KWTRP

CLINICAL TRIAL PROTOCOL

The effect of fractional doses of pneumococcal conjugate vaccines (PCV10 and PCV13) on immunogenicity and vaccine-serotype carriage in Kenyan infants

GENERAL INFORMATION

Protocol Number:	**QA1075**
Trial Registration Number:	
Investigational Product(s):	**Pneumococcal Conjugate Vaccines: Synflorix (PCV10; GlaxoSmithKline plc.) and Prevnar13 (PCV13; Pfizer Inc.)**
Funder:	**The Bill & Melinda Gates Foundation; 500 Fifth Avenue North; Seattle, WA 98109; USA.** **Tel: +1 (206) 709-3100**
Sponsor:	**London School of Hygiene & Tropical Medicine; Keppel Street, London, WC1E 7HT, United Kingdom.** **Tel: +44 (0) 20 7636 8636** **Email: Patricia.Henley@lshtm.ac.uk**
Product Manufacturer(s):	**1. GlaxoSmithKline plc., 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom. Tel: +44 (0)20 8047 5000** **2. Pfizer Inc., 235 East 42nd Street NY, NY 10017, USA. Tel: +12127332323**

Confidentiality Statement

The information contained herein is privileged or confidential and may not be disclosed unless such disclosure is required by applicable laws or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you, which is indicated as privileged or confidential. This confidentiality statement also applies to data generated during the course of the study.

INVESTIGATOR'S APPROVAL OF THE PROTOCOL

The effect of fractional doses of pneumococcal conjugate vaccines (PCV10 and PCV13) on immunogenicity and vaccine-serotype carriage in Kenyan infants

Protocol Number:

The undersigned acknowledge possession of and have read the Fractional Dose PCV Trial protocol versions 1.0 (dated 16th October 2017), 2.0 (dated 09th January 2018) and 3.0 (dated 01st May 2018). Having fully considered all the information available, the undersigned consider that it is ethically justifiable to give pneumococcal conjugate vaccines in fractional doses to the selected participants according to the agreed protocol.

I understand that all information concerning fractional doses of pneumococcal conjugate vaccines supplied to me by the London School of Hygiene and Tropical Medicine (LSHTM) and their agents/partners in connection with this study and not previously published is confidential information. This includes the Investigators' Brochure, Clinical Trial Protocol, Case Report Forms and any other preclinical and clinical data provided by LSHTM.
I understand that no data are to be made public or published without prior knowledge and written approval by LSHTM.
By my signature below, I hereby attest that I have read, understood and agreed to abide by all the conditions, instructions and restrictions contained in the Fractional dose PCV trial protocol and in accordance with the most recent Declaration of Helsinki and Good Clinical Practice and all applicable regulatory requirements.
I acknowledge that the Sponsor of the study, LSHTM, has the right to discontinue the study at any time.

Principal Investigator Signature	**Date**
[Principal Investigator name and title/position/role]	

CONTENTS

GLOSSARY OF TERMS AND ABBREVIATIONS:

AE	Adverse Event
ATP	According-to-protocol
CI	Confidence Interval
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
EPI	Expanded Programme on Immunization
ERC	Ethics Review Committee
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titre
GMFI	Geometric Mean Fold Increase
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Intradermal
IgG	Immunoglobulin G
IM	Intramuscular
IRB	Institutional Review Board
ISF	Investigator site file
ITT	Intention to treat
IU	International Units
NRA	National regulatory authority
PI	Principal Investigator
PIS	Patient information sheet
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction

1 LAY SUMMARY

Formal Title: The effect of fractional doses of pneumococcal conjugate vaccines (PCV10 and PCV13) on immunogenicity and vaccine-serotype carriage in Kenyan infants.

Lay Title: A trial to compare the immune response and the proportion of infants still carrying bacteria in their nose after varying doses of the pneumonia vaccines ('PCV10' and 'PCV13') in Kenyan infants.

What is the problem/background? Before the introduction of pneumonia vaccines in 2000, around 700,000- 1 million children died each year as a result of infection with the bacteria *Streptococcus pneumoniae* and the resulting diseases, namely, meningitis, sepsis and pneumonia. Most of the deaths were in Africa and Asia. Where the vaccines have been introduced, they have been highly effective and have already reduced disease. However, at USD 10 per child, they are not affordable to most low-income countries without financial support from Gavi, the Vaccine Alliance. In Kenya, a 10-valent PCV has been implemented since 2011. The greater part of the vaccine cost is subsidized by Gavi. However, in 2022 Gavi will begin to reduce its subsidies to Kenya over a 5-year period so that by 2027 Kenya will be paying the whole cost alone. A reduction in the cost of the PCV programme may be necessary for Kenya to keep delivering its PCV programme.

What questions are we trying to answer? This project aims to assess whether lower doses of the two commercially available pneumonia vaccines can protect Kenyan infants as well as the full dose and can be delivered safely. The results could be used to enable countries unable to afford the full cost of the pneumonia vaccine, to continue delivering it in the childhood immunisation programme in the absence of Gavi support.

Where is the study taking place, how many people does it involve and how are they selected? The study will take place at multiple health facilities in Kilifi County. A total of 2100 infants will be involved. Infants will be selected from those eligible for routine immunisations. Infants with acute illness will be excluded from enrolment into the study. HIV infection will be recorded but not used as an exclusion criterion.

What does the study involve for those who are in it? Participants will be randomised in equal numbers to one of seven groups to receive either PCV10 or PCV13 at the full dose or lower dose schedules.

Infants will receive the first dose of the three-dose schedule at 6 weeks of age and then mothers and infants will be invited back to the study clinic 6 further times during the course of the study. Infants will receive the 2nd and third doses of the vaccine, at 10 and 14 weeks or at 14 weeks and 9 months of age. They will have a small amount of blood taken at their first visit, and 4 weeks after the 2nd and 3rd doses, some participants will also have a small amount of blood drawn at the time of the 3rd dose and at their last study visit at 18 months of age. Two swabs will be taken from the mucous in the nose to look for the presence of the bacteria.

What are the benefits and risks/costs of the study for those involved? There is a small risk that the children in this study who receive the lower dose schedules will be less well protected than those who receive the full dose. However, because the vaccine has been in use for 6 years already in Kenya and will continue to be in use in the routine immunization system throughout the study, the bacteria is much less common than it was and the likelihood of developing disease is very low. As participants in the study, infants will have access to the study medical staff and will be able to present with any illness at an early stage and receive free treatment and/or referral to the sub-district hospital up until the age of 18 months (when the study ends). If, after final analyses, the lower doses are found to not give a good enough immune response, all infants in those groups will be given a single booster vaccination with the full dose.

If a low dose of the vaccine stimulates a protective immune response, infants who were randomly selected to be given the PCV13 will have the added benefit of immunization against three additional pneumococcal bacterial types (3, 6A, 19A) contained in the study vaccine (PCV13) but not contained in the vaccine used in the national programme (PCV10). 900 of the 2100 children recruited into the study will receive PCV13.

How will the study benefit society? If the pneumonia vaccines are effective at lower doses, the whole community may benefit. If lower doses can be administered the cost of the vaccine will fall meaning it may continue to be delivered by the government for longer.

When does the study start and finish? The study will start upon receipt of ethical clearance. Data collection, analysis and write up will take place over 42 months.

2 TITLE OF THE PROJECT

The effect of fractional doses of pneumococcal conjugate vaccines (PCV10 and PCV13) on immunogenicity and vaccine-serotype carriage in Kenyan infants

3 LIST OF INVESTIGATORS

KEMRI Investigators:

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Non-KEMRI Investigators:

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Professor Frederick Were; Professor of Paediatrics at the University of Nairobi, Chair of the Kenyan NITAG.

Dr. Christian Bottomley; Associate Professor in Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.

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4 ABSTRACT

Currently, two pneumococcal conjugate vaccines (PCV) are licensed for inclusion in routine immunisation schedules in low- and middle-income countries (LMICs). Both vaccines have proven highly effective in stimulating vaccine-serotype-specific immune responses, reducing vaccine-serotype carriage and reducing the incidence of invasive pneumococcal disease (IPD) and hospitalised pneumonia. Worldwide, over 50 LMICs have introduced PCV with the support of Gavi, the Vaccine Alliance; however, as economies grow and countries transition out of Gavi support, the sustainability of their PCV programmes is at risk. PCV is currently the most expensive vaccine in the routine immunisation schedule in Gavi-supported countries. This study aims to provide evidence which may enable a substantial decrease in the cost of PCV programmes, therefore increasing the sustainability of PCV programmes in LMICs. We propose to assess whether fractional (20% and 40%) doses of pneumococcal conjugate vaccine (PCV10 and PCV13) in a 2p+1 schedule (2 primary doses followed by a booster dose) induce non-inferior immunogenicity and effects on vaccine-serotype carriage when compared to the full dose. These lower doses would convert new 4-dose vials of PCVs into 10- or 20-dose vials, ready for immediate implementation in LMIC programmes.

5 INTRODUCTION/ BACKGROUND

Pneumococcal conjugate vaccines (PCVs) have proven to be highly effective in stimulating vaccine-serotype specific immune responses[1-3], reducing vaccine-serotype carriage[4-7] and causing significant declines in invasive pneumococcal disease (IPD)[8, 9]. In 2004, four years after the introduction of PCV7 in the USA, the incidence of Invasive Pneumococcal Disease (IPD) among children aged <5 years had declined by 84% and the incidence of vaccine-serotype IPD had declined by 92%[6]. These findings are supported by similar surveillance figures in Western Australia[8], Northern Canada[10] and England, where further declines were apparent after the switch from PCV7 to PCV13[11].

Currently, two PCVs are available for introduction into the routine immunisation schedules of low- and middle-income countries (LMICs), Synflorix® (GlaxoSmithKline plc.) covers 10 pneumococcal serotypes and Prevnar 13® covers 13 serotypes (Pfizer Inc.). Although there is now evidence that immune correlates of protection for vaccine serotype-specific IgG responses may vary by serotype[2], both vaccines have been licensed based on the immune correlate of protection for vaccine serotype-specific IgG responses of 0.35 mcg/ml IgG established using PCV7[12, 13]. There is little evidence of cross-protection against non-vaccine pneumococcal serotypes[9, 12]. The World Health Organization (WHO) currently recommends PCV10 or PCV13 for use in routine immunisation programmes in a three dose schedule: in a primary series at 6, 10 and 14-20 weeks of age (the '3p+0' schedule), or two primary doses at 6-8 weeks and 14-16 weeks with a booster at least 6 months after the 2nd dose (e.g. 11-15 months of age; the '2p+1' schedule)[12]. In high income countries, where disease incidence generally peaks later in childhood than in LMICs[14], the 2p+1 schedule has demonstrated effective direct protection against carriage and IPD and additionally stimulates strong herd protection at the population level[11, 15, 16]. In most LMICs, including Kenya, rates of pneumococcal disease peak in the first 6 months of life, and uptake of vaccines scheduled for the second year of life is low, so a 3p+0 schedule has been adopted to ensure direct protection from disease as early in life as possible[14]. However, there is evidence that the IgG concentrations after 2 primary doses delivered with a 2 month interval are equivalent to those produced after 3 doses that are each 1 month apart[17, 18]. Additionally, data from Australia indicate that a 3p+0 schedule of PCV13 may have resulted in less substantial declines in IPD compared to those seen in the UK or USA, where 2+1 and 3+1 schedules have been used respectively[19]. As PCV programmes mature and evidence accrues, schedules in LMICs may also change to 2p+1 in order to take advantage of the potential additional benefits of herd protection[19-21]. This approach is supported by recent data from South Africa, a relatively high transmission setting, where a 2p+1 schedule of PCV7 has demonstrated a 48-60% reduction in carriage prevalence at 12 months of age compared to a PCV-unvaccinated historical cohort[22, 23]. IgG concentrations pre-boost were greater than 0.35 mcg/ml for all 7 vaccine types indicating that, importantly, direct protection may have been maintained in the period between the primary series and boost dose[24]. Persistence of high IgG concentrations could be due to the persistence of the vaccine-induced immune response and/or natural boosting through exposure to circulating

vaccine-types[25].In the UK, 2.5 years after vaccination in a 2p+1 schedule, >75% of children had circulating IgG to 5 of the 7 PCV7 serotypes at concentrations >0.35 mcg/mll[26]. Protection from carriage has been demonstrated out to at least 4 years post-vaccination in some studies for at least some PCV7 serotypes[27]. Further data are needed on the duration of protection after a 2p+1 schedule in LMIC settings, both between the primary series and boost dose and after the booster into the 2nd year of life[16, 27].

Safe and immunogenic co-administration of PCV7/9/13 with routine childhood immunisations has been demonstrated for all antigens in the schedule, including Diphtheria-Tetanus- acellular Pertussis vaccine with or without Inactivated Polio Vaccine and hepatitis B vaccine components, Measles-Mumps-Rubella, Varicella, Haemophilus influenzae Type b (Hib) and meningococcal conjugate vaccines [28-32]. Immunological responses to PCV in Kenyan infants are high; over 90% of a cohort of children following the routine immunisation schedule of 3p+0 achieved the immune correlate of protection 4 weeks after the third dose for all PCV7 serotypes[33].

6 JUSTIFICATION

Since 2010, Gavi, the Vaccine Alliance, has supported PCV introduction in over 50 'Gavi-eligible' LMICs (countries with a gross national income (GNI) per capita <1580 USD). At the current cost of US$3.10-3.50 per dose, PCV is the most expensive vaccine in the EPI schedule for many LMICs[34]. At US$10 per fully immunised child, PCV is one of the biggest barriers to countries self-financing their routine vaccination schedules and the sustainability of the PCV programme is of concern in countries that are transitioning out of Gavi support. Gavi predicts that Kenya will enter the 'accelerated transition phase' in 2022, at which point vaccine co-financing commitments will increase sharply for 5 years until Kenya's routine immunisation (RI) programme is fully self-financed. In 2015, the Kenyan government funded just 10% of their RI programme expenditure[35]; the EPI programme is anticipating potentially dropping antigens from their vaccination schedule to meet the funding shortfall. Both the EPI programme and the Kenya National Immunisation Technical Advisory Group are actively examining alternative policy options for prevention of pneumococcal disease. Furthermore, for those middle-income countries ineligible for Gavi support, a reduction in the cost of PCV may enable vaccine introduction where currently it is prohibitively expensive. In 2016, only 56% of MICs had introduced PCVs compared with 76% of low-income countries (LICs)[36]. As of September 2017, only 57% of the world's infants lived in countries that had introduced PCV[37, 38].

One approach to reducing the financial cost of PCV programmes is to use a fractional dose of antigen at each vaccination. Fractional doses of antigen have been shown to induce non-inferior immune responses in trials of vaccines against *Haemophilus influenzae* type b (Hib)[39-44], *Neisseria meningitidis*[45] and Yellow Fever[46-49] and are under investigation for Inactivated Polio Vaccine (IPV) using novel injection devices for intradermal delivery[50-54]. Both the diphtheria CRM_{197} and tetanus toxoid-conjugated Hib vaccines with antigen doses as low as 1.25 mcg (1/8th of the marketed dose) stimulated non-

inferior immune responses when compared to the full dose[39]. Intramuscular doses of 2.5 mcg (1/4th of the full dose) of *Neisseria meningitidis* serogroups A and C polysaccharide within a conjugate vaccine elicited high geometric mean titres of antibody in Filipino infants[45]. A 0.1 ml dose of Yellow Fever vaccine (1/5th of the standard dose), delivered via subcutaneous or intramuscular injection, is now endorsed by WHO as a preventative measure in areas at risk of epidemics[55, 56].

Specific to pneumococcal vaccines, an early trial of a pentavalent pneumococcal conjugate vaccine (pentavalent PCV) documented serotype-specific immune responses that reached the immune correlate of protection (0.35 mcg/ml – established following later efficacy trials) after a dose of just 0.5 mcg of antigen without adjuvant (approximately 1/5th of the current dose in PCV13 – see Table 1)[57]. Pentavalent PCV was administered to 400 infants in the USA in the 1990s in formulations of 5, 2 or 0.5 mcg of polysaccharide; 1 month after the third vaccine dose all three formulations elicited adequate serotype-specific immune responses for protection (>0.35 mcg IgG/ml)[57]. Additionally, there is some evidence that African children elicit higher antibody responses than European or American children[58], which may mitigate against any potential diminution in immunogenicity with reducing dose.

Following the request by Gavi-eligible countries to reduce the cold-chain requirements of PCV[59], Pfizer and GlaxoSmithKline (GSK) have developed 4-dose presentations of PCV containing a preservative, which will be available for ministries of health to purchase from Unicef from 2018. The presence of a preservative in these 4-dose vials, which is not in the 2-dose vials of PCV10, reduces the risk of contamination during multi-dose administration and enables multi-dose vials to be used for up to 28 days following first puncture, minimising vaccine wastage. The 4-dose presentations are not available for use in this study; the trial will use single dose formulations to deliver a single full or fractional dose as a proof of concept. However, if this trial provides evidence that fractional doses elicit non-inferior immunogenicity to full doses using the single dose formulations, LMICs could operationalise fractional dose delivery by using the 4-dose vials as 10 or 20 dose vials, as soon as the trial results are known. Vaccine implementers in LMICs are familiar with multi-dose vials, particularly 10-dose/20-dose vials that are used to deliver BCG, and re-classifying a 4-dose vial of PCV as either a 10-dose or 20-dose vial would effectively deliver 40% or 20% fractional doses. Here we propose to evaluate whether fractional doses of PCV10/13 induce non-inferior immunogenicity in a proof of concept study, if the trial yields propitious results, a further small study could be conducted to document the feasibility of delivering 10 or 20 doses from a single 4-dose vial. A 20% dose of PCV13 in 0.1 ml volume would deliver a dose of saccharide similar to the lowest dose previously found to elicit an adequate immune response in the pentavalent PCV trial. This study was performed without the advantage of an adjuvant[57]. The 20% dose of PCV10 would deliver a lower dose of antigen than published in previous studies; however, PCV10 has demonstrated broadly equivalent effectiveness to PCV13 despite using saccharide doses approximately half those of PCV13. The different vaccines use different carrier proteins[60, 61] and therefore both the 40% and 20% doses need to be tested for both products to allow results to be generalizable to Kenya and/or other

LMICs currently using PCV13. A 20% doses, at a volume of 0.1ml represents the smallest volume currently thought to be feasible to deliver as an intramuscular injection in infants[55].

Table 1. The available vaccine formulations and proposed fractional (20% and 40%) dose of PCV10 and PCV13

Serotype saccharide dose (µg)	1	3	4	5	6A	7F	9V	14	18C	19A	19F	23F	6B
PCV13	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	4.4
40%-PCV13	0.88	0.88	0.88	0.88	0.88	0.88	0.88	0.88	0.88	0.88	0.88	0.88	1.76
20%-PCV13	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.88
PCV10	1.0		3.0	1.0		1.0	1.0	1.0	3.0		3.0	1.0	1.0
40%-PCV10	0.40		1.2	0.40		0.40	0.40	0.40	1.20		1.20	0.40	0.40
20%-PCV10	0.2		0.6	0.2		0.2	0.2	0.2	0.6		0.6	0.2	0.2

If fractional doses generate non-inferior vaccine serotype-specific immune responses and similar impact on vaccine serotype carriage as the full dose, the cost of PCVs could be reduced by 50-75%. This would represent a substantially greater cost reduction than that achieved in recent price reductions (10% reduction in 2017)[62], or by reducing to a two-dose schedule (33%).

7 HYPOTHESIS

The null hypothesis is that there is a difference in the geometric mean concentrations of IgG elicited by Kenyan infants following three fractional doses of PCV10/ PCV13 (at 20% or 40% dose) in a 2p+1 schedule compared to full doses in a 2p+1 schedule.

8 AIM & OBJECTIVES

8.1 AIM

To assess whether fractional doses (20% or 40%) of 10 or 13-valent Pneumococcal Conjugate Vaccine (PCV13/ PCV10), administered in a schedule consisting of two primary doses and one booster dose, induce serotype-specific immunogenicity and carriage prevalence at 18 months of age, that are non-inferior to the effects achieved with full doses.

8.2 Primary objective

To determine whether fractional doses of PCV13/ PCV10 elicit non-inferior immunogenicity compared to full doses when delivered in a 2p+1 schedule with primary analyses at 4 weeks

after the booster dose (10 months of age) and secondary analyses at 4 weeks after the primary series (18 weeks of age). For the primary objective, immunogenicity will be assessed as the ratio of the geometric mean concentrations of IgG in the fractional/full dose arms. Secondary analyses will assess the proportion of infants achieving antibody levels above the threshold for protection (0.35 mcg IgG/ ml).

8.3 Secondary objectives

- To determine the functionality of the immune response to full and fractional doses at the 1-month post-boost time point using an opsonophagocytic assay.
- To compare vaccine efficacy against carriage of non-PCV10 serotypes 6A and 19A in the full dose PCV13 arms when compared to the fractional dose arms, using the full dose PCV10 2p+1 arm as a control, with primary analyses at 18 months of age and secondary analyses at 9 months of age. The carriage prevalence of the common vaccine serotypes (PCV10 serotypes) in the fractional dose arms will also be compared against the carriage prevalence in the full dose arms.
- To compare frequency and severity of local injection-site reactions and vaccine-related adverse events in the 28 days following immunization after fractional dose delivery and a full dose delivery.
- To determine the concentration of circulating IgG after the primary series of the 2p+1 schedule, prior to boost, at 9 months of age and after the boost at 18 months of age, estimate the duration of direct protection conferred by full and fractional dose schedules and use seroepidemiology to monitor acquisition rates.
- To compare carriage prevalence at 9 and 18 months of age and IgG concentrations at 4 weeks after the primary series after full dose of PCV10 in a 3p+0 schedule, and full/ fractional doses of PCV10/13 in a 2p+1 schedule.

9 TRIAL DESIGN

9.1 Overall Study Design

A phase IV individually-randomised controlled trial of full or fractional (20% or 40%) doses of PCV10/ PCV13, given as a 3-dose schedule to infants: 2 doses at 6 and 14 weeks of age and a booster dose at 9-12 months (the 2p+1 schedule) or 3 full doses at 6, 10 and 14 weeks of age (the 3p+0 schedule) (Figure 1.).

At 6-8 weeks of age, 300 infants will be enrolled at random into each of the seven trial arms and followed until 18 months of age. The seven trial arms:

A. **Full dose PCV13 vaccination in a 2p+1 schedule.** This arm will demonstrate immunogenicity and carriage endpoints for an alternative schedule to 3p+0 as recommended by WHO, in the Kenyan population.

B. **40% fractional dose PCV13 vaccination in a 2p+1 schedule.**

C. **20% fractional dose PCV13 vaccination in a 2p+1 schedule.**

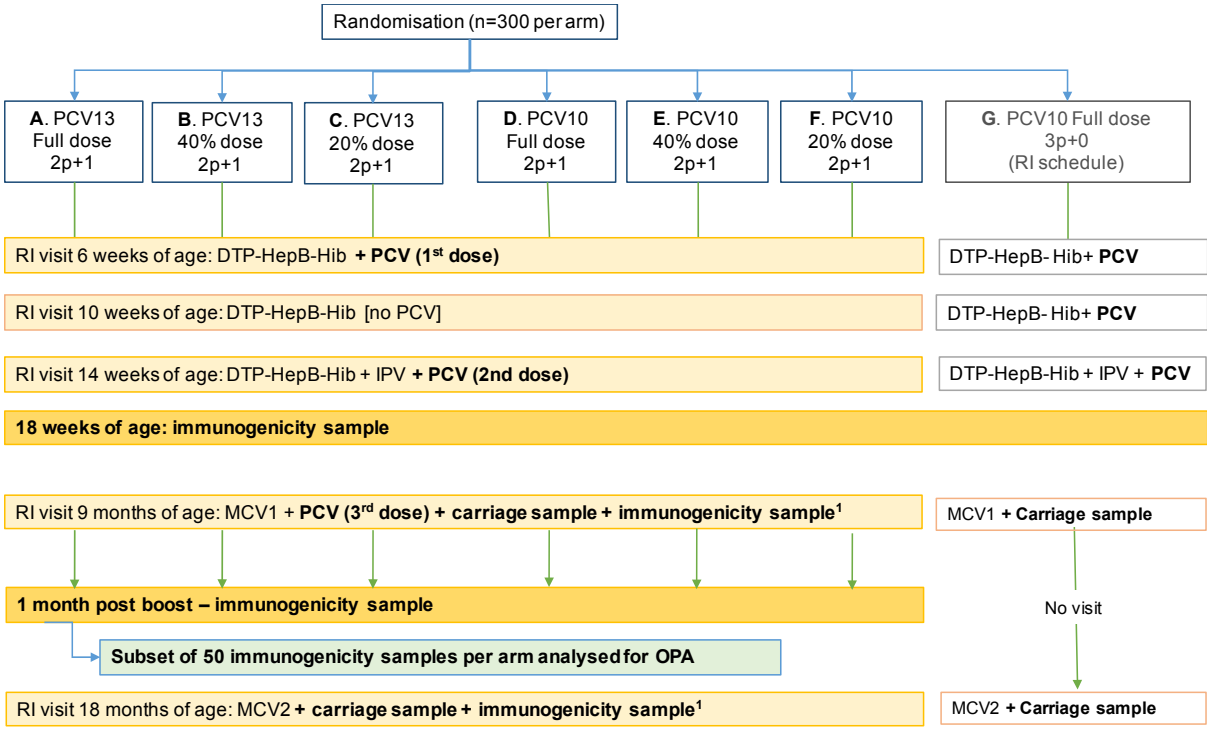
D. **Full dose PCV10 vaccination in a 2p+1 schedule.** This arm will demonstrate immunogenicity and carriage endpoints for an alternative schedule to 3p+0 as recommended by WHO, in the Kenyan population.

E. **40% fractional dose PCV10 vaccination in a 2p+1 schedule.**

F. **20% fractional dose PCV10 vaccination in a 2p+1 schedule.**

G. **Full dose PCV10 vaccination in a 3p+0 schedule.** This arm would represent the current vaccine and schedule in the Kenyan routine immunisation programme and would act as an additional comparison arm.

Figure 1. Clinical trial flow



[1] Immunogenicity samples at 9 and 18 months of age will only be drawn from 150/300 participants in each arm.
RI = routine immunisation.

9.2 Description of the study population

The proposed trial will be conducted out of the KEMRI Wellcome Trust Research Programme (KWTRP) Centre for Geographic Medical Research - Coast (CGMRC), with approximately 8 clinics in Kilifi, Ganze, Malindi, Magarini sub-counties in Kilifi County. The final selection of clinics will depend on the agreement of the County and Sub-County health management teams. The following clinics are proposed, in the first instance:

- Ganze Health Centre & Bamba Sub-District Hospital (Ganze sub-county)
- Gongoni Health Centre, Mambrui Dispensary, Marikebuni dispensary (Magarini sub-County)
- Gede Health Centre ((Malindi sub-county)
- Matsangoni health centre and Kilifi County Hospital (Kilifi North sub-county)

A further 1-2 other health facilities may be utilised if the above health centres cannot be used or if recruitment is slower than expected, including: Malindi General Hospital (Malindi Town sub-county), Vitengeni Health Centre (Ganze sub-county) and Chasimba health centre (Kilifi South sub-county).

KWTRP CGMR-Coast has significant experience in recruitment of infants and young children to vaccine trials in a variety of different areas including past trials including 300 infants in Kilifi[33], 600 toddlers in Malindi[63] and 447 infants in Mtwapa/Pinglikani[64].

PCV10 was introduced in the national EPI programme in Kenya in 2011 in a three-dose schedule at 6, 10 and 14 weeks of age, with no booster dose (the '3p+0' schedule). In Kilifi County, a catch-up campaign in under 5-year olds was completed. PCV10 is delivered concomitantly with DTP-HepB-Hib (pentavalent) vaccine and oral Polio vaccine[65]. In Kilifi, the median age at receipt of the first dose of PCV10 in 2013-2016 was 6.1-6.3 weeks (personal communication I. Adetifa). At 14 weeks of age, IPV is also administered. In an evaluation of the impact of the new vaccine introduction in 2013 it was estimated that *S. pneumoniae* vaccine-serotype carriage had been reduced from 34% to 13% in children under 5 years of age in Kilifi[4]. This had been further decreased to 7% in 2016 but may be higher in areas outside of Kilifi in which no catch-up campaigns were conducted. It is expected that the fractional doses will be effective in preventing the acquisition of vaccine-serotype (VT) carriage, but if they are not, this will be apparent within the trial as study infants will be exposed (by contact with older children) to the vaccine serotypes. Furthermore, the reduction in vaccine type carriage prevalence over time has been matched by a commensurate increase in carriage of non-vaccine serotypes, particularly those contained in PCV13 but not in PCV10 (3, 6A and 19A) which are now found in 22% of all children under 5 years (cross sectional survey in Kilifi 2016; unpublished observation).

Although Kenya currently delivers PCV in a 3p+0 schedule, there is increasing pressure for LMICs to switch to a 2p+1 schedule to take advantage of the hypothesised increased herd protection with a booster dose[20]. In preparation for a potential future change in schedule we have designed the study to deliver fractional doses in a 2p+1 schedule; however, we are also incorporating a single arm of 3p+0 to 'bridge' the findings to the existing schedule. PCV7, PCV9 and PCV13 can be delivered concomitantly with DTP-HepB-Hib (pentavalent vaccine) and other routine immunisations including measles with no effect on the immunological responses to any of the antigens [29, 32, 60, 61, 66, 67]. There is currently no routine vaccination visit at 11-15 months of age in Kenya; however, measles vaccine first dose (MCV1) is delivered to children at 9 months of age and measles second dose was

introduced in 2015 for children 15-18 months of age (MCV2). In future, the delivery of the booster dose in the 2p+1 schedule could be integrated with MCV1 or MCV2 or other health interventions e.g. vitamin A supplementation. In Kenya, 75% of children received MCV1 in 2015[68] and 88% of children were fully vaccinated with the three doses of pentavalent vaccine by 1 year of age[69]. The National Vaccines and Immunization Program (NVIP) have begun to strengthen second year of life vaccinations and increase uptake of Measles second dose at 15-18 months of age. The World Health Organization also proposed to SAGE (April 2016) a new focus on the second year of life in the integration of immunisation and child-health services[70]. However, the most recent data for MCV2, from the first year of its introduction in Kenya in 2015, indicated only 28% coverage[68]. Therefore, for the purposes of this study, we will integrate the booster dose with MCV1 at 9 months of age.

Across the coastal region of Kenya, 97% of women attend at least 1 ANC appointment at their local health facility, at a median of 5 months of gestation[69]. In 2014, 85% of women attending ANC nationally were tested for HIV and PMTCT programmes were available in >95% of health facilities[71]. HIV prevalence in women who had had at least 1 child was 6.1% with an estimated mother-to-child transmission rate of 15% leaving 0.9% of infants with HIV infection[71]. We intend to execute the study as a pragmatic trial, including all infants regardless of HIV status; however, the prevalence of HIV in infants will be too low to permit a sub-group analysis of the impact of fractional doses among HIV-infected (or even HIV-exposed but uninfected) infants.

9.3 Trial procedures

9.3.1 Recruitment

Participants will be recruited from approximately 8 clinics in Kilifi, Ganze, Malindi, Magarini sub-counties in Kilifi County (see Section 9.2). The county and sub-county health management teams and relevant departments of the national Ministry of Health will be consulted regarding the choice of clinic sites. Community meetings will be organized with advice and input from the Ministry of Health staff at each clinic, local community health volunteers, community representatives and community liaison staff, to explain the need for a study of fractional doses of PCVs, the study requirements, and the risks and benefits of participation. These community-wide meetings will be used to sensitise the families and relatives of any mothers and infants who may be interested in participating. There will be time for question and answer sessions. Information sheets will be distributed, and any mothers considering participation will be asked to register their names and contact details with the community health volunteer and/or the study fieldworkers so that they can be contacted by phone or at home prior to their infant becoming 6 weeks of age.

With advice and input from the Ministry of Health staff, community representatives, community liaison staff and the agreement of local health facilities, information sessions will be organised in the waiting areas of antenatal care clinics and/or invitations to meetings about the study will be distributed to mothers waiting for their antenatal care appointment. Any

mother considering participation will be asked to register their name and contact details with the Ministry of Health staff at the clinic and/or our fieldworkers so that they can be contacted by phone or at home prior to their infant becoming 6 weeks of age.

Community health volunteers may be employed to identify women who are pregnant or have recently given birth so that they and/or the study's fieldworkers can contact them and their families at home to give them information about the study prior to their infant's visit to the health centre at 6 weeks of age.

It will be stated explicitly that participation may result in the parent's child attaining inadequate immunity to pneumococcal vaccine serotypes; however, the results of the trial will be reviewed by an Independent Data and Safety Monitoring Board and if there is evidence of inadequate immunity all children in the fractional dose arms will receive a 'top-up' full dose of PCV10.

9.3.2 Screening

With the agreement of Ministry of Health staff at each clinic, the MOH staff will identify parents who are bringing their infants for their birth or 6 week of age vaccination visit and approach these parents and infants with information about the study. Ministry of Health or study staff will assess whether the family has been previously mobilised in the community and assess interest in enrolment onto the study. Before any study specific procedures are conducted the study team will explain the material contained in the information sheet and the parent(s) will be given an opportunity to discuss the material and ask questions. The parent will be required to read the full consent or receive a full oral explanation in an appropriate language. Parents will be asked individually by the study team if they understand all parts of the consent and will be given another opportunity to ask any questions and seek clarification. The parent will be asked to sign the informed consent form (ICF) or if unable to sign, to place a thumbprint on the ICF in the presence of an impartial witness.

The information sheet will include details of the potential risks/ benefits to the parent's child of participating in the study, the study requirements, the use of the blood samples and their right to refuse and/or withdraw from the study at any point without affecting any of the other health services or care they receive and without having to disclose a reason for their refusal or withdrawal.

During the informed consent, parents will be given the contact details of a designated study staff member and the MOH staff at their local clinic and will be advised to contact either the MOH staff member or the study team (by telephone or by coming to the study site) if their child has a health problem. Parents may be contacted by phone by a member of the study team to be reminded about their child's participation in the study and the follow-up visits. The contact details of the parent will be taken by the study team at the screening visit. A copy of the consent form and participant information sheet (PIS) will be provided to the parent.

Mothers and infants will then be screened for eligibility. Mothers and infants will undergo a medical history, physical examination, and the mother will be either asked for her ANC HIV test result or tested for HIV using a rapid HIV diagnostic test as per the national guidelines. If the mother is HIV+ the clinic MOH and study team will organise for her infant to be tested for HIV using PCR as per the national guidelines, if they have not already been tested under the routine testing programme in Kenya. At this initial visit the investigator will assess the likelihood of compliance with protocol requirements prior to enrolment. HIV positive mothers and their infants will be referred to the health facility's HIV testing and treatment services at the end of the study visit.

9.3.3 Inclusion & exclusion criteria

The study will recruit infants in Kilifi, Ganze, Malindi, Magarini sub-counties in Kilifi County, who are healthy and whose parents are willing to participate in the study. Inclusion/exclusion criteria will mimic those of the routine immunisation programme. The trial is aiming to emulate national vaccine policy in order to generate data to support policy decisions, so all healthy infants will be enrolled irrespective of HIV status. Infants with acute illness at the time of enrolment will be excluded from the trial.

Inclusion criteria:

- Healthy infants aged 6-8 weeks of age
- HIV positive or negative but with no symptoms of current clinical immunosuppression i.e. HIV infection at WHO clinical stage 1 [72].
- Parents are willing to provide informed consent for their child to participate in the study
- Parents and infant are likely to remain in the study area until the infant is 18 months of age and comply with study requirements including the requirement to return to the same health facility to obtain all other childhood vaccines.

Exclusion criteria:

- Infants >8 weeks of age at time of enrolment
- Signs or symptoms of immunosuppression or HIV infection clinical stage 2 or above.
- Acute illness (e.g. febrile disease) on the day of vaccination
- Contraindications precluding vaccination (e.g. hypersensitivity to any component of the vaccine, including diphtheria toxoid)
- Previous PCV vaccination
- Family are planning to migrate out of the study areas before the end of the study follow-up
- Family are planning to obtain the subsequent vaccine doses of the routine immunisation schedule elsewhere and therefore their child may receive a full dose under the routine vaccination programme.

9.3.4 Enrolment

If parents and their infants meet the inclusion and none of the exclusion criteria above, the infant will be enrolled on the study by study staff at each clinic. If the infant is 6-8 weeks of age, randomisation will be completed the same day. After randomisation, a baseline questionnaire requesting information on sociodemographic characteristics, behavioural and environmental factors influencing pneumococcal transmission will be administered. A blood sample will be taken from the infant to perform a full blood count, screen for anaemia and assess HIV status as necessary. The results of the blood tests will not be used for the eligibility assessment but may inform the clinical care of the participant. An aliquot of this sample will be stored frozen in case there is any reason to suppose (from the final analyses) that the randomisation did not lead to three groups with equivalent starting concentrations of anti-capsular IgG.

9.3.5 Randomisation & blinding

The infant will be randomised to one of the seven vaccine schedules and dosages by the study team at the clinic. At randomisation, half of the participants randomised to arms A-F (150 of every 300 in each arm) will be allocated to a sub-group with an additional blood draw at 9 and 18 months of age. This blood draw will be analysed to assess IgG persistence (Table 2a).

Infants will be randomised using pre-prepared sealed envelopes containing randomisation codes. Randomization codes will be prepared before recruitment starts by a person outside of the study. Allocations will be concealed until the envelope is opened by a member of the unblinded study team at each clinic during vaccine preparation. Participants will not be informed of the allocated vaccine and vaccine will be prepared by the unblinded team who will mask the barrel of the syringe to avoid observation of the volume. This will be important to avoid differential loss to follow up across the trial arms. Participants will be told that this is to avoid them becoming aware of the vaccination type before the end of the trial. Other than the vaccination team, other study personnel e.g. those observing reactogenicity and laboratory personnel will be blinded to the type of vaccine received by each participant. The study personnel preparing and administering the vaccine will not be blind to allocation in order to administer the vaccine, but will then not participate in safety assessments and will not reveal vaccination allocations to other trial personnel.

Blinding of the seventh, control, arm of vaccination with the full dose of 3p+0 schedule will be broken when participants return for their second visit at 10 weeks of age and those in the seventh arm (arm G) receive their 2nd PCV dose. This break in blinding is not expected to affect rates of withdrawal from the study or assessment of the study outcome measures. Participants in the other 6 arms will remain blinded as to full/fractional PCV10/PCV13 allocation and participants in the seventh arm will not contribute local injection site reaction data (See Table 2a and 2b: Time and events Schedule).

9.3.6 Vaccination

Each infant will be assigned a study ID card/ sticker which will be fixed (stuck/ stapled) to the front of their routine immunisation vaccination booklet in order to clearly identify the infant as a trial participant, stickers with text to that effect will be inserted next to the relevant space for PCV administration in the routine immunisation booklet. Health workers in the surrounding area will be mobilised and informed about the trial and pictures of the study ID card/sticker will be circulated to them to attempt to avoid mistaken administration of full dose PCV in routine immunisation.

The study team vaccinating nurse, or 'vaccinator', will be responsible for preparation and administration of the vaccines as randomised. They will be responsible for the accompanying documentation. The vaccinator will prepare and administer the specified dose of vaccine intramuscularly (IM) in the anterolateral thigh muscle, as far as possible the routine immunisation guidelines will be followed, which state the right anterolateral thigh muscle. The location (Left versus Right) of the IM injection will be confirmed in the source documents.

Other routine immunisations required will be administered as per Kenya routine immunisation schedule recommendations e.g. DTP-HepB-Hib (pentavalent vaccine), at an alternative site.

MOH staff (blinded) and/or blinded study staff will conduct safety surveillance that will include 30 minutes of observation directly after vaccination. During the observation time, all parents who enrol their child onto the study will be counselled on:

- the importance of returning to the same health facility for all subsequent infant vaccinations;
- information regarding adverse events and parents will be asked to observe infants in the following seven days e.g. injection site reactions;
- the signs and symptoms of respiratory distress in an infant as outlined also in the informed consent form e.g. cough, fast breathing, abnormal noise or movements when breathing;
- how to contact study staff for help;
- general points to reduce their child's risk of respiratory disease i.e. the importance and benefits of breastfeeding and good nutrition, and the potential harm to their child of exposure to tobacco smoke and fumes from solid fuel cooking stoves.

Personnel assessing safety outcomes and laboratory personnel will be blinded to the type of vaccine received by each participant. The study personnel preparing and administering the vaccine will not be blind to allocation in order to administer the vaccine, but will then not participate safety assessments and will not reveal vaccination allocations to other clinic or trial personnel.

Parents will be told they will be contacted and either invited back to the clinic 7 days after vaccination to report any adverse events/ reactions or visited at home (whichever preferred) by a study fieldworker. Parents will be able to telephone study staff at any point to report possible adverse events, which will initiate an examination at the clinic, as appropriate.

Table 2a: Time and Events Schedule – Trial arms A, B, C, D, E, F (the 2p+1 schedule)

Study visit +/-window	D0[1] (dose 1)	D7	D28 +/- 3d	D56 +/- 3d (dose 2)	D63 /+ 2d	D84 +/- 1wk	D228 +/- 2 wks (Boost)	D235	D256 +/- 1wk	D502 +/- 2 wks
Infant's approx. age	**6wk**	7wk	10wk	14wk	15wk	18wk	9m	9m	10m	18m
Clinic visit code	**V1**		**V2**	**V3**		**V4**	**V5**		**V6**	**V7**
Informed consent	X									
Maternal medical history and infant clinical exam	X									
HIV testing (if necessary)	X									
Inclusion and exclusion criteria checked	X									
Completion of questionnaire	X									
Blood sample[2]	X					X	(X[3])		X	(X[3])
Randomization	X									
Full/ fractional dose PCV administration (IM injection)	X			X			X			
Administration of other routine vaccinations	DTwP-HepB-Hib		DTwP-HepB-Hib	DTwP-HepB-Hib; IPV			MCV1			MCV2
Observation for immediate post-vaccination reactions (within 30 minutes of vaccination)	X			X			X			
Home visit by fieldworkers - active assessment of all local injection site reactions, adverse events and severe adverse events in the 7 days following vaccination		(X)			(X)			(X)		
Active assessment of all adverse events and severe adverse events in the past 28 days at the clinic			X			X			X	
Nasopharyngeal swab for analysis of carriage prevalence							X			X
Total Blood Volume (ml)[4]	2ml					2ml	(2ml[3])		2ml	(2ml[3])

[1] D0= Screening & enrolment; [2] On vaccination visits, blood will be drawn before vaccination; [3] At randomisation, 150/300 (half) the participants in each arm will be allocated to have an additional blood draw at 9 and 18 months of age in order to assess IgG persistence; [4] Volume to not exceed 1ml/kg.

Table 2b: Time and Events Schedule – Trial arm G (the 3p+0 schedule)

Study visit +/-window	**D0**[1] (dose 1)	D7	D28 +/- 3d (dose 2)	D35	D56 +/- 3d (dose 3)	D63 /+ 2d	D84 +/- 1wk	D228 +/- 2 wks	D256 +/- 1wk	D502 +/- 2 wks
Infant's approx. age	**6wk**	**7wk**	**10wk**	**11wk**	**14wk**	**15wk**	**18wk**	**9m**	10m	**18m**
Clinic visit code	**V1**		**V2**		**V3**		**V4**	**V5**	**V6 (no visit)**	**V7**
Informed consent	X									
Maternal medical history and infant clinical exam	X									
HIV testing (if necessary)	X									
Inclusion and exclusion criteria checked	X									
Completion of questionnaire	X									
Blood sample[2]	X						X			
Randomization	X									
Full dose PCV administration (IM injection)	X		X		X					
Administration of other routine vaccinations e.g. DTP-HepB-Hib, OPV, IPV and MCV1.	DTwP-HepB-Hib		DTwP-HepB-Hib		DTwP-HepB-Hib; IPV			MCV1		MCV2
Observation for immediate post-vaccination reactions (within 30 minutes of vaccination)	X		X		X					
Home/clinic visits - active assessment of all local injection site reactions, adverse events and severe adverse events in the 7 days following vaccination		(X)		(X)		(X)				
Active assessment of all adverse events and severe adverse events in the past 28 days			X				X			
Nasopharyngeal swab for analysis of carriage prevalence								X		X
Blood volume (ml)[3]	2ml						2ml			

[1]D0= Screening & enrolment; [2]before vaccination; [3]To not exceed 1ml/kg

9.3.7 Follow-up Visits

Parents and infants will attend 6 or 7 scheduled facility visits during the trial including screening and enrolment (Table 2a and 2b).

For trial arms A-F:

- At D7, D63 and D7PB (7 days after the booster dose) i.e. 7 days after each vaccination with full or fractional doses of PCV in a 2p+1 schedule home visits will be made by fieldworkers; injection site reactions will be assessed, parents will be asked about symptoms since vaccination.
- At D28 parents will be asked to return to the health facility for routine vaccinations according to the EPI schedule (2nd dose of pentavalent vaccine and OPV), no PCV vaccine will be administered but adverse events in the 28 days since vaccination will be solicited.
- At D56, or at approximately 14 weeks of age, the infant will receive their 2nd full or fractional dose of PCV. Allocation will be indicated to the vaccinator by the participant number and a randomization log and concealed from the parent by using blinding tape over the barrel of the syringe. The location of the IM injection will be noted in source documents. At the same visit to the health facility, the third dose of pentavalent vaccine will be administered alongside IPV at different sites as per the routine immunisation schedule.
- At D84, or approximately 18 weeks of age, and at the D28PB visit, a blood sample will be drawn for immunogenicity analyses by study staff and adverse events will be solicited for the 28 days since vaccine administration.
- At D228 or approximately 9 months of age, infants will be invited to the clinic for their third and final PCV vaccination. Before vaccination, half of the participants in each arm will have an additional small blood draw at this visit, as allocated during randomisation. The vaccine will then be administered and the location of the IM injection will be noted in the source documents. The infant's first dose of measles vaccine will be administered into the upper arm as per the routine immunisation schedule. A single nasopharyngeal swab will be taken for the carriage analyses.

For trial arm G:

- At D7, D35 and D63 i.e. 7 days after each vaccination with full doses of PCV in a 3p+0 schedule home visits will be made by fieldworkers; injection site reactions will be assessed and site noted, parents will be asked about symptoms since vaccination.
- At D28 parents will be asked to return to the health facility for routine vaccinations according to the EPI schedule (2nd dose of pentavalent vaccine and OPV), and a second dose of PCV10 vaccine will be administered. Allocation will be indicated to the vaccinator by the participant number and a randomization log. At this point the blind is broken.
- At D56, or at approximately 14 weeks of age, the infant will receive their 3rd full dose of PCV10. Allocation will be indicated to the vaccinator by the participant number and

a randomization log. At the same visit to the health facility, the third dose of pentavalent vaccine will be administered alongside IPV at different sites as per the routine immunisation schedule.

- At D84, or approximately 18 weeks of age, a blood sample will be drawn by study staff for immunogenicity analyses and adverse events will be solicited for the 28 days since vaccine administration.
- At D228 or approximately 9 months of age, infants will be invited to the clinic for the infant's first dose of measles vaccine as per the routine immunisation schedule. A single nasopharyngeal swab will be taken for the carriage analyses.

9.3.8 Unscheduled Visits

Parents will be reminded to contact the study team or MOH clinic team if their infant experiences any symptoms of illness between scheduled study assessments.

Any interventions required to treat a disease or condition in an enrolled participant will be allowed. Concomitant administration of other vaccines included in the Expanded Programme of Immunization (EPI) is accepted. All concomitant interventions will be determined by asking the participant at the scheduled visits and recorded in the appropriate CRF pages.

The study team or MOH clinic staff will provide medical care to participants during the study follow-up period for acute illnesses. The study team will not become responsible for long-standing chronic conditions that were present before vaccination, or that are unrelated to vaccination, and medical care will be provided within Government of Kenya guidelines, but will help to facilitate treatment in national primary or secondary care where that is judged clinically appropriate.

9.3.9 End of study visit

At 18 months of age, the parent and child will be invited back to the health facility for their final study visit. A single nasopharyngeal swab will be taken for analyses of carriage prevalence. Half of the participants in each of the trial arms A-F will have an additional small blood draw at this visit, as allocated during randomisation. The contact details of the parent will be updated and they will be informed that if results indicate that the fractional dose elicited an inferior immune response to the full dose, they will be asked to return to the study clinic one last time for a full dose to 'top-up' protection (if this is not known already).

To reduce loss to follow-up at the 18-month of age visit, the study team will contact participants by phone at around 13-17 months of age to remind them about their participation in the study and about the remaining final study visit.

9.3.10 Study participant withdrawal criteria

In accordance with the principles of the current revision of the Declaration of Helsinki, a parent has the right to withdraw their child from the study at any time and for any reason, and is not

obliged to give his or her reasons for doing so. In addition, the participant may be withdrawn for any of the following reasons:

- Participant non-compliance with study requirements (for example follow-up visits) despite reminders and attempts to make contact
- Participant/ family moves out of the study area and cannot be traced
- A SAE, which requires discontinuation of the study involvement or results in inability to continue to comply with study procedures e.g. a case of pneumococcal vaccine-type disease
- Participant receives full dose(s) of PCV vaccine within the routine immunisation system in Kenya.

9.3.11 Managing withdrawals

The study team will continue to follow up all vaccine recipients until the end of the study wherever possible. The reason for withdrawal will be recorded in the Case Report Form (CRF) if given. If withdrawal is due to a SAE, appropriate follow-up visits or medical care will be arranged, with the agreement of the participant, until the event has resolved, stabilized or a non-study related causality has been established. Any child who develops vaccine type invasive pneumococcal disease will be unblinded and withdrawn from the study. If the child was allocated to a reduced dose arm, they will be given full dose PCV10 in three doses 4 weeks apart (if aged <12 months) or 1 dose (if aged≥12 months).

Following Good Clinical Practice (GCP) guidelines, data on participants who specifically withdraw their consent for use of their data will not be included in the data analysis. However, participants who withdraw from follow up without withdrawing consent for use of their data will be included.

9.3.12 Replacing withdrawn participants

No withdrawn subjects will be replaced in the dataset.

10 TREATMENT OF STUDY PARTICIPANTS

10.1 The Product(s)

Where possible, the 4-dose vial formulations of two licensed products, Synflorix and Prevnar13, will be used in this study (Table 3).

If the 4-dose vial formulation is not available in time for the study to start due to reasons out of the investigators' control e.g. in the manufacture and/or supply of the 4-dose vials, single dose formulations will be used as specified below.

Table 3. Specifications of the two vaccines included in the study.

Manufacturer	Commercial name	Target serotypes	Conjugate protein(s)	Adjuvant	Presentation
GlaxoSmithKline plc.	Synflorix; PCV10	1, 4, 5, 7F, 9V, 14, 18C, 19F, 23F, 6B	Protein D (outer membrane protein from Non-Typeable Hib), or Diphtheria Toxoid (serotype 19F only), or Tetanus Toxoid (serotype 18C only)	Aluminum phosphate	Suspension for intramuscular injection; 1, 2 or 4 dose vials
Pfizer Inc.	Prevnar13; PCV13	1, 4, 5, 7F, 9V, 14, 18C, 19F, 23F, 6B, 3, 6A, 19A	Diphtheria CRM_{197}	Aluminum phosphate	Suspension for intramuscular injection; 1 dose pre-filled syringe or 4 dose vials

10.2 Dose selection

Fractional doses will be administered according to specific vaccine preparation and administration SOPs. The antigen doses included in each full and fractional dose administration are documented in Table 4.

Table 4. The antigen dose in the available full dose vaccine formulations and the estimated antigen dose in the proposed fractional (20% and 40%) dose formulations.

Vaccine formulation	Vaccine-serotype specific saccharide dose per administration (µg)												
	1	3	4	5	6A	7F	9V	14	18C	19A	19F	23F	6B
PCV13	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	4.4
40%-PCV13	0.88	0.88	0.88	0.88	0.88	0.88	0.88	0.88	0.88	0.88	0.88	0.88	1.76
20%-PCV13	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.88
PCV10	1.0		3.0	1.0		1.0	1.0	1.0	3.0		3.0	1.0	1.0
40%-PCV10	0.40		1.2	0.40		0.40	0.40	0.40	1.20		1.20	0.40	0.40
20%-PCV10	0.2		0.6	0.2		0.2	0.2	0.2	0.6		0.6	0.2	0.2

10.3 Product management & storage

Vaccine stocks will be obtained from appointed distributors of the manufacturers. For each batch documentary evidence will be obtained to ascertain origin of products, and to demonstrate maintenance of cold chain from manufacturer to the distributor. The vaccine will be held at a central store, refrigerated at +2 °C to +8 °C, and dispensed to clinic sites as necessary. Vaccine will be continually temperature monitored and the number of excursions and cumulative time outside of the refrigerator will be recorded.

Vials will be discarded if total time between 8°C and 25°C exceeds 4 days (96 hours) as indicated by the vaccine vial monitor (VVM)[60, 61].
Vials will be discarded if the vaccine ever freezes.

The 4-dose vials will be used until the 28th day following the first puncture as per WHO recommendations[73], provided that:

- The expiry date has not passed.
- The vaccines are stored under appropriate cold chain conditions.
- The vaccine vial septum has not been submerged in water.
- Aseptic technique has been used to withdraw all doses.
- The vaccine vial monitor (VVM), if attached, has not reached the discard point (see package insert or study specific vaccine preparation and administration SOPs).

The date of first puncture and number of administrations from each vial will be recorded by vaccinating nurses according to vaccine preparation and administration SOPs.

If single dose formulations are used, which do not contain preservative, a single full/ fractional dose will be administered as per vaccine preparation and administration SOPs and the remaining volume will be discarded on the day of first puncture as per WHO recommendations[73].

10.4 Dispensing Procedures

The study vaccinating nurse will be responsible for preparation and administration of the vaccines as randomised. They will be responsible for the accompanying documentation.

The vaccine dose to be administered will be guided by the randomization process. The dose will be a full dose (0.5ml), a 40% dose (0.2ml) or a 20% dose (0.1ml) administered intramuscularly in the anterolateral thigh.

Any concomitant routine immunisations will be administered according to the routine immunisation schedule instructions. Site of all vaccinations will be recorded in clinical source documents.

10.5 Unblinding

The primary endpoint of immunogenicity will be assessed at 4 weeks post-third dose administration. The trial data and safety monitoring board (DSMB) will review the results and if the non-inferiority criteria are not met as per the statistical analysis plan, the DSMB will authorise unblinding in order to allow a full dose of vaccine to be administered to fractional dose recipients.

Prior to this time point, unblinding will not be necessary unless as per DSMB request for SAE review; apart from those participants in trial arm G. Study staff and parents of participants enrolled in trial arm G will become unblinded to the allocation at the clinic visit at 10 weeks of age, due to the difference in the PCV schedule. Blinding beyond 10 weeks could be maintained through a placebo injection given to the other 6 arms, however, the discomfort to the participants would outweigh any benefit to the participant or the study. As long as blinding is maintained among trial arms A-F, the unblinding of arm G is unlikely to impact the main outcome assessments (objective assessments of immunogenicity and carriage) or retention (participants in trial arms A-F would remain with a 33% chance of being allocated to the full dose arms).

10.6 Prior/Concomitant Therapy

Concomitant therapy will be documented, the site of administration of concomitant vaccines will be documented. Previous PCV vaccination or planned PCV uptake under the routine immunisation programme, outside of the trial, will be noted for exclusion.

10.7 Rescue vaccination

The primary endpoint of immunogenicity will be assessed at 4 weeks post-third dose administration. The DSMB will review the immunogenicity results from the time point at 4 weeks post-third dose and if the non-inferiority criteria are not met as per the statistical analysis plan, the DSMB will authorize unblinding in order to allow a full dose of vaccine to be administered to fractional dose recipients as a rescue dose.

The study is not powered to allow non-inferiority to be assessed in a subset of the immunogenicity samples therefore results from all participants will be required prior to DSMB review. The timing of the shipments of samples to UCL, the immunological analyses and the DSMB review meeting will mean that the outcome of the DSMB's review may only be available when some of the trial participants have already exited trial follow-up. If participants undergo their last study visit before the DSMB has reviewed all the data, the contact information for the participant's parents will be updated by study staff at their last study visit and they will be told they will be contacted by study staff in the near future and may be asked to return to the clinic for an additional vaccination. Fieldworkers and/or community health volunteers (CHVs) will be employed to keep in touch with any participants who have already exited the trial before the DSMB review in order to invite them back to the clinic if necessary. All participants will be recruited in Kilifi County where the risk of morbidity attributable to pneumococcal vaccine types is very low (see Ethics section 18).

Any child who develops vaccine type invasive pneumococcal disease will be unblinded and withdrawn from the study. If the child was allocated to a reduced dose arm, they will be given full dose PCV10 in three doses 4 weeks apart (if aged <12 months) or 1 dose (if aged≥12 months).

11 LAB PROCEEDURES

11.1 Blood sample management & testing

Venous blood samples will be collected at baseline (2ml), the D84 visit (approximately 18 weeks of age; 2ml) and, in trial arms A-F, at the 1-month post-boost visit (10-13 months of age; 2ml). Half of the participants enrolled onto trial arms A-F (150 in each arm) will have additional blood draws at 9 months and 18 months of age (2ml at each visit). A cumulative total of 4-10mls of blood will be collected from each participant by the end of the trial, depending on randomisation and allocation. The sample at baseline will be tested for anaemia in order to inform clinical care of the infant. All serum will be separated within 48 hours of sample collection and stored at -20 degrees Celsius at the KWTRP CGMR-Coast laboratories. All samples will be shipped to the UCL WHO Reference Laboratory for Pneumococcal Serology based at the Great Ormond Street Institute of Child Health. If any remaining volume is not shipped to UCL, samples will be stored at the KWTRP CGMR-Coast laboratories. Sample management will include monitoring of the number of freeze-thaw cycles experienced by each sample in a laboratory database.

At the UCL WHO Reference Laboratory for Pneumococcal Serology, sera will be assayed for antibodies to all vaccine-type capsular polysaccharides using the WHO reference ELISA following adsorption with cell wall polysaccharide and 22F polysaccharide at a concentration of 10 mcg/ ml (Details available at http://www.vaccine.uab.edu/ELISA%20Protocol.pdf). This assay is based on the original Wyeth assay used to generate the correlate of protection of 0.35 mcg/ml.

A subset of 50 sera from each of the trial arms A-F, at the 1 month post-boost time point will be used to estimate the functionality of the immune response to all vaccine serotypes using the multiplexed Opsono-Phagocytic Assay (MOPA; details available at http://www.vaccine.uab.edu/UAB-MOPA.pdf).

The result of the mother's most recent HIV test will be recorded at the study screening visit using the information in their 'Mother & Child Health Handbook' or alternative clinical source notes, if unavailable, rapid diagnostic tests will be performed according to Government of Kenya guidelines. If a mother is living with HIV, a dry blood spot will be taken from the infant in order to process with PCR as per Government of Kenya guidelines. The result of the HIV test, performed at the national testing laboratory in Mombasa, will be recorded in the 'Mother & Child Health Handbook' or alternative clinical records and study clinical source documents, when the result becomes available.

11.2 Nasopharyngeal swab sample management & testing

Standard methods for administering and processing nasopharyngeal swabs for culture will be used to ensure that results are comparable with previous studies[74, 75]. A single, deep, nasopharyngeal rayon swab will be taken at 9 and 18 months of age and transported in 1 ml skim milk-tryptone-glucose-glycerin (STGG) transport medium to the KWTRP CGMR-Coast laboratories. A primary culture will be prepared on blood agar with gentamicin before the sample is frozen at -70C. One colony on the plate will be selected at random for serotyping by latex agglutination and confirmatory Quellung reaction. Polymerase Chain Reaction (PCR) will be performed for quality control purposes on 10% of the samples and as a confirmatory test for samples that have ambiguous or negative Quellung tests. Minor serotypes, relative abundance and density may be assessed at a later date using the stored samples should the initial culture results prove difficult to interpret. Carriage will be defined if a serotype is isolated by latex agglutination and confirmatory Quellung reaction[75]. Swab medium will be stored at the KWTRP CGMR-Coast laboratories.

12 ASSESSMENT OF SAFETY

12.1 Identification of Adverse Events (AEs) and Severe Adverse Events (SAEs)

Measures will be put in place to identify any adverse or serious adverse events (including any cases of pneumococcal disease) in study participants:

- Study staff will assess the general health of the child at every study visit;
- Fieldworkers based in the communities around each study clinic will be educated in the signs and symptoms of respiratory distress in infants and will visit every child at home for their 7-day post vaccination check-up. They will also be points of contact in the community to help parents access study staff for medical advice and referral if necessary.
- Parents will be told verbally and it is written in the informed consent form that they should contact study staff for free medical consultation and treatment in case of any illness in their child. Parents will be given the phone number of the clinical officers on the trial and their local fieldworker.
- Hospital staff at the Kilifi and Malindi referral hospitals will be sensitised about the trial and asked to notify study staff if they suspect a child presenting to the hospital (for any reason) is a study participant.

Any AE will be evaluated for seriousness (see section 12.2), relatedness, severity and expectedness by the treating physician. Solicited and unsolicited AE and SAE will be recorded in all participants in the CRF. If further medical attention is needed, the study team will organise referral and emergency admission to Kilifi County Hospital.

12.2 Definitions and monitoring of AEs and SAEs

AEs and SAEs will be defined in accordance with the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (38).

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, when applicable, to be followed in the study sites will be specified in an SOP.

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. This definition is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhoea, influenza, injection site reactions and accidental trauma (e.g. sprained ankle)
- 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.

12.3 Reporting AEs and SAEs

Both PCV10 and PCV13 are licensed products and had been administered to over 109 million children in LMICs by the end of 2016[34].

All AEs that are not serious will not be reported individually but will be recorded in the CRF and summarised in an annual safety report.

All SAEs will be reported individually using an SAE form including an assessment of relatedness, severity and expectedness. The treating physician will ensure that as much information as possible is provided in the SAE form and if necessary will discuss with the PI or designee prior to submission. The PI will receive the SAE form within 24 hours of the event. If the event is life threatening, and/or suspected to be related to the vaccination the PI (or designee) will be informed by telephone within 24 hours of the event. Specimens from study participants presenting with respiratory disease will be cultured in order to detect whether the respiratory disease is pneumococcal and whether any pneumococcal disease is vaccine-type.

The minimum information required for the initial SAE report:
- Participant's study number, age and sex
- Description of the event
- Date of vaccination (s)
- Reporter information
- Preliminary assessment of relatedness
- Severity
- Preliminary assessment of expectedness

The principal investigator (PI) (or designee) will ensure that the information provided on the SAE form, is legible, does not have abbreviations or personal and institutional identifiers, and is as complete as possible. The PI (or designee) is responsible for safety monitoring and reporting SAEs and updates of SAEs to the DSMB, Sponsor, IRB/IEC and regulatory authorities as appropriate (Table 6). Those that are life-threatening or suspected to be causally related to vaccination will be reported to the DSMB, Sponsor and vaccine manufacturers, this will include any cases of suspected vaccine-type pneumococcal disease at any time point in the study follow-up.

All SAEs identified will be tabulated and reported annually in summary form to Kenyan Regulatory Authorities and the LSHTM ethics committee.

12.4 Reporting SUSARs

Any SAE that are suspected to be causally related to vaccination and are unexpected will be defined as SUSARs and will require expedited reporting to the DSMB, Sponsor, IRB/IEC and regulatory authorities which have approved the clinical trial and other organisations as required under the terms of the individual contracts (e.g. relevant pharmaceutical companies).

A detailed description of DSMB functions and responsibilities and guidelines on the transmission flow of SAEs /SUSARs will be provided in the DSMB charter. Table 6 provides details on the person responsible of reporting and timelines.

Table 6: Safety assessments reporting responsibilities

Safety event	Reported to	Reported by	The form of the report	Timeline
All SAEs	PI (or designee)	Treating physician	SAE form	Within 24 hours of awareness of event.
	KEMRI Scientific and Ethics Review Unit	PI (or designee)	Annual AE/SAE summary report	Annually
	Kenya Pharmacy and Poisons Board	PI (or designee)	Annual AE/SAE summary report	Annually
	LSHTM Research Ethics Committee (Sponsor)	PI (or designee)	Annual AE/SAE summary report	Annually
All life threatening SAEs and/or those suspected to be causally related to the vaccine	KEMRI Scientific and Ethics Review Unit	PI (or designee)	SAE form	Within one working day of notification of the event.
	Kenya Pharmacy and Poisons Board	PI (or designee)	SAE form	Within one working day of notification of the event.
	LSHTM Research Ethics Committee (Sponsor)	PI (or designee)	SAE form	Within one working day of notification of the event.
	DSMB	PI/ Sponsor (or designee)	SAE form	Within one working day of notification of the event.
	Pfizer Inc.	PI/ Sponsor (or designee)	SAE form	Within the delay established by their procedures
	GlaxoSmithKline plc.	PI/ Sponsor (or designee)	SAE form	Within the delay established by their procedures

12.5 Emergency Procedures

During vaccination, staff trained in basic life support will be available in case of adverse reactions around vaccination. An emergency kit will also be available and checked at each vaccination visit.

There will be no mandated pauses of vaccination triggered by SAEs unless the investigators, sponsors, or DSMB express concern.

12.6 Procedures for reporting any protocol violation(s)

Protocol violations will be reported to the sponsor and IRB/IEC and regulatory authorities as specified in their guidelines.

13 STATISTICAL ANALYSES

13.1 Primary analyses and Sample size

The primary endpoint of non-inferiority will be reached if the lower CI around the ratio of geometric mean concentration (GMC) of IgG (fractional/full dose) is ≥0.5 (i.e. the 2-fold criterion) at 1-month post-boost dose (10 months of age).

A secondary endpoint will assess the proportion of 'responders', defined as those with serotype-specific IgG antibody concentration ≥0.35 mcg/ml[13] at 4 weeks after the primary series (18 weeks of age). Non-inferiority will be achieved if the lower limit of the 95% confidence interval (CI) around the difference in the proportion of 'responders' (fractional dose group – full dose group) is >-10%[76] post-primary series (18 weeks of age) for at least 8 of the 10 vaccine types in the PCV10 arms and at least 10 of the 13 vaccine types in the PCV13 arms. Assessments of non-inferiority will be made separately for each of the vaccine type serotypes. Our primary endpoint will be reached across all arms if non-inferior immunogenicity is achieved for the 10 serotypes in PCV10 as this is the standard of care in Kenya currently.

The required sample size for the trial was calculated in order to ensure good power to detect both the primary and secondary immunogenicity endpoints, this approach is recommended in trials where both primary and secondary endpoints are important to determine the success of the intervention[77]. The proportion of children achieving the correlate of protection (IgG ≥0.35 μg/ml) varies across PCV10/13 serotypes after the primary vaccination series and by schedule (range 63.5-98.4%)[33, 76, 78-80]. In a prior study of PCV7 in Kilifi, the average proportion of children reaching the threshold antibody concentration across serotypes at 18 weeks of age was 87%[33]. The average proportion reaching the threshold antibody concentration at 18 weeks of age after 2 primary doses, 2 months apart, in European[81], Israeli[17, 82] and South African children[24] was also approximately 87% across 10 serotypes but serotype specific responses ranged between 63-97%. On this basis, to detect non-inferior immunogenicity (% responders) to 10 of the 13 serotypes in the PCV13 arms or 8 of the 10 serotypes in the PCV10 arms at 18 weeks of age with 90% power, we would need to enrol 300 infants per arm to declare non-inferiority using a margin of 10%, accounting for serotype-specific response rates, multiple serotype-specific comparisons and 5% loss to follow up at 4 weeks after the booster dose. Additionally, this sample size would allow us to perform an analysis on *all* vaccine types with a 12% non-inferiority margin with 84% power.

The 10-12% non-inferiority margin has been determined considering the public health consequences of a commensurate loss of protection, assuming 87% of infants achieve protection with the full dose.

There will be >99% power to declare non-inferiority using the criterion that the lower limit of the 95% CI for the ratio of GMCs (fractional/full dose) is >0.5. Based on the IgG GMCs elicited post boost in South Africa, which ranged between 13 and 35 mcg/ml for the PCV7 serotypes[24], we hope to be able to estimate GMCs with precision +/- 2-4 mcg/ml.

There will therefore be four pairwise comparisons of each vaccine type serotype for the primary endpoint of non-inferiority (i.e. full dose vs 20% dose; and full dose vs. 40% dose for each vaccine).

A co-primary analysis, which has a precedent in PCV licensure analyses[83], will determine whether the immune responses elicited by the fractional doses (20% and 40% doses) are non-inferior to the lowest serotype-specific immune response elicited by the full dose PCV, 4-weeks after the primary series. In PCV13 licensure analyses, the immunogenicity of new PCV13 serotypes, not included in PCV7, were assessed in non-inferiority comparisons with the lowest response observed among the PCV7 serotypes in PCV7 recipients, the response to serotype 6B, for which there was existing evidence of both efficacy and programmatic effectiveness[83]. In adapting this approach to our study, non-inferiority will be achieved if the lower limit of the 95% confidence interval (CI) around the difference in the proportion of 'responders' (fractional dose serotype '*x*' – full dose 6B) is >-10%.

The timing of the primary endpoint, at 4 weeks after the booster dose, aligns with the aim to assess the effectiveness of the whole three dose schedule (rather than partial vaccination with 1 or 2 doses). It will give an indication of protection in the second year of life, this is clinically relevant as it is thought that the enhanced protection in the second year of life, as a result of a booster dose, has an important impact on carriage and transmission in toddlers, which may enhance herd protection, compared to a 3p+0 schedule[20]. In a 2p+1 schedule in Kenya, a smaller proportion of children may reach the protective threshold of antibodies after the 2 primary doses in early infancy, compared to after three primary doses, but in the context of low rates of disease after 6 years of PCV10 implementation, young infants would be protected by the indirect protection afforded by the reduced transmission of pneumococci. The timing of the endpoint corresponds to previous literature analysing 2p+1 schedules and is in line with standard practice to analyse non-inferiority trials in the ATP population.

13.2 Secondary analyses

We will present the serotype-specific difference in proportions of children with evidence of vaccine serotype carriage by trial arm. In Kilifi, residual carriage of PCV10 serotypes under the routine immunisation schedule has been estimated in 2016 at 6%; assuming 300 per arm, we expect to estimate the combined prevalence of PCV10 serotypes in each arm with an accuracy of ±2.7%. Carriage of the 3 additional PCV13 serotypes in children aged under 5

years in Kilifi in 2016 was 22%; assuming 300 per arm, we expect to estimate combined prevalence of PCV13 serotypes in each arm with an accuracy of ±5.0%.

The indirect effect of the PCV10 programme, which has been implemented in Kenya for 6 years, has reduced the carriage prevalence of PCV10 serotypes in Kilifi to 6% among children <5 years; this limits the power to examine the direct effect of different doses of PCV13 on carriage of the serotypes contained in PCV10. However, the population impact of the PCV10 programme has also led to an increase in the carriage prevalence of the serotypes that are contained in PCV13 but not in PCV10 (3, 6A and 19A). We will use carriage of these serotypes in the PCV10 full dose arm as a control against which to test of the direct effect of the full and fractional doses of PCV13. The effectiveness of PCV13 against carriage of serotype 3 is limited[22 67] so we will concentrate in this analysis on serotypes 6A and 19A; the combined carriage prevalence of these serotypes among children aged <5 years in Kilifi is 19%. Assuming this prevalence at 18 months of age among the children receiving full dose PCV10, 300 infants per arm would confer 92% power to detect a 50% reduction in carriage in any of the PCV13 arms (leading to a prevalence of 9.5%); and 78% power to detect a 40% reduction in any of the PCV13 arms (leading to a prevalence of 11%). These effect estimates would be in line with previous literature on the direct effect of PCV13 on carriage prevalence[64-66]. A total of 290-300 per arm at 18 months of age would confer just over 80% power to determine whether full and fractional dose arms exhibit non-inferior prevalence of PCV10 vaccine-type carriage using a non-inferiority margin of 5%.

The results from the multiplex opsono-phagocytic assay (MOPA) to all vaccine serotypes plus 6C will be used to compare IgG functionality after 3 full doses of PCV10 or PCV13 with that after 3 fractional doses of PCV10 or PCV13 at 1-month post boost. Antibody function will also be compared between products for comparable schedules. The correlation between IgG concentration and functional activity following a third dose of PCV delivered in a 2+1 schedule will be assessed. Exploratory analyses will derive a functional correlate of protection against carriage using the post booster MOPA titre and vaccine type carriage at 18 months of age for serotypes 19A and 6A.

To evaluate the safety of the fractional dose delivery we will describe:

- the proportion of infants in each trial arm experiencing specified local vaccination site reactions (e.g. redness, swelling) within the 30 minutes immediately after vaccination as observed by study personnel;
- the proportion experiencing local/systemic adverse reactions, e.g. injection site abscess, in the 7 days after vaccination, as reported by mother or the legal guardian who accompanied the infant to the vaccination session at a day 8 visit.

We do not expect to have the statistical power to determine a difference in the risks of injection site abscess between arms as the risk of injection site abscess is expected to be low. Pentavalent vaccine delivered in 10-dose vials in Kenya resulted in 128 abscesses per 100,000 injections[84]. If this baseline level of risk applies to the 3 immunisations given to 1200

children in the fractional dose groups we would expect to see no more than 5 abscesses throughout the whole study.

The sera of all participants in the seventh trial arm (Arm G) will be assayed for immunogenicity to **7** serotypes (the PCV7 vaccine types) at 4-weeks post-primary series only. The proportion of responders in Arm G at 4-weeks post-primary series will be compared to that of the PCV10/13 2p+1 arms at 4-weeks post-primary series. Non-inferiority will be achieved if the lower limit of the 95% confidence interval (CI) around the difference in the proportion of 'responders' (2p+1 - 3p+0) is >-10%[76]. Assuming the proportion of children reaching the threshold antibody concentration across serotypes at 18 weeks of age is on average 87%[33], with 300 per arm, we would have 85% power to declare non-inferiority using a margin of 10%, accounting for 7 serotype-specific comparisons.

IgG GMCs in a random selection of half the participants in trial arms A-F at 9 months of age (pre-boost) and at 18 months of age (9 months post-boost) will be used to 1) estimate the duration at which GMCs remain above the threshold for protection in the first 2 years of life after a 2p+1 schedule of full or fractional doses and 2) to monitor carriage acquisition rates.

13.3 General statistical methods

The total number of individuals for each of the following categories will be presented: screened for eligibility, screen failures, consented individuals, vaccinated individuals with 1, 2 and 3 doses, participants completing the study follow-up period, and reason for follow-up discontinuation. Participant demographics and baseline characteristics will be described and compared between trial arms.

The ATP population will comprise randomized participants in arms A-G who received three doses of their allocated study vaccine in the allocated schedule and have at least one post-third dose vaccination blood sample (for immunogenicity analyses) or at least one carriage sample at 18 months of age (for carriage analyses). This population will be used for the primary endpoint analysis of non-inferiority.

The ITT population will include all randomized participants who received at least 1 dose of their allocated vaccine schedule, who submitted at least one immunological/carriage sample and for whom the eligibility criteria were correctly applied.

The safety population will include all subjects in trial arms A-F who received a study vaccine. Adverse events occurring during the study follow up period will be analysed and compared between groups. This will be a descriptive analysis and will include adverse events which started on or after the day of vaccine administration for each dose up to and including 28 days later.

A detailed statistical analysis plan (SAP) will be finalized after the study has started (and before the database lock).

14 DATA MANAGEMENT

14.1 Hardware and software

The CRFs in this study will be entered into an electronic database, e.g. OpenClinica, that is compliant with Good Clinical Data Management guidelines and 21 CFR Part 11 regulations on clinical data management systems for use in clinical trials. This will be done via secure web interface with data checks used during data entry to ensure data quality. The database will be activated for the study only after successfully passing a formal design and test procedure.

Computers will be used for data entry of paper forms. Management and maintenance of computers will lie with the operational support and data managers at the study site.

14.2 Data security, access and back-up

The database will be kept in a locked server-room. Only the system administrators have direct access to the server and back-ups. Passwords (site investigator, statistician, monitor, administrator etc.) will regulate permission for each user to use the system and database, as he/she requires.

All data entered into the CRFs has identifiers 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 inbuilt audit function. Time, table, data field and altered value, and the person are recorded.

Back-ups of the whole system including the database will be run internally several times per day. Back-ups will be stored in a secure location.

14.3 Direct access to source data/documents

Source documentation will be held securely by the trial team in KWTRP CGMR-Coast. Access will be granted to monitors responsible for quality assurance, for data entry staff and for purposes of medical care. Access will also be granted for audit by statutory authorities and others. Non-study team members will not be granted access. Qualified staff will supervise data collection and entry on a regular basis. Data managers will support onsite data entry teams.

15 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Choice of investigators

Investigator CVs are detailed in Appendix 3.

15.2 Monitoring

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

Internal monitoring by the KWTRP CGMR-Coast monitoring team will be performed according to ICH GCP including but not limited to visits to the clinical sites for study initiation, during the 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.

Monitors will participate as detailed in a monitoring plan that will be prepared prior to the study. This will cover instructions for monitoring the main aspects of the implementation of the clinical studies, as follows:

- 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
- Sponsor 's Responsibilities
- Responsibilities of the Monitors
- Records of GCP training

15.3 Training to ensure quality of the study

GCP training and protocol-specific training will be delivered to the whole study team. The objective will be to ensure that the study team members are well prepared and trained, and understand the details of the study, the design and the study procedures. A training plan will be maintained, GCP and GDP will be topics of annual refresher training for all staff.

16 INTELLECTUAL PROPERTY

The vaccine products assessed in the clinical trial are all licensed and in routine use, and therefore no product-related IP will arise from this trial. In the unexpected event that other findings lead to IP then KEMRI guidelines will be followed in terms of registering and exploiting the IP.

However, any intellectual property rights that arise from the work will be safeguarded according to the current KEMRI guidelines and the Industrial Property Act of 2001, sections 32, 58 and 80. The scientific and intellectual contributions of all persons involved in the research will be appropriately acknowledged in all publications and presentations arising from the work.

17 TIME FRAME/DURATION OF THE TRIAL

Total study duration is 42 months; timelines will be determined by the receipt of approval from KEMRI ethics committee and the Kenyan Pharmacy and Poisons Board but are estimated as follows, by activity:	**Time period following ethical approval**
Study staff recruitment, procurement etc.	Month 1 - 6
Community engagement and mobilization	Month 3 - 6
Screening, and vaccinations for main study.	Month 6 - Month 25
Follow Up for main study (overlaps with vaccinations)	Month 6 - Month 34
Feedback to study participants, complete laboratory analyses, complete data analysis and write up	Month 34 – month 42

18 ETHICS

18.1 Human Subjects

Ethical approval will be sought from KEMRI Scientific & Ethics Review Unit (SERU) and the LSHTM Ethics Committee. Written informed consent will be obtained from at least one parent of all infants enrolled onto the study.

The potential risks to participants include risks related to administration of the vaccine:

- The vaccines are licensed products. In children under 5 years, the most frequently reported adverse reactions to PCVs are those associated with all vaccines, these can include one or multiple of the following symptoms: injection site reaction, fever, irritability, drowsiness, restless sleep, decreased appetite, vomiting, diarrhoea and rash.
- Extending the use of the 4-dose multi-dose vial to provide 10 or 20 administrations may increase the risk of injection site reactions e.g. swelling and localised inflammation due to contamination. If 4-dose vials are used, this will be closely monitored.
- Serious reactions to PCV injection are rare and include hypersensitivity reaction generally associated with diphtheria toxin.

Other potential risks are that despite the small dose-ranging study of a pentavalent PCV showing good responses to saccharide doses as small as 0.5 mcg/ml, there is a small risk that

the 20% and the 40% doses may elicit inferior immunogenicity to the full dose in the fractional dose study arms [57]. The unprotected/partially protected children would then not benefit from direct protection of the vaccine but would benefit from the indirect protection generated by the continued routine administration of PCV10 in the national EPI programme, which has led to dramatic decreases in vaccine type carriage[85] and IPD[86]. In the Kilifi Health and Demographic Surveillance System (KHDSS) in 2016, there were 3.2 cases of vaccine-type IPD per 100,000 person years (pyo) in under 5s[87]. This amounts to 1 case every 31,250 person years. Among the 2100 trial participants followed for 1.5 years, we will observe a total of 3,150 pyo – which means there is a 10% chance that we will see one case of vaccine-type IPD in the study, and a 90% change we will see no vaccine-type IPD. one of the advantages of undertaking this study at KWTRP CGMR-Coast is that it has a strong history of IPD surveillance and we will therefore be able to detect IPD if it occurs in the trial population. Any cases observed will be reported to the DSMB. Although the risk of IPD is very small we will establish procedures to detect it at an early stage when treatment can avert a severe outcome; this will be done by providing participants with easy access to study medical staff. Children with signs of sepsis, pneumonia or meningitis will be investigated with bacterial culture of blood and/or cerebrospinal fluids as appropriate to detect the serotype of pneumococcus causing IPD. If any case of IPD occurs, it will be referred to the DSMB as an SAE. Members of staff at the hospitals in Kilifi and Malindi will be engaged by the study team to enable treatment of referrals if necessary and to notify the study team if a participant presents to the hospital in an unscheduled visit. Any child who develops vaccine type invasive pneumococcal disease will be unblinded and withdrawn from the study. If the child was allocated to a reduced dose arm, they will be given full dose PCV10 in three doses 4 weeks apart (if aged <12 months) or 1 dose (if aged≥12 months).

If, after final analyses, the fractional doses are found to be inferior, all children in those groups will be given a single, full dose booster PCV.

The potential benefits of participation are as follows:

- Participants will be given the phone numbers of study clinicians and local fieldworkers and/or will be able to present at the clinic with any illness and receive free treatment and referral throughout the course of the study. This is in contrast to government-funded care at local clinics, where waiting times may be lengthy and care is not always free of charge. Rapid referral will be made to Hospital in Kilifi or Malindi in case of any serious illness.

- There will be periodic follow up by phone or by home visits in between the study visits near the end of follow up in order to maintain contact with the participant and actively follow up on their health. For trial participants the benefit of increased access to medical care is likely to outweigh the extremely low risk of IPD caused by vaccine type infection.

- If the vaccine is efficacious at low dose, participants in the PCV13 arms will have the added benefit of immunization against three additional serotypes (3, 6A, 19A) contained in the

study vaccine (PCV13) but not contained in the 10-valent vaccine used in the national programme.

18.2 Community Considerations

If fractional dose administration delivers inadequate protection, the risk to the community is limited due to the low prevalence of vaccine types and established herd protection since the national introduction of PCV10 in 2011. If the vaccine is efficacious at low dose, the potential benefits to the community are significant. PCV is one of the most expensive vaccines in the routine immunisation schedule, a 50-75% reduction in its cost may mean it can be sustained in the routine immunisation schedule after transition from Gavi co-funding.

We will use existing community engagement strategies to inform communities about the study. A community engagement plan specific for the study will be developed between the CLG team and the investigators. We will organize community barazas in towns and surrounding areas, meetings with chiefs, sub-chiefs, community representatives, and the Department of Health in Kilifi County and surrounding areas to inform them about the study.

Research findings will be disseminated to participants and the participating communities upon completion of the study in dissemination meetings.

18.3 Informed Consent

The rationale for the study, its aims, the study requirements and potential outcomes will be discussed with chiefs, community leaders and community representatives in specific meetings. Subsequent meetings will be organized with potential parents/ guardians of trial participants; the study, its rationale, its aims, the study requirements and potential outcomes including the risks and benefits of participation and potential inconvenience and procedures required for participation will be described in detail.

One parent will sign and date the informed consent form before any study specific procedures are performed on infants. All informed consent documents will be translated into Kiswahili and Giriama.

We will emphasize the following;

- Participation in the study is entirely voluntary.
- Declining to participate involves no penalty or loss of medical benefits.
- If the parent agrees for their child to participate they may not know which study vaccine the child receives for the length of the study.
- The parent may withdraw their child from the study at any time.
- A volunteer is free to ask questions at any time to allow him or her to understand the purpose of the study and the procedures involved.

- There is no direct benefit from participating. The benefits will be realized in the long-term for the community by contributing towards the sustained delivery of a pneumococcal vaccine.
- Volunteers will be compensated for travel, time and inconvenience of participating.

18.4 Compensation

We will compensate participants for travel required to attend study visits and for lost time using the standard figures determined by the Community Liaison Group and stipulated in the informed consent form. Fieldworkers and the Community Liaison Group will devise a standard set of travel times/distances and expenses likely to be incurred by parents bringing their child to each facility, which will be recorded in an SOP and will govern the amount each parent receives.

As such, the amount of compensation a parent receives will be based on:

- Compensation for loss of wage - this is a set amount based on KEMRI-Wellcome Trust research Programme guidelines for benefits and payments to research participants. Given the timing and potential length of visits and the time it may take for parents to travel to the clinic and return home, Ksh350 will be given in compensation for 1 day of lost wages.
- Reimbursement for travel costs - this will be based on reported distance between the parent's home and the health facility and local fieldworker knowledge. Fieldworkers will develop a local list of standard distances and costs for the areas around each of the health facilities in this study. Given previous projects it is anticipated the costs could be between Ksh200-1000 per return journey.

All compensation received by parents will be documented and the parent will be required to sign or thumbprint to confirm receipt.

18.5 Patient Data Protection/Confidentiality

Paper based clinical records will be kept in locked cabinets in the study clinics and subsequently at KWTRP CGMR-Coast. All electronic data, including immunological and carriage data will be kept in anonymized databases linked by a unique participant identification number to clinical data.

18.6 Data Sharing

After the trial ends, a clean final database(s) of anonymized, de-identified individual-level clinical, laboratory and safety data will be produced by KWTRP CGMR-Coast. This will be shared with LSHTM statistician and trial team in order for the final analyses to take place as per the statistical analysis plan. A clean de-identified database will be provided as publically

available ('open access') or upon reasonable request, after the final study publication is published, as per the relevant medical journal regulations.

Information collected or generated during this study may be anonymised for use to support PCV policies and/or further research. Any further research using information from this study must first be approved by a local or national expert committee to make sure that the interests of participants and their communities are protected.

18.7 Safety

The study team will provide medical care to participants during the study follow-up period for acute illnesses. The study team will not become responsible for long-standing chronic conditions that were present before vaccination, or that are unrelated to vaccination. Medical care will be provided within Government of Kenya guidelines.

18.8 Material Transfer Agreement (if applicable)

Where samples will be shipped to the WHO reference laboratory for pneumococcal serology at University College London, U.K., a Material Transfer Agreement (MTA) will be developed. This will include the following information.

- Identification of the provider and recipient
- Identification of the material and the volume of material
- Definition of the trial and how the material will and will not be used
- Maintenance of confidentiality of background or supporting data or information, if provided.

19 ARCHIVING AND RECORD RETENTION

19.1 Overview

Data collection will occur at each clinic using paper or electronic CRFs. Any paper or electronic data in source documents will be transported by designated study staff. Data entry clerks will use password protected computers and double enter any data collected on paper forms onto an electronic database, e.g. OpenClinica, that is compliant with Good Clinical Data Management guidelines and 21 CFR Part 11 regulations on clinical data management systems for use in clinical trials.

19.2 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 the 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
- CRFs
- 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)
- Monitoring reports
- Relevant communication
- SAE reporting processes and other relevant SOPs
- Annual reports to ethics committee and regulatory authorities
- Participant screening log
- Participant identification code list (mapping patient onto anonymized study ID)
- Participant enrolment log
- Product accountability information
- Clinical study report

19.3 Source documents

All protocol required procedures along with information necessary to report the observations and tests described in this protocol are recorded in CRFs. Any entries captured on CRFs that are derived from source documents e.g. hospital record, will have the source documents included as part of the participant's file. Where source documents for specific entries are not available, this must be explicitly mentioned. Any requested information that is not obtained as specified in the protocol should have an explanation noted on the CRF or in a note to file as to why the required information was not obtained.

CRFs will be completed and signed and authorized in a timely and accurate manner by designated study staff. All data on the CRFs must be legibly recorded. The investigator or a designated, qualified individual must review all CRFs for accuracy and consistency with any relevant source documentation, and sign the CRFs upon completion. Any corrections will be made on the CRFs by striking through the incorrect entry with a single line and entering the correct information adjacent to it. The correction will be initialled and dated by the investigator

or a designated, qualified individual. Any corrections made after data entry has begun will be notified to data managers for correction of electronic databases.

19.4 Record keeping and retention

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 following local regulations.

The Sponsor will securely store the final study database with all archive tables for at least 10 years. The Sponsor also keeps the central Trial Master File and interim and final reports both in electronic and in hard copy form for at least 10 years. KWTRP CGMR-Coast will archive paper CRFs and study files following local laws.

20 FINANCING AND INSURANCE

20.1 Budget

	USD $	Kenya Shilling (Ksh)
a) Personnel, salaries and benefits disbursements	1,456,065	131,045,863
b) Participant related costs	217,231	19,550,808
c) Equipment	73,407	6,606,601
d) Supplies		
Laboratory consumables	127,713	11,494,188
Clinical consumables	225,924	20,333,177
e) Travel and accommodation		
Local (return Nairobi)	2,700.00	243,000.00
international	0	0
f) Transportation and running costs etc.	293,684	26,431,560
g) Operating expenses	249,928	22,493,490
h) Animals acquisition etc.	0	

i) Consultancy fees	0	
j) Contingency fees (15% of above)		
k) Institutional administrative overheads	396,998	35,729,803
Total	3,049,650	274,468,500

20.2 Justification of the Budget

This work is funded by the Bill & Melinda Gates Foundation and the National Institute of Health Research Mucosal Pathogens Research Unit in the UK. The study is part of the KEMRI-Wellcome Trust Research Programme; costs for staff time, patients and supplies are based on those incurred by similar vaccine trials.

Details on the costings provided above are as follows:

- Personnel, to ensure the smooth operation of the trial: 1 trial coordinator, 1 finance and admin support officer, 2 clinical officers, 8 nurse vaccinators, 16 fieldworkers, 1 pharmacist, 2 drivers, 1.2 FTE lab technicians, 1 FTE data entry clerks and 0.5 FTE Data manager, 0.05 FTE senior clinical trials support for 2.5-3 years.
- Participant related costs include: Compensation and reimbursement for travel, refreshments and stationary (average Ksh1,750 per participant assuming 10 visits plus 1 unscheduled visit per participant), patient referral costs to hospital in the event of SAE (allow an additional 30 USD per participant, assuming not all participants will require this service), stakeholder engagement and dissemination meetings.
- Equipment are small items for the clinics (assuming 8 clinics): Additional fridges for clinics (8), physical examination equipment (weighing scales, stadiometers; 8), portable emergency kits (8), cabinets/ desks, vaccine carriers, blood sample carriers (16), data entry equipment (14 tablets and 1 desktop computer)
- Laboratory supplies include all consumables and reagents for: a full heamogram on all baseline blood samples, HIV testing of 6% of baseline samples via PCR if national testing is not available, serum separation and preparation for shipping, nasopharyngeal swab processing, culture, quellung and 10% PCR.
- Clinic supplies include: blood collection sets (3 per participant plus wastage), nasopharyngeal swabs (2 per participant plus wastage), vaccine supply (3 doses per participant plus wastage), vaccination consumables, gloves etc.
- Travel and accommodation costs will include some KWTRP team travelling to Nairobi for meetings with key stakeholders and to disseminate the results
- Transportation costs include the purchase of 2 vehicles, 8 motorbikes and running costs (tax, fuel, insurance and servicing) for all items for 3 years.
- Operating expenses include: GCP training/ refresher training, communications for field staff (phone credit), contribution to clinic utilities bills, contribution to Malindi hospital office space, transport coordination costs and community liaison coordination costs,

LSHTM staff work permit (1), ethics and regulatory authority submissions fees, data management software and Microsoft licencing, postage, printing etc.
- Institutional overheads are charged at 15% as per funder guidelines.

20.3 Insurance

The vaccine manufacturers are liable for any harm arising from negligent manufacture but have not undertaken to sponsor the trial. The sponsor, LSHTM, provides insurance to cover the clinical trial and KWTRP CGMR-Coast will provide indemnity for study staff.

21 TRIAL MANAGEMENT

21.1 The Sponsor

LSHTM takes responsibility for initiating, registering and conduct of the trial, and as such, will be involved in the study design, data collection, management and analysis, and interpretation of data, and writing of the report. LSHTM takes responsibility for ensuring the trial is monitored properly and results made available.

Lead staff based at KWTRP CGMR-Coast will communicate regularly with the LSHTM PI on general trial progress, challenges experienced and any necessary amendments requiring ethical review.

21.2 The Data and Safety Monitoring Board (DSMB)

A DSMB will be convened by the Sponsor, and will receive safety data as described above. A detailed description of DSMB functions and responsibilities and guidelines on the transmission flow of SAEs /SUSARs will be provided in the DSMB charter.

22 REPORTING, DISSEMINATION AND NOTIFICATION OF RESULTS

22.1 The Clinical Trial Report

The results of the trial will be reported in a Clinical Study Report generated by the Sponsor, containing CRF data, laboratory data and safety data. The Sponsor will register and disclose the existence of the results of the clinical trial on an international clinical trials registry in accordance with good practice. Individual participant identifiers will not be used in any publication of results.

22.2 Publications

Results will be published in an open access format, consistent with Good Publication Practices, the International Committee of Medical Journal Editors guidelines and funder requirements. The primary trial results will be published including all investigators currently

listed on the protocol as authors. Local investigators and Programme members will take prominent roles in the primary trial results write-up. Secondary analyses will also be developed as part of KWTRP's commitment to capacity development to ensure that co-investigators have additional opportunities for individual scientific output.

22.3 Dissemination

Results will be disseminated to the Kenyan Ministry of Health and KENITAG (the Kenyan National Immunisation Technical Advisory Group) and other relevant stakeholders in vaccine policy.

Results will be disseminated locally in the areas where the study was conducted and participants will be invited to meetings to receive feedback on the trial outcomes.

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APPENDICES

Appendix 1: Roles of Investigators

Investigator	Institution	Role
Anthony Scott	LSHTM/KWTRP CGMR-Coast	Principal Investigator: Oversight of design, conduct, quality assurance and interpretation of results and publication.
Katherine Gallagher	LSHTM	Co-investigator (to be based at KWTRP): design, conduct, data quality, sample integrity, organisation of lab analysis and quality control procedures, collation of data, analysis and interpretation and publication.
Mainga Hamaluba	KWTRP CGMR-Coast	Lead of clinical trial team in Kilifi, input into design, conduct, data quality control, assurance and analysis, interpretation of results and publication.
Mary Kaniu	KWTRP CGMR-Coast	Managing the recruitment, follow up and overseeing the clinical treatment of study participants.
Angela Karani	KWTRP CGMR-Coast	Laboratory sample management, processing and shipping and laboratory analysis plan.
Jimmy Shangala	KWTRP CGMR-Coast	Programme pharmacist responsible for vaccine import, liaison to Pharmacy and Poisons Board, product storage, cold-chain management, product accountability, supervision of pharmaceutical technician and unblinded staff.
Pharmacy technologist – to be confirmed pending recruitment	KWTRP CGMR-Coast	Pharmacy technologist, maintenance of product storage and cold chain, product accountability and allocation, quality assurance of unblinded documentation.
Daisy Mugo & Elizabeth Gardiner	KWTRP CGMR-Coast	Laboratory technologists, storage and processing of blood samples and carriage analyses

Investigator	**Institution**	**Role**
Mark Otiende	KWTRP CGMR-Coast	Programme statistical support and analysis
Clinical officers (2) – to be confirmed pending recruitment procedures	KWTRP CGMR-Coast	Managing the clinical care of participants across clinical sites. Assisting quality control to ensure good clinical and documentation practice.
Ifedayo Adetifa	KWTRP CGMR-Coast	Epidemiological input into the design of the protocol and implications of findings.
Fred Were	University of Nairobi	Oversight of trial design for relevance to vaccination policy questions in Kenya
Christian Bottomley	LSHTM	Study statistician: input into design, randomization and analysis plan, analysis and interpretation.
David Goldblatt	UCL	Lead on immunological lab assays, interpretation of results and publication
Peter Smith	LSHTM	Senior clinical trials expertise, input into the design, statistical analysis plan, DSMB charter and interpretation of final results.
Patricia Henley	LSHTM	Sponsor's Representative

Appendix 2: Informed consent form in English

KEMRI-Wellcome Trust Research Programme
Patient Information and Informed Consent Form

Formal Title: The effect of fractional doses of pneumococcal conjugate vaccines (PCV10 and PCV13) on immunogenicity and vaccine-serotype carriage in Kenyan infants.

Lay Title: A trial to compare the immune response and the proportion of infants still carrying bacteria in their nose after varying doses of pneumonia vaccines in Kenyan infants.

Institutions	Investigators
KEMRI CGMR (Coast) (KWTRP)	Anthony Scott (PI), Mainga Hamaluba, Mary Kaniu, Angela Karani, Jimmy Shangala, Mark Otiende, Daisy Mugo, Elizabeth Gardiner, Ifedayo Adetifa
University of Nairobi and KENITAG	Prof Fredrick Were
LSHTM	Katherine Gallagher, Peter Smith, Christian Bottomley
UCL	David Goldblatt

What is KEMRI?

KEMRI is a government organization under the Ministry of Health, which carries out medical research. Research is different from normal medical treatment because research aims to find better ways of preventing and treating illness in the future for everybody's benefit. One of the projects in KEMRI is looking for better ways to use the existing pneumonia vaccines.

KEMRI is working on this study in collaboration with the London School of Hygiene and Tropical Medicine (LSHTM), the Ministry of Health in Kenya and University College London (UCL), UK. LSHTM and UCL are universities in the UK. This study will be taking place only in Kenya but if it is beneficial, the impact may reach other low-income countries also. In Kenya research will be conducted by KEMRI.

What is this research about?

There are two pneumonia vaccines in use across the world, one protects against 10 types of pneumococcal bacteria (PCV10), the second protects against 13 types of pneumococcal bacteria (PCV13). Before governments started to deliver pneumonia vaccines many children died each year as a result of infection with the bacteria called *Streptococcus pneumoniae*. The bacteria cause diseases like meningitis and sepsis as well as pneumonia.

In Kenya the pneumonia vaccine that protects against 10 types (PCV10) has been delivered to young babies 6 weeks old as part of the routine immunisation schedule since 2011. The vaccine has worked very well and has reduced the amount of pneumococcal disease in Kenya. However, at the moment the vaccine is expensive. Researchers are worried that when the external funding stops the vaccine delivery may stop in Kenya because the vaccine is so expensive. We think, but we do not know for sure, that a smaller dose of vaccine may work just as well as the full dose. We want to measure whether this is true and smaller doses of the

two different pneumonia vaccines are enough to protect Kenyan infants and can be delivered safely. The results could be used to make the vaccine cheaper and allow the vaccination programme it to be delivered for longer in Kenya. We will measure this by giving some children a smaller dose of the vaccine and some children the full dose then we will compare how many antibodies are made in the blood to protect them from the bacteria.

Where is the study taking place, how many people does it involve and how are they selected?

The study will take place at multiple health facilities in Kilifi County, including: Ganze health centre, Bamba sub-district hospital, Gongoni health centre, Mambrui dispensary, Marikebuni dispensary, Gede health centre, Matsangoni health centre and Kilifi County Hospital, Additionaly Malindi General Hospital, Vitengeni health centre and Chasimba health Centre may be utilised. A total of 2100 infants will be involved. Infants will be selected as they come for routine immunisations at 6 weeks of age and all healthy infants will be eligible for enrolment onto the study if parents provide their consent.

What will the study involve?

If you agree for your child to take part in this study, you and your child will have a medical examination and information in your Mother & Child Handbook and/or doctors' notes will be reviewed by the study staff. If you are HIV positive and your child's HIV status is not known we will organise for your child to be tested, this is according to national guidelines on standard care in Kenya. HIV positive mothers and their infants will be referred to the health facility's HIV testing and treatment services. Your HIV infection status and your child's HIV infection status will be recorded for the study for information only and will not determine whether or not you can take part in the study. The information will be kept confidential.

If you agree and your child is healthy enough to receive his/her routine vaccinations, they will be randomly selected to be in one of seven groups. Your child will have an equal chance of being selected for each one of seven groups. Neither the study staff nor you will be able to choose the group that your child is allocated to. Depending on which group your child is in, they will receive:

1. PCV10 at the full dose according to the routine immunisation schedule of Kenya: at 6, 10 and 14 weeks of age i.e. the standard of care in Kenya.
2. PCV13 at a full dose (the normal dose) in a schedule of 3 doses at 6 weeks of age, 14 weeks of age and 9 months of age
3. PCV13 at a 40% dose (a reduced dose) in a schedule of 3 doses at 6 weeks of age, 14 weeks of age and 9 months of age
4. PCV13 at a 20% dose (a reduced dose) in a schedule of 3 doses at 6 weeks of age, 14 weeks of age and 9 months of age
5. PCV10 at the full dose (the normal dose) in in a schedule of 3 doses at 6 weeks of age, 14 weeks of age and 9 months of age
6. PCV10 at a 40% dose (a reduced dose) in a schedule of 3 doses at 6 weeks of age, 14 weeks of age and 9 months of age

7. PCV10 at a 20% dose (a reduced dose) in a schedule of 3 doses at 6 weeks of age, 14 weeks of age and 9 months of age

Your child will receive the first dose at 6 weeks of age then you will be invited back to this clinic a further 6 times until your child is 18 months of age. The vaccine will be given as usual via an intramuscular injection into your child's thigh. Four of these 6 visits will be at the same time as their routine immunisation visits, but you will have to come back 2 more times in addition to these routine visits so it is important you plan to stay in this area until your child is 18 months of age.

Using a clean needle, we will take a small amount of blood from your child at either three time points, or five time points, between now and 18 months of age. At their first study visit (today), 2ml (or half a teaspoon) will be taken to make sure he/she is healthy. We will take a further 2ml at 18 weeks of age and again at 10 months of age, to test whether their body has generated a good immune response to the vaccine at different doses. Some infants will be randomly chosen to have two extra blood samples taken at 9 months of age (2ml) and at 18 months of age (2ml). A swab will be taken from the nose at 9 months of age and at their last study visit at 18 months of age to look for the presence of the bacteria.

A summary of the study procedures:

Infant's age	**6 weeks**	**10 weeks**	**14 weeks**	**18 weeks**	**9 months**	**10 months**	**18 months**
Routine immunisations (KEPI)	Pentavalent vaccine, Polio vaccine	Pentavalent vaccine, Polio vaccine	Pentavalent vaccine, Polio vaccine		Measles vaccine		Measles vaccine
Study procedures							
All children	Consent, medical check-up						
1 out of every 7 children (300 children in total) randomised to the full dose pneumonia vaccination in the routine schedule	**Pneumonia vaccine** Blood sample (2ml)	**Pneumonia vaccine**	**Pneumonia vaccine**	Blood sample (2ml)	Nose swab		Nose swab
6 out of every 7 children (1800 children in total) allocated to full/fractional dose pneumonia vaccination	**Pneumonia vaccine** Blood sample (2ml)		**Pneumonia vaccine**	Blood sample (2ml)	**Pneumonia vaccine** Nose swab (blood sample (2ml) in some infants only)	Blood sample (2ml)	Nose swab (blood sample (2ml) in some infants only)
Total time for the study visit (maximum)	1-2 hours	1 hour	1 hour	30 minutes	1 hour	30 minutes	30 minutes

After each vaccination, your child will be observed for 30 minutes to make sure they are ok.

Seven days after each pneumonia vaccination, a member of the study team will contact you by phone or at your home in order to check your child is ok. They will ask about any illness since vaccination and any reactions around the site of injection.

Are there any risks or disadvantages to my child for taking part in the study?

Our priority for every child is their well-being.

There may be some pain and bruising associated with blood drawing, which will resolve after a few days. There is a small risk of local infection after injection. This risk is minimized by use of pre-packaged sterile equipment and trained staff. We will ask you to report to us if you are worried or think your child has an infection.

As with any routine vaccination, your child may feel pain at the injection site. Some children may have fever after the vaccine is given, other symptoms include irritability, drowsiness, restless sleep, decreased appetite, vomiting, diarrhoea and rash. These should disappear after a few days. Very rare serious side effects can be seen immediately after any vaccination. These include skin swelling, shortness of breath and light-headedness or fainting. Medical equipment necessary to treat serious reactions is available.

We do not know for sure whether the smaller dose will work as well as the full dose of vaccine. There is a risk that the children in this study who are selected to receive the smaller doses (4 out of every 7 children) will generate a less good immune response compared to those who receive the full dose. This means that these children may only be partially protected from infection and becoming sick. As participants in the study, your child will have access to the study medical staff and will be able to present with any illness at an early stage and receive free treatment and/or referral throughout the course of the study, up until they are 18 months old. If your child presents any of the following signs please contact a member of the study team immediately:

- cough or fast breathing;
- abnormal noise when breathing;
- abnormal movements when breathing - nostril flaring in time with the breath or nodding of the head in time with the breath;
- fever, difficulty feeding or drinking, lethargy or convulsions.

Until the study is finished, neither you, nor your child will know which vaccine or dose your child has received. If, after the study finishes, we find out that the smaller doses do not work as well as the full doses, all infants in those groups will be given a single, full dose, booster vaccination which should leave them fully protected until later in life.

This study will involve taking your time and you may have travel costs. In addition to reimbursement of transport fares based on standardized KEMRI rates (between Ksh200-1000 per return journey dependent on distance travelled and transport expenditure), we will compensate you for inconvenience and time or wages lost on that day at a rate of Ksh350 for each time you come to the clinic.

Are there any benefits for taking part?

If your child participates in this study, they will receive medical care for acute illnesses from the day of the first dose of vaccine until the completion of the study free of charge. Our study team will make a first assessment and treat any simple conditions. If your child needs to be referred to a government health facility, we will help you with transport and cover initial costs. Treatment of chronic illnesses or long term injuries unrelated to the study procedures will not be paid for by the study. If your child is found to have such illnesses/injuries, they will be referred for treatment under the existing government programs.

Your child may be randomly allocated to a group to receive the full dose of one of the vaccines (3 in every 7 children will be allocated to full dose groups); children who receive the full dose of PCV13 (1 in every 7 children) will have an added benefit of protection against three additional types of bacteria that are not contained in the vaccine used in the national programme (the PCV10 vaccine).

At present we cannot be sure that the smaller doses will protect people. When we have results from the trial we will provide feedback to all participants.

If the vaccines work well at a smaller dose, there are substantial potential benefits to the community. The vaccine is one of the most expensive vaccines in the routine immunisation schedule, if we are able to halve its cost, or more, this may mean it can be delivered in the routine immunisation schedule for many more years.

What will happen if I refuse to allow my child to participate?

All participation in research is voluntary. You are free to decide if you want your child to take part or not. You will still receive the recommended standard of care at the clinic even if you do not take part. If you do agree to participate, we would like you to understand that you are free to change your mind at any time and withdraw from the research. This will not affect your health care now or in the future. The clinicians running the study may withdraw you from the study if you are unable to comply with the study visits or for your safety.

What happens to my child's samples?

The blood samples will be coded with the study identification number but no personal information such as name or date of birth will be included. This is to ensure that samples can only be linked to the participants by people closely concerned with the research. The nasal swab samples will be processed and stored in KEMRI-Wellcome Trust research programme, Kilifi, but the blood samples will be sent to London, England. This is because we need the tests to be done in a WHO reference laboratory. Any remaining blood samples will be stored at our research laboratories in KEMRI, Kilifi. In the future, new research may be done on these stored samples. Any future research must first be approved by a national independent expert committee to ensure that participants' safety and wellbeing are protected.

Who will have access to information about me in this research?

All our research records are stored securely in locked cabinets and password protected computers. Only the people who are closely concerned with the research will be able to view all the information from participants just to be sure that the study is being run correctly and the health of every participant is protected and they will keep the information confidential. In order to use the information from this study, we will share anonymized information (that is, information with names and personal details removed) with LSHTM and government agencies so as to show the comparison of immune responses for volunteers getting different doses of the vaccines.

Who has allowed this research to take place?

This study had been approved by KEMRI Scientific and Ethics Review Unit and London School of Hygiene and Tropical Medicine Ethics Committees to make sure the research is conducted properly and that participants' safety and rights are respected. They have looked carefully at this work and agreed that the research is important, relevant to Kenya and follows nationally and internationally agreed guidelines. This includes ensuring that all participants' safety and rights are respected.

The local and international committees will be informed about any serious side effects that are noticed, and if we receive new information about the vaccine during the course of the trial, we will inform you.

What if I have any questions?

You may ask any of our staff questions at any time. You can also contact those who are responsible for this research:

1. Katherine Gallagher Tel: 0798 899 995
2. Mary Kaniu Tel: 0709 983 939

If you want to ask someone independent anything about this research, please contact:

The Community Liaison Manager, KEMRI – Kilifi, Tel: 041 7522 063, Mobile: 0723 342780
OR

The Head, KEMRI Scientific and Ethics Review Unit, P. O. Box 54840-00200, Nairobi; Telephone numbers: 0717 719477; 0776 399979 Email address: seru@kemri.org

This research is supported by LSHTM, who provide insurance for any treatment or compensation in the unlikely event of any injury resulting from this trial.

KEMRI – Wellcome Trust Programme Informed consent form for:

Formal Title: The effect of fractional doses of pneumococcal conjugate vaccines (PCV10 and PCV13) on immunogenicity and vaccine-serotype carriage in Kenyan infants.

Lay Title: A trial to compare the immune response and the proportion of infants still carrying bacteria in their nose after varying doses of pneumonia vaccines in Kenyan infants.

I, _____ (Parent's name), have had the trial explained to me. I have understood all that I have read and have had explained to me and had my questions answered satisfactorily. I understand that I can change my mind at any stage. I consent for my child _____ (Child's name) to take part in this study.

☐ Please tick **I agree for my child to take part in this research**

☐ Please tick **I agree to my child's samples being stored and used for future research**

☐ Please tick **I agree to my child's samples being exported to the United Kingdom**

☐ Please tick **I agree to being contacted by study staff, if necessary, after the last study visit in order to hear the results of the trial**

Parent's Name (print): _____ **Date & Time:** _____

Parent's signature/ thumbprint in the presence of a witness:

_____

Where parent/guardian cannot read, ensure a witness observes consent process and signs below:

I attest that the information concerning this research was accurately explained to and apparently understood by the subject and that informed consent was freely given by the subject.

Witness' signature: _____ Date _____

Witness' name: _____ Time _____

I (KEMRI person taking consent) certify that I have followed the SOP for this study and have explained the study information to the study participant named above, and that he/she has understood the nature and the purpose of the study and consents to the participation in the study. He/ She has been given opportunity to ask questions which have been answered satisfactorily.

Designee /Investigator's / Signature: ---------- Date: ----------

Designee /Investigator's Name: ---------- Time: ----------

THE PARTICIPANT SHOULD BE GIVEN A SIGNED COPY AND A COPY KEPT IN FILE.

Appendix 3: Non-KEMRI Investigator CVs

Curriculum vitae: Katherine E. Gallagher, BA MSc PhD **September 2017**
Katherine.Gallagher@lshtm.ac.uk; +44 7725 310 366

Current post: Assistant Professor; Faculty of Epidemiology and Population Health, Department of Infectious Disease Epidemiology; London School of Hygiene and Tropical Medicine.

Education

2013-2016	Medical Research Council (MRC) UK PhD Studentship in Vaccine Research, Clinical Research Department, London School of Hygiene and Tropical Medicine.
2012-2013	MSc Epidemiology, London School of Hygiene and Tropical Medicine (Distinction).
2008-2011	BA Biological Natural Sciences (Major: Pathology), University of Cambridge (2i).

Prior Experience:

August 2016-August 2017 **International Study Coordinator EBOVAC1;** Assistant Professor, Clinical Research Department; London School of Hygiene and Tropical Medicine.

Based in London, I was the academic coordinator for the portfolio of projects funded by the EBOVAC1 grant, including an ongoing Phase 1 trial in Tanzania (25 adult participants) and a large Phase 2 clinical trial in Sierra Leone (976 adult and paediatric participants). The trials involved a candidate heterologous prime-boost vaccine regimen against Ebola Virus Disease (AD26.ZEBOV and MVA-BN-Filo). In addition, I was actively involved in the set up and site preparations in Sierra Leone for a further phase 2 trial of AD26.ZEBOV and MVA-BN-Filo, the rVSV vaccine and placebo (The PREVAC trial) under the same funding (EUR 58 million). Aside from tracking recruitment, reporting to ethics and regulatory authorities, managing Sponsor communications and working with the QA manager to respond to audit findings, I also input into legal contracts, SOPs, protocol amendments and source documents. I attended lab calls and organised the testing of samples for two ancillary studies in Sierra Leone investigating the prevalence of asymptomatic Ebola in screened participants and the effect of malaria infection on vaccine-induced immune response.
I prepared grant proposals and budgets to: 1) extend safety follow up in Tanzania from 12 months to 5 years (Janssen Registry Protocol) 2) to extend immunological follow up in Sierra Leone for 4 years and enrol an additional 200 paediatric participants (EC IMI2 Call 8) and 3) to extend the PREVAC trial follow up for 4 years to extend immunological and safety data collection (EDCTP).

September 2013- 2016 **MRC UK PhD Vaccine Research Studentship; Mwanza Intervention Trials Unit (MITU) the National Institute for Medical Research (NIMR), Tanzania.** Supervisor: Dr Deborah Watson-Jones**;** London School of Hygiene and Tropical Medicine.

2014	Project coordinator: Case-control study to analyse the association between HPV and subsequent HIV acquisition (MRC PHIND funding scheme, PI Deborah Watson-Jones).
2014-2016	Co-investigator & project coordinator: Collating lessons learnt from HPV vaccine demonstration projects and national programmes in 46 low and middle-income countries (BMGF USD 1,326,272, PI Deborah Watson-Jones). This project was requested to specifically analyse the value of demonstration projects in order to inform policy on whether funding for them should continue.
2014-2015	Project lead: Investigating the impact of HPV vaccine campaign activities on the provision of routine primary healthcare services in NW Tanzania (The Chadwick Trust fellowship & the LSHTM Travelling Scholarship GBP 10,000; PI K Gallagher).
Dec' 2014-Feb' 2015	Interim site coordinator for the EBOVAC1 Phase 1 trial of a heterologous prime-boost vaccine against Ebola Virus Disease. Mwanza. Initial 3 months of trial set-up due to gaps in recruitment.

Publications

1) **The associations between human papillomavirus prevalence, persistence or clearance and subsequent HIV acquisition in Tanzanian and Ugandan women: a nested case-control study**. Gallagher K.E., Baisley K., Hayes R., Kapiga S., Vandepitte J., Grosskurth H., Vallely A., Kamali A., De Sanjose S., Changalucha J., Watson-Jones D. *Journal of Infectious Disease 2016; first published online March 6, 2016.*
2) **Social mobilization, acceptability, and consent procedures for human papillomavirus vaccination in low- and middle-income countries.** Severin Kabakama[1], Katherine E Gallagher[1,2,*], Natasha Howard[3], Sandra Mounier-Jack[3], Helen ED Burchett[3], Ulla K Griffiths[3], Marta Feletto[4], D Scott LaMontagne[4], Deborah Watson-Jones[1]. *BMC Public Health 2016, 16:834.*
3) **Lessons learnt from human papillomavirus vaccine delivery in low and middle-income countries**. Gallagher K.E., Griffiths U.K., Burchett H., Howard N., Kabakama S., Mounier-Jack S., LaMontagne D.S., Watson-Jones D*. PloS one. 2017;12(6):e0177773. doi: 10.1371/journal.pone.0177773.*
4) **The impact of HPV vaccination campaign activities on routine primary healthcare services in Kilimanjaro region, Tanzania.** KE Gallagher, T. Erio, K Baisley, S Lees, D Watson-Jones. *(Accepted; BMC Health Services Research)*
5) **Human papillomavirus (HPV) vaccine coverage achievements in low- and middle-income countries 2007-2016** Gallagher K.E., Griffiths U.K., Burchett H., Howard N., Kabakama S., Mounier-Jack S., LaMontagne D.S., Watson-Jones D*. (Accepted, Journal of Papillomavirus research)*
6) **Factors influencing completion of multi-dose vaccine schedules in adolescents: a systematic review.** K. E. Gallagher, E. Kadokura, L. O. Eckert, S. Miyake, S. Mounier-Jack, M. Aldea, D. A. Ross, D. Watson-Jones. *BMC public health* 2016, **16**(1):172
7) **The status of HPV vaccination programs in low and lower middle income countries.** LaMontagne DS, Bloem PJN, Brotherton JML, Gallagher KE, Badiane O, Ndiaye C. Progress in HPV vaccination in low- and lower-middle-income countries. International Journal of Gynecology & Obstetrics. 2017;138:7-14. doi: 10.1002/ijgo.12186.
8) **The value of demonstration projects for new interventions: the case of human papillomavirus vaccine introduction in low-income and lower-middle-income countries.** *Howard N, Mounier-Jack S, Gallagher KE, et al. Human vaccines & immunotherapeutics 2016:1-3.*
9) **What works for human papillomavirus vaccine introduction in low and middle-income countries?** Howard N, Gallagher KE, Mounier-Jack S, Burchett HED, Kabakama S, LaMontagne DS, et al. Papillomavirus Research. 2017;4:22-5. doi: http://dx.doi.org/10.1016/j.pvr.2017.06.003.

CV: Professor David Goldblatt

Date of birth: 16 March 1960

Nationality: Irish

Education

MB, CH, B (University of Cape Town) 1983

MRCP (UK) 1986

PhD (Immunology, University of London) 1991

Current position

Professor of Vaccinology and Immunology
ICH Infect, Imm, Infla. & Physio Med
UCL GOS Institute of Child Health

30 Guilford Street, London WC1N 1EH, UK

Recent Publications

Pneumococcal conjugate vaccine given shortly after birth stimulates effective antibody concentrations and primes immunological memory for sustained infant protection. Scott JA, Ojal J, Ashton L, Muhoro A, Burbidge P, **Goldblatt D.** Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2011;53(7):663-70. Epub 2011/08/26. doi: 10.1093/cid/cir444. PubMed PMID: 21865175; PubMed Central PMCID: PMCPMC3166350.

Immunogenicity of a reduced schedule of pneumococcal conjugate vaccine in healthy infants and correlates of protection for serotype 6B in the United Kingdom. **Goldblatt D**, Southern J, Ashton L, Andrews N, Woodgate S, Burbidge P, et al. The Pediatric infectious disease journal. 2010;29(5):401-5. Epub 2009/12/17. doi: 10.1097/INF.0b013e3181c67f04. PubMed PMID: 20010312.

Dosing Schedules for Pneumococcal Conjugate Vaccine: Considerations for Policy Makers. Whitney CG, **Goldblatt D**, O'Brien KL. The Pediatric infectious disease journal. 2014;33(Suppl 2 Optimum Dosing of Pneumococcal Conjugate Vaccine For Infants 0 A Landscape Analysis of Evidence Supportin g Different Schedules):S172-S81. doi: 10.1097/INF.0000000000000076. PubMed PMID: PMC3940379.

Colonisation endpoints in Streptococcus pneumoniae vaccine trials. Auranen K, Rinta-Kokko H, **Goldblatt D**, Nohynek H, O'Brien KL, Satzke C, et al. Vaccine. 2013;32(1):153-8. Epub 2013/09/11. doi: 10.1016/j.vaccine.2013.08.061. PubMed PMID: 24016803.

Comparative immunogenicity of 7 and 13-valent pneumococcal conjugate vaccines and the development of functional antibodies to cross-reactive serotypes. Grant, L. R., O'Brien, S. E., Burbidge, P., Haston, M., Zancolli, M., Cowell, L., . . . **Goldblatt, D**. PLoS One, 2013, 8(9), e74906. doi:10.1371/journal.pone.0074906

Immunogenicity and serotype-specific efficacy of a 9-valent pneumococcal conjugate vaccine (PCV-9) determined during an efficacy trial in The Gambia. Saaka M, Okoko BJ, Kohberger RC, Jaffar S, Enwere G, Biney EE, Oluwalana C, Vaughan A, Zaman SM, Asthon L, **Goldblatt D**, Greenwood BM, Cutts FT, Adegbola RA. Vaccine. 2008 Jul 4;26(29-30):3719-26.

Bacteria, polysaccharides, vaccines and boosting: measuring and maintaining population immunity. **Goldblatt D**. Arch Dis Child. 2008 Aug;93(8):646-7.

Optimising the use of conjugate vaccines to prevent disease caused by Haemophilus influenzae type b, Neisseria meningitidis and Streptococcus pneumoniae. Trotter CL, McVernon J, Ramsay ME, Whitney CG, Mulholland EK, **Goldblatt D**, Hombach J, Kieny MP; SAGE subgroup. Vaccine. 2008 Aug 18;26(35):4434-45.

Natural human antibodies to pneumococcus have distinctive molecular characteristics and protect against pneumococcal disease. Baxendale HE, Johnson M, Stephens RC, Yuste J, Klein N, Brown JS, **Goldblatt D**. Clin Exp Immunol. 2008 Jan;151(1):51-60.

PERSONAL HISTORY - Peter George SMITH

ACADEMIC QUALIFICATIONS

Qualification	Discipline	Institution	Dates
B.Sc. (1st class)	Applied Mathematics	Northampton College of Advanced Technology (now City University)	1959-63
D.Sc.	Medical Statistics	City University	1983
HonMFPH		Faculty of Public Health (Hon. Member)	1992-
FMedSci		Academy of Medical Sciences (Fellow)	1999-

HONOURS

CBE	For services to the Spongiform Encephalopathy Advisory Committee and to Tropical Disease Research	2001
Donald Reid Medal	For distinguished contributions to epidemiology	2003
Ronald Ross Medal	For outstanding contributions to research in tropical public health	2016

CURRENT POSITION

Professor of Tropical Epidemiology	London School of Hygiene and Tropical Medicine, UK.	1989-present

CURRENT MEMBERSHIP OF SOME RELEVANT COMMITTEES

Member of Independent Data Monitoring Committee, for Sanofi-Pasteur clinical trials of dengue vaccines.	2008-present
Chair of Scientific Review Board and Member of Governance Council of the INDEPTH Effectiveness and Safety Studies of Anti-malarials in Africa (INESS).	2009-present
Chair of the Programme Board for Global Health and Vaccination Research (GLOBVAC) of the Research Council of Norway.	2011-present
Member of Global Burden of Disease Independent Advisory Committee.	2013-present
Member of WHO Product Development for Vaccines Advisory Committee (PD-VAC).	2014-present
Member of DFID/MRC/Wellcome Trust Global Health Trials Funding Committee.	2014-present
Member of Technical Advisory Group (TAG) for BMGF-supported Indian Platform for Research Excellence Related to National Aims (PRERNA) (comprising The Society for Applied Studies (New Delhi), Christian Medical College (Vellore), and KEM Hospital Research Centre (Pune)).	2015-present
Therapeutic Expert (Vaccines) to Wellcome Trust Independent Review Panel for ClincalStudyDataRequest.com	2015-present
Member of WHO Respiratory Syncytial Virus (RSV) Vaccine Technical Advisory Group	2015-present
Member of Scientific Advisory Committee (SAC) of the Coalition for Epidemic Preparedness Innovations (CEPI)	2016-present
Member of Advisory Group to the WHO Global Respiratory Syncytial Virus (RSV) Surveillance Pilot	2016-present
Member of Scientific Advisory Committee of European and Developing Countries Clinical Trials Partnership (EDCTP).	2017-present
Member of World Bank and CEP International Task Force on Strengthening Country Capacity for Vaccines Research and Development	2017-present

PUBLICATIONS

Over 350 scientific publications including relevant publications below:

Nuffield Council on Bioethics (PGS member of Working Party) (2002). The ethics of research related to healthcare in developing countries. Nuffield Council on Bioethics, London.

Jaffar S, Leach A, Smith PG, Cutts F, Greenwood B (2003). Effects of misclassification of causes of death on the power of a trial to assess the efficacy of a pneumococcal conjugate vaccine in The Gambia. Int J Epid 32, 430-436.

Moorthy VS, Reed Z, Smith PG (2007). Measurement of malaria vaccine efficacy in phase III trials: report of a WHO consultation. Vaccine 25, 5115-5123.

Moorthy VS, Reed Z, Smith PG (2009). Clinical trials to estimate the efficacy of preventive interventions against malaria in paediatric populations: a methodological review. Malaria J 8:23.

Moorthy VS, Reed Z, Smith PG on behalf of the WHO Malaria Vaccine Advisory Committee (MALVAC) (2009). MALVAC 2008: Measures of efficacy of malaria vaccines in phase 2b and phase 3 trials - scientific, regulatory and public health perspectives. Vaccine 27, 624-628.

Global Advisory Committee on Vaccine Safety (PGS chair) and World Health Organization secretariat (2009). Global safety of vaccines: strengthening systems for monitoring, management and the role of GACVS. Expert Review of Vaccines 8, 705-716.

Schmidt H, Smith PG (2009). Ethical excellence: the 2008 Declaration of Helsinki and its potential impact on research in developing countries. International Clinical Trials, Spring issue: pp74-77.

Bentsi-Enchill AD, Schmit J, Edelmam R, Durbin A, Roehrig JT, Smith PG, Hombach J, Farrar J (2013). Long-term safety assessment of live attenuated tetravalent dengue vaccines: deliberations from a WHO technical consultation. Vaccine 31, 2603-2609.

Feikin DR, Kagucia EW, Loo JD, Link-Gelles R, Puhan MA, Cherian T, Levine OS, Whitney CG, O'Brien KL, Moore MR, and the Serotype Replacement Study Group (including Smith PG). (2013). Serotype-specific changes in invasive pneumococcal disease after pneumococcal conjugate vaccine introduction – A pooled analysis of multiple surveillance sites. PLoS Med. 10(9):e1001517.

Mangtani P, Abubakar I, Ariti C, Beynon R, Pimpin L, Fine PEM, Rodrigues LC, Smith PG, Lipman M, Whiting PF, Sterne JA (2014). Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. Clin Infect Dis 58, 470-480.

Rid A, Saxena A, Baqui AH, Bhan A, Bines J, Bouesseau M-C, Caplan A, Colgrove J, Dhai A, Gomez-Diaz R, Green SK, Kang G, Lagos R, Loh P, London AJ, Mulholland K, Neels P, Pitisuttithum P, Cor Sarr S, Selgelid M, Sheehan M, Smith PG (2014). Placebo use in vaccine trials: Recommendations of a WHO expert panel. Vaccine 32, 4708-4712.

Smith PG, Morrow RH, Ross DA [Editors] (2015). Field trials of health interventions: a toolbox (3rd Edition). Oxford University Press, Oxford

Bottomley C, Bojang A, Smith PG, Darboe O, Antonio M, Foster-Nyarko E, Kampmann B, Greenwood B, D'Alessandro U, Roca A (2015). The impact of childhood vaccines on bacterial carriage in the nasopharynx: a longitudinal study. Emerging Themes in Epidemiology 12: 1.

Baiden R, Oduro A, Halidou T, Gyapong M, Sie A, Macete E, Abdulla S, Owusu-Agyei S, Mulokozi A, Adjei A, Sevene E, Compaoré G, Valea I, Osei I, Yawson A, Adjuik M, Akparibo R, Ogutu B, Upunda GL, Smith PG, Binka F (2015). Prospective observational study to evaluate the clinical safety of the fixed-dose artemisinin-based combination Eurartesim® (dihydroartemisinin/piperaquine) in public health facilities in Burkina Faso, Mozambique, Ghana and Tanzania. Malaria J 14,160.

Hosangadi D, Smith PG, Giersing BK (2017). Considerations for using ETEC and Shigella disease burden estimates to guide vaccine development strategy. Vaccine (published online) https://doi.org/10.1016/j.vaccine.2017.09.083.

22.3.1.1.1.1 Curriculum vitae: Dr Christian Bottomley
September 2017

Surname: **Bottomley** **Forenames: Herbert Christian**

Current post: Associate Professor in Medical Statistics and Epidemiology

Address: MRC Tropical Epidemiology Group
Faculty of Epidemiology and Public Health,
London School of Hygiene and Tropical Medicine,
Keppel Street, London WC1E 7HT, UK.

Telephone: 020-7927- 2533
Email: christian.bottomley@lshtm.ac.uk

Qualifications:

1997	BA	Biology, University of Oxford: 2(i)
2000	MA	Biostatistics, University of California, Berkeley
2001	Mres	Modelling Biological Complexity, University College London
2006	PhD	Mathematical Biology, University College London

Posts held:

2000 - 2001	Statistician, California Department of Health Services
2005 - 2006	Lecturer and Research Associate, University College London
2006 - 2008	Statistician, University College London
2008 - 2010	Research Fellow, LSHTM
2010 - 2015	Assistant Professor, LSHTM
2015 -	Associate Professor, LSHTM

Current citizenship roles:

LSHTM:

- Deputy Exam Board Chair, Distance Learning Epidemiology (2016-)
- Research Degree Coordinator, Dept Infectious Disease Epidemiology (2014-2017)
- Course Organiser, *Design and Analysis of Epidemiological Studies*
- PhD Supervision: 1 completed, 2 ongoing
- Seminar Organizer, Dept Infectious Disease Epidemiology (2009 -)
- Coordinator of MRC TEG fellowship scheme (2009-2013)

External:

- Associate Editor, *Tropical Medicine and International Health*
- Guest Editor, *PLoS Neglected Tropical Diseases*
- Reviewer, *Lancet Global Health*, *Journal of the Royal Society Interface, Trends in Parasitology, PLoS One, American Journal of Epidemiology, International Journal of Parasitology, American Journal of Tropical Medicine & Hygiene, Parasitology, European Child & Adolescent Psychiatry, Mathematical Biosciences, Vaccine*
- Steering committee membership: *Valuing active life in dementia* (2015-); *10 Top TipsTrial* (2012-2013); *A web-based intervention for heart disease management* (2007-2009)
- Data Safety & Monitoring committee membership: A randomized, controlled, doubleblind, phase 3 trial to evaluate the effects of maternal or neonatal

pneumococcal conjugate vaccination on pneumococcal carriage in infants up to nine months of age – The PROPEL Trial (2016-)
- Fellow of the Royal Statistical Society (2006-)

Recent research funding

2017 - 2021 Pre-delivery Administration of Azithromycin to Prevent Neonatal Sepsis and Death: a Phase III Double-Blind Randomized Clinical Trial. Funding: Medical Research Council UK Grant amount: £2.2m. Role in the project: co-investigator.

2013 - 2018 Epidemiological & statistical research on health problems of developing countries: MRC Tropical Epidemiology Group. Funding: Medical Research Council UK Grant amount: £3,913,897. Role in the project: named collaborator

2015 - 2017 Neglected Tropical Diseases Modelling Consortium Workpackage: Reaching the 2020 goals for human onchocerciasis. Funding: Bill and Melinda Gates Foundation. Grant amount: £403,890. Role in the project: named collaborator

2015 - 2016 NTD-Support Centre. Funding: Bill and Melinda Gates Foundation. Grant amount: $428, 519. Role in the project: trial statistician

2011 - 2014: Reduction of early mortality among HIV-infected subjects starting antiretroviral therapy: a randomised trial (The REMSTART trial). Funding: EDCTP. Grant amount: ~ €4m. Role in the project: named co-investigator

Fredrick N Were, MBCHB, MMED, FNIC, PHD, EBS

Current positions:
Professor of Pediatrics & Dean School of Medicine, University of Nairobi;
Chair of the Kenyan National Immunisations Technical Advisory Group (KENITAG);
Chief Researcher, Kenya Paediatric Research Consortium.

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Upper Hill Med Centre. 1st floor
Ralph Bunche Road
Box 20956-00200 Nairobi

Recent publications:

Building Learning Health Systems to Accelerate Research and Improve Outcomes of Clinical Care in Low- and Middle-Income Countries. English M, Irimu G, Agweyu A, Gathara D, Oliwa J, Ayieko P, **Were F**, et al. (2016) PLoS Med 13(4): e1001991.
doi:10.1371/journal.pmed.1001991

Characteristics of admissions and variations in the use of basic investigations, treatments and outcomes in Kenyan hospitals within a new Clinical Information Network Ayieko P, Ogero M, Makone B, Julius T, Mbevi G, Nyachiro W, **Were F**. et al. Vol. 101. 2015.

Delivery outcomes and patterns of morbidity and mortality for neonatal admissions in five Kenyan hospitals. Jalemba Aluvaala, Dorothy Okello, Gatwiri Murithi, Leah Wafula, Lordin Wanjala, Newton Isika, Aggrey Wasunna, **Fred Were**, Rachael Nyamai, and Mike English. Vol. 61. 2015. Journal of Tropical Peadiatrics.

Evaluating the level of adherence to Ministry of Health guidelines in the management of Severe Acute Malnutrition at Garissa Provincial General Hospital, Garissa, Kenya. Warfa O, Njai D, Ahmed L, Admani B, **Were F**, Wamalwa D, et al. Pan Africa Medical Journal. 2014. 214 p.