distributed, and parents/caretakers will have the opportunity to ask questions.

9.9.2 Individual consent

During the information sessions, the household representative will be asked to sign an informed consent form if they wish that the children of the target age group living in their household participate in the vaccination activities. On the day of the vaccination activities in a given village, a study team will continue to deliver information about the study and the nature of the vaccination activity, highlighting that participation is voluntary. Children will be asked to come to the vaccination site with a parent or guardian. Households who present to vaccination sites who have not previously signed informed consent documents will be given the opportunity to do so at the vaccination site with dedicated study staff.

Written informed consent will be sought prior to inclusion in the pre- and post-vaccination surveys. The potential participants and their parent(s)/guardian(s) will have the study explained in depth to them and, in addition, will receive a patient information sheet. They will have the opportunity to ask questions to study staff prior to giving consent. Informed, witnessed, written consent will be recorded (ICF) from each participant and applicable parent(s)/guardian(s) for study participation, and other specific aspects of the trial.

The ICFs designed for this study are based on the description in the 2013 Revision of the Helsinki Declaration and other documents related to GCP.

Designated study staff will review the consent form with potential participants or representatives. The consent form will also be verbally explained in the appropriate local language. The informed consent process will ensure with high confidence that potential participants have an understanding of the potential risks and benefit of participation in the study, the study procedures, their right to refuse and/or withdraw from the study at any point without affecting the health services or care they receive, and without having to disclose a reason for their refusal or withdrawal.

9.10 Participant privacy and confidentiality

The study staff will ensure that the participants' privacy is maintained.

No individual information will be collected at vaccination sites.

Pre- and post- survey participants will be identified by initials, age (and date of birth if known), sex and a unique ID number. All documents and electronic data will be stored securely and only accessible by study staff and authorized personnel. The study will make the information anonymous as soon as it is practical to do so.

The Investigator Site File and associated source documents will be retained for at least 10 years after the completion of the study. Written approval from the Sponsor will be obtained prior to destroying records.

All study related documents will be kept in locked cabinets at the study site. Filing cabinets with the study data and the participant information will be locked and accessed only by authorized persons from the Sponsor and Regulatory Authorities.

Participant personal data will be kept confidential and the privacy of all participants will be protected as far as permitted by law and following GDPR regulations. To ensure traceability and following

standard practice, nasopharyngeal samples will be labelled with participant initials, in addition to a unique ID number, sex and age. Only staff involved with the study conduct and local and international regulatory agencies may review these records.

10 Administrative aspects

10.1 Protocol amendments

The Sponsor will amend the study protocol as needed to ensure that the clinical investigations are always conducted according to appropriate and up-to-date protocols. Amendments will be submitted for approval to the regulatory authorities and Ethics Committees. Changes requiring amendments will be defined according to guidance from regulators and include any significant change in the design of the study or the addition of a new test or procedure.

10.2 Protocol deviations and violations

A protocol violation is any departure from the approved protocol, trial documents or any other information relating to the conduct of the study, which may affect the safety of trial participants or the study outcomes. Examples include failure to obtain informed consent (i.e. no documentary evidence) or enrolment of participants that do not meet inclusion/exclusion criteria.

A protocol deviation is any departure from the approved protocol, trial documents or any other information relating to the conduct of the trial that does not result in harm to the trial participants and does not significantly affect the study outcomes. Examples of deviations include missed study visits or a visit date outside the study visit window or an isolated incident of a missed or incomplete study procedure or study evaluation. Serious or repeated protocol violations or deviations will require assessment of the root cause and implementation of corrective and preventive action plans. They may constitute grounds to interrupt the trial.

Any changes from protocol-specified procedures and study-related SOPs occurring during the conduct of the trial will be documented and reported as protocol violations or deviations. Protocol violations will be reported to the Sponsor and reviewing ethical committees, as appropriate and in accordance with the requirements of the involved committees.

10.3 Insurance

ICH GCP defines the extent of the responsibility of the Sponsor.

The involved volunteer participants will be insured, in accordance with applicable laws and regulations, against financial loss resulting from personal injury and/or other damages, which may arise because of this study.

10.4 Funding and other support for the trial

EDCTP will fund the study. The manufacturer will provide vaccines free of charge and other support will be provided by Epicentre in the area of deployment.

11 Data handling and record keeping

11.1 Overview

A Data Management team will be located at the study site. For surveys, all data will be collected on tablet computers using electronic CRFs (eCRF). Information about AE and SAE will be collected at health centers on paper CRFs.

11.2 Investigator site file (ISF)

The investigators will maintain appropriate medical and research records for this study, in compliance with ICH E6 GCP and regulatory and institutional requirements for the protection of confidentiality of participants. The principal investigator, co-investigator, and clinical research staff will have access to records. The investigators will permit authorized representatives of the Sponsor, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

The ISF will be maintained at the study site containing at least the following documents and information:

- Signed protocol and amendments
- Electronic questionnaires and paper case report forms (CRF)
- Current informed consent form and all revisions
- Current participant information sheet and all revisions
- Any other written information given to the study team
- Financial aspects of the study
- Insurance statement
- All signed agreements/contracts
- Dated and documented approval of ethics committee and regulatory authorities
- Signed CV's of all investigators and any study personnel (updated regularly as changes occur)
- Instructions for handling of investigational product and study related materials
- Monitoring reports
- Relevant communication
- Signed informed consent forms
- Signed, dated, and completed CRFs
- SAE reporting
- Notification by Sponsor of safety information
- Annual reports to ethics committee and regulatory authorities
- Investigational product accountability
- Authorization/signature sheet
- Documentation of investigational product destruction
- Clinical study report

11.3 Source Documents and CRFs

In this study the following documents have been designated as source documents:

1. Vaccination cards
2. Survey questionnaire responses
3. Hospital records in case of hospitalization
4. Paper versions of AE and SAE CRFs
5. Tally sheets from vaccination sites

If information is collected from different sources other than those specified above, then they will be recorded and documented.

The only paper CRFs will be used to document AEs and SAEs. For the purposes of the surveys, all information will be collected on password-protected tablet computers (see below). A guide for filling in survey questionnaires will be developed and tested with study staff. Data about AE/SAE from paper CRF will be double-entered by data entry clerks using password protected laptops

The study Data Managers are responsible for data management, integrity and security of paper and electronic data. Epicentre Research Department's Data Protection and Compliance Officer supervises those activities. The study's data management plan will describe all activities that will be conducted to ensure the safety and quality of data.

11.4 Record keeping

The ISF including a copy of the final completed CRFs, as well as all source documentation is retained by the investigator and one copy will be maintained by the Sponsor, who will ensure that it is stored with other study documents, such as the signed informed consent forms, protocol, the investigator's brochure and any protocol amendments, in a secure place for 10 years.

11.5 Data management

11.5.1 Hardware and software

The survey questionnaires will be saved directly from tablet computers into a REDCap database. Information about AE/SAE recorded on paper CRFs will be entered directly into REDCap. The REDCap system uses a MySQL database via a secure web interface with data checks used during data entry to ensure data quality. It also includes a complete suite of features to support HIPAA compliance, including a full audit trail and user-based privileges and will conform to ICH GCP requirements. The REDCap system will be activated for the study only after successfully passing a formal design and test procedure. The primary study database will be located on the REDCap server in Paris. Responsibility for implementing the REDCap system lies with the Epicentre. Management and maintenance of the REDCap server lies with the data manager at the study site.

11.5.2 Data security, access, and back-up

The REDCap server will be kept in a locked server-room. Only the system administrators have direct access to the server and back-up tapes. A role concept with personal passwords (site investigator, statistician, monitor, administrator etc.) regulates permission for each user to use the system and database, as he/she requires.

All data are transferred to the database using Secure Sockets Layer (SSL) encryption. Each data point has attributes attached to it identifying the user who entered it with the exact time and date.

Retrospective alterations of data in the database are recorded in an audit table. Time, table, data field and altered value, and the person are recorded (audit trail).

A multi-level back-up system is implemented. Back-ups of the whole system including the database are run internally several times per day and on external tapes once a day. The back-up tapes are stored in a secure location.

11.5.3 Archiving

The Sponsor will securely store the final study database for at least 10 years. The Sponsor will also keep the Trial Master File and interim and final reports both in electronic and in hard copy form for at least 10 years.

12 Data Analysis

Analysis of all endpoints will be described in a Statistical Analysis Plan. This SAP will include all conventions on data, descriptive and statistical analyses to be performed on collected data during the conduct of the study. A brief overview is provided below.

Information on the total number of individuals per cluster for each of the following categories will be presented: screened individuals, screen failures (together with reasons for screen failure), consented participants for the baseline survey, the vaccination and the follow up survey.

Participant demographics and baseline characteristics will be described at the cluster level. For each arm of the trial the number of clusters, the average number of clusters by demographic and baseline characteristics, such as household composition, average prevalence of exposure to indoor smoke, etc will be described and compared to ensure comparability.

All analyses of outcome will be performed at the cluster level, controlling for clustering effects. For each cluster we will calculate the prevalence of NP carriage and present VT carriage in clusters allocated to full dose, fractional dose and control arm, including the 95% confidence interval. Proportions will be compared using chi square or Fisher's exact test, as appropriate and adjusting for the clustering effect accounting for the intracluster correlation coefficient.

For the analysis of superiority of the full dose vaccination arm compared to the control arm, the comparisons will be done using a chi square test at the 0.05 significance level.

For the non- inferiority analysis, the 95%CI around the difference in the in the proportion of children with VT carriage (full dose group – fractional dose group) will be calculated and the non-inferiority will be achieved if the lower limit of this 95%CI is >-7.5%.

All sensitivity analyses and adjusted analyses will be described in the SAP. Sensitivity analyses will include, but not be limited to, analyses investigating potential seasonal differences in NP carriage of pneumococci.

Safety analysis will be based on the entire study population. Safety and tolerability of PCV10 will be assessed by comparing the frequency (%) of AEs and SAEs in full-dose and fractional-dose arms to the control arm using the Fisher's exact test. Safety data will be presented in tabular and/or graphical

format and summarized descriptively. Data will be analyzed according to an intention-to-treat approach. In the unlikely event of clusters receiving incorrect interventions, or being only partially vaccinated, per-protocol analyses will be repeated on the primary endpoint.

13 Quality assurance and control

13.1 Electronic and central data validation

A designated person will supervise data collection and entry on a regular basis. The data manager will support onsite data entry teams. This process will be defined in the Data Management SOP.

13.2 On-site monitoring

13.2.1 Framework for monitoring

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures. A monitoring plan will be finalized prior to study initiation.

Monitoring will be performed according to ICH GCP including but not limited to regular visits during the clinical study and a closeout visit. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

13.2.2 Implementing monitoring and audits at study sites

Monitors will participate in all key, planned activities, collaborating with implementation of the study. They will therefore comply with all the planned monitoring visits.

The monitoring plan will detail the frequency of monitoring visits and audits at the study site. The Study Monitoring Plan will cover instructions for monitoring the main aspects of the implementation of the study, including at least:

- Study authorizations and approvals and communication with the ethics committees
- Duties and Responsibilities of the Investigator/Institution
- Suitable resources
- Medical care for the participants
- Clinical Study compliance with the agreed protocol
- Laboratory aspects
- Informed consent of participants
- Data management, records and reports
- Stopping rules, early termination, or suspension of the study
- Sponsor 's Responsibilities
- Responsibilities of the Monitors
- Auditor's Responsibilities

13.2.3 Training to ensure quality of the study

Study staff will receive specific training focused on the activities they will be performing. Specific training will be conducted prior to the cross-sectional surveys, mass campaign and interviews. The objective of this training program is to ensure that investigators are well prepared and trained, and understand the details and design of the study prior to implementation of the study.

GCP training or GCP refresher training will be provided to pre-identified staff.

13.3 Data Safety Monitoring Board

The remit and functions of the DSMB will be described in the DSMB Charter.

The aim of this committee is to protect the safety of trial participants while maintaining the study's scientific goals according to the protocol and in accordance with international and local standards. A first DSMB meeting will be convened before the study commences and the DSMB Charter and Terms of Reference will be set at this first meeting. Thereafter, DSMB meetings will be conducted every 3 months.

13.4 Inspections

The investigators and institutions involved in the study will ensure that regulatory authorities may conduct monitoring and auditing and inspection of the study implementation. This includes official reviews of documents, facilities, records, and any other resources that are deemed by the authorities to be related to the study and that may be located at the study site or the Sponsor 's and/or contract research organization's facilities, or at other establishments deemed appropriate by the regulatory authority.

13.5 Completion or termination of the study

Upon completion of the study, a summary of the study's outcome and any required reports, if relevant, will be provided to the ERBs where required, and any reports will be provided to the regulatory authorities if applicable.

After completion or termination of the study all documents, summaries, and reports for ERBs or the regulatory authorities should be kept in the investigator site file (ISF).

13.6 Publication policy and final report

Timely reports of progress will be made available to MOH and health officials and other stakeholders, including communities.

A final report of the study will be prepared and shared with relevant partners as described above. The project will publish overall results in international peer-reviewed scientific journals and in relevant national journals and media. The results of the cluster randomized trial will be reported following the CONSORT extension for cluster-randomized trials.[3]

[3] http://www.consort-statement.org/extensions/overview/cluster-trials

14 Study Organization

14.1 Study Team

A field study team will consist of nurses, communication officers, laboratory personnel, data management personnel, monitors, administrator and logistician. The field study team in Niger will be overseen by the Site Principal Investigator. He will be supported by a Project Coordinator, who will be responsible for maintaining communications between the field and office study teams.

The field team will be supported by a clinical study and project administration team located in Paris.

The qualitative component of this project will have their own dedicated team and will be led by qualitative researchers from the Université Abdou Moumouni.

14.2 Trial Steering Committee

A Trial Steering Committee (TSC) will be put in place, with members comprised of a relevant mix of people with experience in pneumococcal disease prevention and epidemiology, as well as knowledge in data management, ethics, and knowledge of the local community.

The overall task of the committee is to provide guidance and independent expertise on study design and conduct and ensure proper execution of the study. The Committee will meet prior to study initiation and at regular intervals thereafter to review study progress, consider recommendations of the DSMB and relevant ethics committees, and to agree on communications regarding the study.

14.3 Study timeline

The overall duration of the study will be 18 months and major milestones are shown in Table 3.

Table 3: Study timeline

	Year 1 (2021)					Year 2 (2022)												Year 3 (2023)					
	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6
Clinical Trial Implementation																							
Preparatory work																							
Ethical and medical approvals																							
Baseline survey																							
Vaccination campaign																							
Follow-up survey																							
Monitoring visits																							
Clinical study report																							
Laboratory Analysis																							
Lab preparatory work																							
Monthly stock reports																							
Monthly sample reports																							
Cost-effectiveness and Modelling																							
Analysis Plan																							
Analysis																							
Reports																							
Policy Uptake and Access																							
Prepatory work																							
Literature Review																							
Informant Interviews																							
Qualitative database closure																							
Report and briefing																							

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Statistical Analysis Plan

Determining whether mass campaigns with fractional dose PCV10 would accelerate herd protection against pneumococcal transmission in Sub-Saharan Africa

Primary Sponsor	Rebecca F. Grais (Epicentre)
Sponsor's Investigator	Matthew E. Coldiron, Epicentre
Co-investigators	Ousmane Guindo, Epicentre Issaka Soumana, Epicentre Aitana Juan-Giner, Epicentre Rabiou Dare, Niger Ministry of Public Health Hassan Adboul Nasser, National Immunization Program Katherine Gallagher, KWTRP and LSHTM Wangeci Kagucia, KWTRP John Ojal, KWTRP and LSHTM Eric Adehossi, Université Abdou Moumouni Anthony Scott, KWTRP and LSHTM Angela Karani, KWTRP Souleymane Brah, Université Abdou Moumouni
Data management	Souna Garba et Chaibou Louali, Epicentre
Statistical analysis	Elisabeth Baudin, Epicentre
Funding	EDCTP

Declaration of Confidentiality

The information contained herein is confidential and therefore are provided in confidence as a potential examiner or investigator.

It is understood that this information will not be disclosed to others without the written permission of the Sponsor, except to the extent necessary to achieve the consent of those who can participate in the study.

Version control and signature page:

SAP		**Effective Date**: 18Sep2023
Version Number and Date: 1.1, 18Sep2023		
Revision		
List of changes: V1.1, 18Sep2023	Correction in the section 4.3 Statistical analysis: Statistical analyses to demonstrate superiority and non-inferiority will be performed at the individual level instead of the cluster level, as described in the section 4.3.2.1 Primary Analysis	
Name and function	**Date** (DD-MMM-YYYY)	**Signature**
Author		
Elisabeth Baudin, Epicentre, Biostatistician		
Reviewed by		
Rebecca F. Grais, Epicentre, Sponsor representative		
Matt Coldiron, Epicentre, Sponsor's investigator		

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Abbreviations

AE	Adverse Event
CI	Confidence Interval
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
IAE	Immediate Adverse Event
IRB	Institutional Review Board
ITT	Intent-to-treat
KWTRP	KEMRI Wellcome Trust Research Programme
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
PP	Per-protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
WHO	World Health Organization

1. Introduction

1.1 Statistical Analysis Plan

A statistical analysis plan (SAP) is a comprehensive and detailed description of the methods for data analyses to be used in a clinical trial. A clear, detailed SAP will avoid post hoc decisions that may affect the interpretation of the data. This SAP includes details on the procedures for creating Tables, Listings, and Graphs from the results of a Phase IV study, which will be carried out to determine whether mass campaigns with fractional dose PCV10 would accelerate herd protection against pneumococcal transmission in Sub-Saharan Africa.

This is a separate document from statistical section of the protocol. Any changes in the statistical methods presented in the protocol and any additional statistical analysis not included in the protocol will be explained in this detailed statistical analysis plan of the study. This SAP includes a statement of the objectives of the trial, as stated in the protocol; identifies all primary and secondary end-points; specifies the hypotheses to be tested and any parameters that are to be estimated, in order to meet the trial objectives; defines the analysis populations to be used; and provides a full and detailed description of the methods of analysis including details of handling of missing data, dropouts, derived variables, etc.

1.2 Rationale

Pneumococcal vaccination campaigns targeting children up to 5 years of age with a full three-dose primary series have been shown to have an effect in the reduction of VT carriage and disease. However, in crises or settings with high prevalence of malnutrition, the high pneumococcal carriage prevalence is likely to extend to older age groups. Therefore, a single dose vaccination of a larger age group might be needed to control VT circulation. Currently, for Gavi-supported countries, such as Niger, PCV13 vaccine has a cost of US$3 per dose. Pneumosil®, a PCV10 manufactured by Serum Institute of India Ltd, has the lowest price at US$2 per dose of all WHO prequalified vaccines.

Even at the lower price point, mass campaigns targeting larger age groups would require many doses and might not be sustainable over time.

Mass campaigns using fractional doses of PCV could be a solution to overcome the high PCV costs, increase vaccine access and expand vaccination benefits through alternative strategies.

2. Study Objectives

2.1 Primary Objective

The primary objective is to evaluate whether a mass vaccination campaign targeting children approximately 1-9 years of age with a full dose of PCV is superior to the absence of vaccine in reduction of VT carriage prevalence at 6 months post-campaign, and subsequently to evaluate if a single 20% dose of PCV is non-inferior to a full dose.

2.2 Secondary Objectives

Analysis of the following secondary objectives will be described in this SAP:

- To measure the age-stratified prevalence of NP carriage of S. pneumoniae in children 1-9 years of age in the study area.

- To determine the effect of a mass vaccination campaign with one full dose of PCV in children 1 to 9 years of age on VT pneumococci carriage 6 months after vaccination
- To assess the occurrence of adverse events (AE) during 7 days and serious adverse events (SAE) during 28 days after administration of fractional and full doses of PCV.

The analyses of the two following secondary objectives will be described elsewhere:

- To model the potential effect of fractional dose PCV campaigns in other contexts using the results of the clinical trial.
- In the setting of a qualitative study, to develop recommendations on how a potential future fractional dose PCV mass campaign could be successfully planned, communicated, delivered and integrated into national immunization programmes using qualitative analysis.

3. Study Design and Assessment

3.1 Study Design

This is a Phase IV, 3-arm, observer-blinded, cluster-randomized controlled trial, implemented in rural villages of the Madarounfa District of Niger.

3.1.1 Study cohorts

Clusters will be randomized to full dose mass vaccination campaigns, fractional dose mass vaccination campaigns or the control arm in 3:3:1 allocation ratio. Clusters will be composed of a village or group of closely-neighbouring villages that share a school or market, and will be limited to a population of between 500 and 4000 persons. Stratified randomization will be used to account for proximity to the nearest health centre (<5 km vs ≥5 km). In the event of significant imbalance in carriage of VT pneumococci between clusters in the baseline survey, randomization may also be stratified by baseline prevalence upon the decision of the Trial Steering Committee. For this reason, randomization will happen after the results of the baseline survey are known.

Vaccination will target all children aged 1 to 9 years of age residing in the selected villages. (If baseline survey data unexpectedly shows very low prevalence of carriage at the extremes of this age range, the target age group may be adjusted upon recommendation of the trial steering committee.) We estimate that children eligible for the vaccination campaigns will represent 30% of the total population. With an estimated average of 2000 people per cluster, vaccination will target approximately 600 children 1-9 years of age in each cluster receiving vaccine. In total, in the 54 clusters receiving vaccine, the mass vaccination campaign with single full- or fractional-dose PCV is expected to target approximately 32,400 children 1-9 years of age.

Prior to the mass vaccination campaign, a cross-sectional survey will be implemented to estimate community-level carriage of VT pneumococci, as well as to collect data on household composition, social interactions and PCV vaccination coverage in the routine EPI. A total of 36 households in each cluster will be invited to participate in the cross-sectional survey. For the purposes of this study, a household is defined as a group of people living under the authority of a head of household, sleeping under the same roof, and sharing at least one meal per day, for at least two weeks, independent of any family ties. Selection of households will be based on probability sampling. The required number of households in each cluster will be randomly selected using simple random sampling based on an exhaustive list of heads of household in the cluster.

Six months after the mass vaccination campaign, the post- vaccination cross-sectional survey will be implemented. This will be used to estimate community level carriage of VT pneumococcus after a single-dose PCV delivered as full or fractional dose as well as carriage in the clusters that received no vaccination. The survey

will target the same number of children as the baseline survey and will follow the same methodology with the households selected by simple random sampling from the sampling frame.

Sampling will be independent between the two surveys.

3.1.1.1 Inclusion and Exclusion Criteria

To participate in each cross-sectional surveys (baseline and post vaccination), one child per household will be randomly selected for the nasopharyngeal sampling if he is eligible for enrolment after meeting the following inclusion criteria:

- Aged 1-9 years
- Residing in the villages included in the study
- Parent or caretaker provides informed consent for the child to participate in the study

Exclusion criteria for participating in the surveys will include the following:

- Head or facial injuries that contraindicate nasopharyngeal swabbing
- Any condition or criteria, including acute or chronic clinically significant abnormality that in the opinion of the investigator might compromise the wellbeing of the participant or interfere with the outcome of the study

For mass vaccination campaigns, all children of the target age group for vaccination, for instance aged 1-9 years of age, residing in the study villages allocated to full or fractional dose arm will be targeted for vaccination. Children meeting the following inclusion criteria will be eligible for vaccination:

- Aged 1-9 years
- Residing in the villages included in the study and allocated to vaccination
- Head of the household or main caretaker provides consent for the child to be vaccinated

Exclusion criteria for vaccination will include the following:

- Hypersensitivity to any component of the vaccine, including diphtheria toxoid
- Vaccination with a PCV vaccine within the previous 4 weeks, as there should be a minimum of 4 weeks between doses
- Moderate or severe febrile illness (temperature ≥39°C) is a temporal contraindication, and the child should not be vaccinated until improvement.
- Any condition or criteria, including acute or chronic clinically significant abnormality that in the opinion of the clinical staff might compromise the wellbeing of the volunteer

3.1.1.2 Withdrawal/Discontinuation Criteria

In accordance with the principles of the Declaration of Helsinki a participant has the right to withdraw from any part of the study at any time and for any reason and is not obliged to give their reasons for doing so.

The mass vaccination consists of a single dose while outcomes are at the community level measured through two cross-sectional surveys. However, individual participants (in surveys or the qualitative study) may withdraw their consent and in that case their data will not be included in the data analysis.

3.1.2 Sample Size and Power Considerations

The sample size has been calculated to respond to the objective of determining whether community level prevalence of VT pneumococci after a fractional dose PCV mass campaign among children aged 1-9 years is non-

inferior to that seen after a mass campaign among children aged 1-9 years using full dose PCV as well as determining the superiority of a full dose PCV mass campaign compared to no vaccination. Based on NP carriage studies conducted in Sub-Saharan Africa settings and considering an estimated coverage of 3 doses of PCV in children < 12 months of age of 48% in the study area, we estimate the prevalence of VT carriage, among 1-9 year old, to be between 25 and 35% and take the middle value, 30%, as an initial estimate. We assume a 50% reduction in PCV10 VT carriage after vaccination with a full dose and consider the prevalence of VT carriage amongst vaccinated children with a full dose 6 months after the vaccination campaign to be 15%.

Based on information from a study conducted in the area, we consider an intra-cluster correlation coefficient of 0.02. To test the non-inferiority of a mass campaign using fractional doses compared to a mass campaign using full doses, we have chosen a non-inferiority margin of 7.5% to ensure that a campaign with fractional doses provide at least half of the benefits provided by a campaign using full doses. We consider a 2.5% level of significance for a one-sided test and 90% power. With these assumptions, 27 clusters with 36 households sampled per cluster would provide a power of at least 90% (1944 individuals, with 972 in the full dose and 972 in the fractional dose arm). Non-inferiority will be achieved if the lower limit of the 95% confidence interval (CI) around the difference in the proportion of children with VT carriage (full dose group – fractional dose group) is > -7.5%.

Given the sample size of the full-dose arm to test non-inferiority as described above, to test the superiority of a mass campaign to the control (non-vaccinated) arm, and considering a 5% level of significance for a two-sided test and 90%, we would need to sample 9 clusters with 30 households apiece in both the full-dose and control arms. Since the non-inferiority evaluation requires a larger sample size, the control arm will include the larger number of participants per cluster, which will lead to >90% power to detect superiority.

For the NP carriage survey, one participant will be sampled from each household. We consider that most households will have a child aged 1 to 9 years of age, but account for 20% refusal to participate and/or absences and increase the number of households to be invited to participate by 20%. All selected households having a child of the target age group will be invited to participate in the social contacts survey. Table 1 summarizes the number of cluster and households to be included in each survey.

Table 1. Initial estimates of clusters and households to be invited to participate in each survey

Allocation	N° clusters	N° households	Total participants
Control arm	9	36	324
Full dose arm	27	36	972
Fractional dose arm	27	36	972
Total	63	108	2268

The baseline prevalence of VT carriage is expected to be between 25 and 35% as described below. In case the results from the baseline survey differ significantly, the sample size may be re-evaluated. Once baseline survey results are available, they will be presented to TSC with simulation on power calculations outlining various

scenarios for the follow-up survey. Sample size may be re estimated and the number of children may be increased following this review.

3.1.3 Randomization and Blinding

Following the results of the baseline survey, clusters will be randomized in a 3:3:1 ratio, with 27 clusters randomized to receive a campaign with the full dose, 27 clusters randomized to receive a campaign with the fractional dose and 9 clusters randomized to the control arm. Randomization will be stratified by proximity to nearest health center (<5 km vs ≥5 km). In the event of significant imbalance in carriage of VT pneumococci between clusters in the baseline survey, randomization will also be stratified by baseline prevalence, after a decision by the trial steering committee. An equal or proportional number of clusters will be randomized to each study arm from each stratum. The study statistician randomization will prepare the material to generate the list (blocked randomization with fixed block size if only one stratum, by minimisation if more than one stratum), and the final list will be generated by an independent statistician who has no contact with study participants. Study implementation will be blinded to the extent possible. Vaccination nurses will not be blinded to the vaccine they are giving, but they will not communicate vaccine allocation to other members of the team or to participating villages. Villages randomized to the control arm will not receive any "dummy" intervention, so will not be blinded to their group allocation. The trial will be observer-blind in that personnel at KWTRP will be blinded to group allocation until after the completion of culture and serotyping in each survey.

3.1.4 Schedule of Study Visits and Procedures

During the baseline and 6 months post-vaccination surveys, one visit will be performed. No follow-up will be done after this visit. During the two surveys, a questionnaire will be filled for each selected household to collect socio-demographics information on the household, including the number of members who live in the household, their age and sex, school or other day care attendance of the children living in the household, PCV vaccination status of children living in the household, exposure to solid fuel smoke, and smoking habits.

For each selected child aged 1 to 9 years, an additional questionnaire will be filled to collect information on the child's recent symptoms of an upper respiratory tract infection, including receiving any antimicrobials in the previous two weeks, and a nasopharyngeal sampling will be performed.

Additionally at baseline, on a selected household member, a social interactions questionnaire will be filled to collect information on the number of contacts with people of different age groups in the last 24h.

During the post vaccination survey, additional information on the PCV vaccination during the study campaign from all children of the targeted age group will be collected.

Vaccination activities will occur at village level and will take place on a pre-scheduled day. All children of the target age group for vaccination, for instance aged 1-9 years of age, residing in the study villages allocated to full or fractional dose arm will be targeted for vaccination. Vaccination will occur at fixed sites in each participating village. Vaccination activities will be timed to happen in the same geographical area at the same

time and will be scheduled as to not interfere with other planned vaccination activities. The number of doses of vaccine administered at each site will be noted on tally sheets.

Data on Adverse Events (AEs) will be collected in a passive surveillance system for 7 days following vaccination (focusing on AEs at the injection site) and data on Serious Adverse Events (SAEs) for 28 days following vaccination. A health professional from the study team will be based in the nearest health centre to the vaccinated villages for 28 days after the vaccination activities and will be the key notifiers of AEs and SAEs to the study team. Moreover, the community health workers from the vaccinated villages will be asked to act as a focal point and communicate to the study team any events that occur during the follow-up period. During the vaccination activities, caretakers will be informed about vaccine safety and will be asked to contact the community health worker or to attend the nearest health centre in case of a health problem.

Data concerning SAEs from participants in villages allocated to the control group will be collected between the first vaccination date up to 28 days after the last vaccination date performed in villages that were allocated to full or fractional dose and located in the catchment area of the same health facility.

3.1.5 Analysis Populations

All data from the surveys will be analysed in an intent to treat approach, ie including all data collected in the household of each selected child. Only data collected in the households of selected children with results of the nasopharyngeal swab will be analysed for the primary outcome.

Analyses of the primary outcome will be repeated on the per protocol population. The per protocol population will include children that provided a NP sample and completed the child questionnaire as well as the household questionnaire and for which no protocol violation was reported and who were in clusters who received the intervention allocated during randomization.
Safety analysis will be conducted in two different groups depending on study intervention:

- In clusters allocated to the control arm, all children aged in the target age group for vaccination campaigns will be considered. The denominator in this study arm will be the population of the clusters according to the census records used to establish the sampling frame for the cluster.
- In clusters allocated to receive full- or fractional-dose mass campaigns, only children who actually received a vaccination will be considered, and the denominator in these study arms will be the number of children vaccinated based on records from the vaccination sites.

3.1.6. Protocol Violation and Deviations

A protocol violation is any departure from the approved protocol, trial documents or any other information relating to the conduct of the study, which may affect the safety of trial participants or the study outcomes. Examples include failure to obtain informed consent (i.e. no documentary evidence) or enrolment of children in one of the two surveys that do not meet inclusion/exclusion criteria.

Incorrect intervention provided during the vaccination will be considered as a protocol violation at the cluster level.

A protocol deviation is any departure from the approved protocol, trial documents or any other information relating to the conduct of the trial that does not result in harm to the trial participants and does not significantly affect the study outcomes. Examples of deviations include isolated incident of a missed or incomplete study procedure or study evaluation, cases of mis-randomization or mis-stratification will also be considered as a protocol deviation.

A final Protocol Deviation Listing will be generated and reviewed by sponsor personnel prior to freezing the database to ensure that all important deviations, including those that may lead to exclusion from analysis, are captured and summarized.

Participants or villages/clusters will be excluded entirely from analysis if they have a protocol deviation defined as a full exclusion that affects the validity of their data (e.g., failure to obtain informed consent).

3.2 Assessment of Objectives

3.2.1 Efficacy Assessments

3.2.1.1 Primary outcome

The primary outcome is the prevalence of vaccine-type NP carriage in children approximately 1 to 9 years of age. It will be assessed before vaccination campaign (baseline survey) and at 6 months post PCV10 vaccination campaign (post vaccination survey). VT pneumococci are defined as those covered by PCV10 (1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 23F).

3.2.1.2 Secondary outcomes

The secondary outcome is the prevalence of non-VT serotypes carriage in children approximately 1 to 9 years of age. It will be assessed as the same timepoints than for the primary outcome, ie during both surveys.

3.2.2 Safety Assessments

The safety outcomes are AE(s) at the injection site occurring withing 7 days after vaccination and SAE(s) occurring within 28 days after the vaccination. SAEs from participants in clusters allocated to the control group will be collected during a period of time from the first vaccination date up to 28 days after the last vaccination date performed in clusters allocated to full or fractional dose, in the geographical area sharing the same health center.

3.2.2.1 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that either results in death; is life threatening; results in persistent or significant disability or incapacity, requires in-patient or extended hospitalization; prolonged of existing hospitalization; is a congenital anomaly/birth defect in the offspring of a study participant; or is a medically important event that may jeopardize the participant or require intervention to prevent one of the above outcomes.

Data collection on the SAE will include the diagnosis of the AE, the intensity, the start and end dates, the outcome, the causality assessment with the vaccine, the seriousness criterion and the actions taken. Age and sex of the participant experiencing the SAE(s) will also be collected.

3.2.2.2 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a clinical trial subject to whom a vaccine has been administered; it does not necessarily have a causal relationship with the vaccine/vaccination. In this study, the recording AEs will be limited to injection-site reactions as site pain injection, redness, swelling, itchiness, infection, etc.

In addition to the diagnostic, the intensity, the start and end dates, the outcome, the causality assessment with the vaccine, the seriousness criterion and the actions taken. Age and sex of the participant experiencing the AE(s) will also be collected.

3.2.2.3 Immediate post vaccination reactions

Immediate reactions post-vaccination will be collected as other AE(s) from previous section.

3.2.2.4 Fatal adverse events

Any event which results in death will be recorded in the AE CRF as other AE from previous section.

Additional information will be reported in the Serious Adverse Event form as the expectedness of the event, the result of the verbal autopsy and all relevant clinical records to provide a complete narrative of the fatal event.

3.2.3 Other Assessments

During both surveys, other information on the households will be collected, including a household census including members' age and sex, the type of residence, occupation of the head of household, highest level of education of the head of household, ethnicity of the head of household, and information about known risk factors for pneumococcal carriage, including exposure to solid fuel smoke, certain indoor cooking practices, and smoking habits.

During the baseline survey only, one randomly-selected household member will be administered a detailed questionnaire about social contacts with people of different ages, their sleeping arrangements, and their level of educational attainment.

During both surveys, one randomly-selected child aged 1 to 9 years will have a NP swab collected. Information will also be collected regarding this child's age, sex, sleeping arrangements, PCV vaccination status, and recent medical history, including medications taken in the last 14 days.

During the follow-up survey only, all children in the target age group for the vaccination campaign will be asked about their participation in the vaccination campaign.

During the vaccination campaigns, the number of children vaccinated will be collected at each site.

4. Statistical Methods

4.1 Timing of Analysis

The primary endpoint will be the change from baseline in VT carriage at 6 months post-vaccination campaign. The reduction in VT carriage will be calculated by comparing the proportion of children carrying VT pneumococci 6 months post-vaccination to the baseline.

4.1.1 Primary Analysis Time Point

The primary analysis time point for the primary endpoints is 6 months post vaccination campaign.

4.2 Methods for Handling Missing Data

In general, missing data will be considered missing at random and no imputation will be performed.

4.3 Statistical Analysis

All results will be displayed by intervention group (full dose, fractional dose or control).

Descriptions of the study population will be provided at the individual level and at the cluster level as appropriate. Statistical analyses to demonstrate superiority and non-inferiority will be performed at the individual level. Non inferiority will be tested if the superiority of the full dose is shown; therefore, no adjustment for multiplicity is necessary.

Comparison between groups will be done at the cluster level using Student's t-test for continuous variables and Chi square test (or Fisher's exact test if more appropriate) for categorical variable.

Safety analysis will be done at the individual level only, and comparison for categorical variables will be done using a Chi square test (or Fisher's exact test if more appropriate). All comparisons will be done at the 0.05 significance level.

Prevalence of carriage will be presented with a 2 sided 95% confidence interval.

All statistical analysis will be performed on the statistical software Stata version 17 or later.

4.3.1 Baseline Characteristics

Information on the total number of participants per intervention group for each of the following categories will be presented: screened households, screen failures (together with reasons for screen failure), consented participants for the baseline survey, the vaccination and the follow up survey, screen failures (with reasons for screen failure) for baseline and post vaccination surveys and reasons for NP not performed.
Information on the total population and population aged 1 to 9 years from the census, as well as breakdown by sex and distance to nearest health facility will be also summarized by cluster.
Number of vaccinees, by sex and age group will be summarized by intervention group. Participant demographics and data collected through questionnaire at baseline and during post vaccination survey (as describe in section 3.2.3) for each group will be given at individual levels using count and percentages for qualitative variables,

mean and standard deviation (SD) for quantitative variables, and at cluster level using means and standard deviation (or median and IQR if appropriate).

Baseline prevalence of carriage (VT and non VT serotypes) will be measured as the proportion of participants that are respectively colonized with any of the 10 serotypes covered by PCV10 and colonized with any other serotypes, excluding non-typable SP and those confirmed as not colonized by SP.

Proportions will be compared using chi square or Fisher's exact test, as appropriate and adjusting for the clustering effect.

4.3.2 Primary Analysis

4.3.2.1 Primary Analysis

The primary analysis is the test of the superiority of the full dose vaccination arm compared to the control arm, on the reduction in NP carriage. The reduction will be calculated by comparing the proportion of children carrying VT pneumococci 6 months post-vaccination to baseline, at the time of vaccination.

This primary analysis on the primary endpoint will be performed on the intent to treat population, using generalised estimating equations (GEE) to estimate risk differences and their associated 95% CI for the effect of the full dose vaccination on the reduction in VT carriage compared to the fractional dose. GEE will be used to account for clustering effect. Adjusted analyses with covariates (including but not limited to age, sex, vaccination coverage, time between baseline survey and vaccination, time between vaccination and follow-up survey, baseline prevalence of VT carriage) and stratification factor will be performed.
The administrative vaccination coverage for each site where vaccination campaign is performed, is obtained by the formula:
(number of vaccinees/number of expected children from the age group 1-9 years old) x 100.

The superiority will be tested at the 0.05 significance level.
For the non-inferiority analysis, the 95%CI around the risk difference in the in the proportion of children with VT carriage (full dose group – fractional dose group) will be using generalised estimating equations (GEE) and non-inferiority will be achieved if the lower limit of this 95%CI is >-7.5%.

Non inferiority analyses will be repeated on the per protocol population. Sensitivity analyses on the primary endpoint will be repeated by analyzing clusters according to the intervention they actually received if misallocation occurred.

In order to account for any potential seasonal variation seen due to timing of the surveys, additional sensitivity analyses will be performed, comparing the difference in prevalence between the full-dose and control arms, relatively to the reduction observed in the control group..

Multivariable logistic regression analyses will be performed to obtain adjusted estimates of risk factors for VT carriage at baseline and after vaccination campaign. The Odds Ratio and95% CI will be adjusted for age and sex. Robust SE will be used to allow for clustering at the cluster level. 4.3.2.2 Secondary Analysis.

4.3.3 Safety Analysis

Safety analysis will be based on the entire study population.

Any adverse events occurring within 7 days after vaccination, serious adverse events, or deaths will be summarized as n (%) of participants having experienced the AE(s), and SAEs or death by arms. Comparisons will be done between full-dose and fractional-dose arms with the control arm, using a Fisher's exact test.

All AEs will be coded to a "Preferred Term" (PT) and primary associated "System-Organ Class" (SOC) according to the MedDRA dictionary (Medical Dictionary for Regulatory Activities, version 25.0).

Counts and proportions will be provided overall and for each PT within each SOC. AE(s) will be tabulated overall and by grade, and by type of AEs:

- AEs non SAEs occurring with 7 days after vaccination
- SAEs
- SAEs leading to death

5. Statistical Tables to be Generated

<Consider appropriate tables for each of these categories and some examples are provided>

5.1 Demographic and Baseline

Table 1.1	Summary of Screening
Table 1.2	Summary of Participant Disposition by intervention group, Analysis Population - Randomized Cluster
Table 1.4	Summary of Protocol Deviations by intervention group - ITT Population
Table 1.5	Summary of Demographics and Baseline Characteristics by intervention group, participants and Cluster level - ITT Population

5.2 Primary and Secondary Analyses

5.3 Safety Analysis

Adverse Events

Table 3.1	Summary of adverse events (AEs) by intervention group
Table 3.2	Adverse events (AEs) by MedDRA coding (SOC and PT) by intervention group, Safety population
Table 3.3	Severity of adverse events (AEs) , Safety population
Table 3.6	Relatedness of adverse events (AEs) , Safety population
Table 3.7	Outcome of adverse events (AEs) , Safety population

Serious Adverse Events

Table 3.1	Summary of serious adverse events (SAEs) by intervention group
Table 3.2	Serious Adverse events (SAEs) by MedDRA coding (SOC and PT) by intervention group, Safety population
Table 3.6	Relatedness of serious adverse events (SAEs) , Safety population
Table 3.7	Outcome of serious adverse events (SAEs) , Safety population
Deaths	
Table 3.22	Summary of deaths by study arm, Safety population

6. Statistical Listings to be Generated

<Adapt and amend as needed>

Participant Data Listings

Listing 1.1	Participants who are screen-failures
Listing 1.3	Listing of protocol deviations
Listing 1.5	Exclusion of villages/cluster from PP populations

Safety Listings

Listing 2.1	Listing of Serious adverse events (SAEs)
Listing 2.3	Listing of Adverse events (AEs)
Listing 2.5	Listing of death narratives

7. Statistical Graphs to be Generated

<Adapt and amend as needed>

Figure 1.1	Study flowchart of study arms, and analysis populations