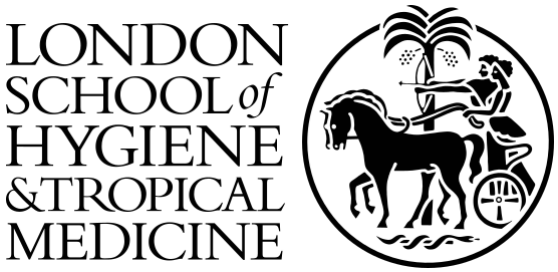

Assessing the impact of a 10-valent pneumococcal conjugate vaccine (PCV10) in the absence of pneumococcal disease surveillance data in Nigeria.

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Declaration

I, Aishatu L Adamu confirm that the work presented in this thesis is my own. Where information had been derived from other sources, I have indicated in thesis. This work has not been submitted previously for an academic qualification.

Signature

August 2024

Aishatu L Adamu

Abstract

Nigeria rolled out the 10-valent Pneumococcal Conjugate Vaccine (PCV10) into the routine childhood immunisation schedule through support from Gavi, the Vaccine Alliance. PCV10 was introduced in the context of the lack of pneumococcal disease data. Because PCV protects against nasopharyngeal carriage and pneumococcal diseases caused by included serotypes (vaccine serotypes - VT), monitoring the serotype distribution in carriage and disease is essential to evaluate vaccine impact fully. Based on the Gavi timelines, the country will transition to fully self-financing the PCV10 programme in a few years, translating to nearly half the total cost of fully immunising a child. Contextual evidence of PCV10 impact will benefit policymakers when deciding on financing and sustaining the PCV10 programme.

Relying on the necessity of pneumococcal carriage for invasion, this PhD addresses the three aspects of evaluating PCV impact:

Firstly, I conducted annual carriage (2017-2020) and vaccine coverage (2018-2020) surveys to assess the population-level impact of PCV10 introduction on pneumococcal carriage and its relationship to PCV10 coverage in children. I found a slow rise in PCV10 coverage accompanied by a significant reduction in carriage prevalence of VT in children aged <5 years and persons aged ≥5 years and a variable increase in carriage prevalence of non-VT. I also found evidence of direct and indirect protection against carriage demonstrated by an inverse relationship between coverage with two doses of PCV10 among children aged <5 years and VT carriage among children aged

<5 years and persons ≥5 years. I found substantial residual VT carriage of 22% in the rural and 12% in the urban sites among children aged <5 years.

Secondly, I assessed the applicability of three carriage-based models, where IPD surveillance is non-existent, to predict the impact of PCV10 introduction on IPD in children aged <5 years. These models predicted varying levels of decline in the overall IPD incidence. Analyses of underlying model assumptions and input data sources indicate the model predictions cannot be accurate because they discount the potential of residual VT carriage to cause IPD, thereby overestimating vaccine impact. Or they ignore the potential capacity of direct protection against VT invasion, thereby underestimating vaccine impact.

Finally, I conducted a cost-of-illness study to assess the economic burden of pneumonia and IPD. I found that costs were substantial to the healthcare provider and households with significant variation by clinical syndrome and level of care. In addition, a third of households encountered catastrophic costs, ranging from 4% of the least poor to 53% of the poorest households.

In conclusion, sustaining the PCV10 programme has reduced the burden of carriage and has also at a minimum reduced a proportionate fraction of invasive disease. Improved PCV10 coverage can improve herd immunity and further drive reductions in VT carriage and subsequent disease. Additionally, the programme will potentially save resources from treatment costs at both provider and household levels. Two adaptations will be required to reliably apply carriage-based models in settings that lack IPD surveillance. Firstly, model input data sources should be more representative

to give a more accurate picture serotype distribution. Secondly, models should be adjusted to capture direct vaccine effects against IPD from persistent VT carriage.

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Preface

This thesis is structured as a 'Research Paper Style Thesis' in accordance with the London School of Hygiene and Tropical Medicine guidelines. The thesis consists of three separate studies investigating inter-related objectives. Each study/objective is presented as a separate chapter with a preamble. Two papers have been published in peer-reviewed journals, while one is in preparation for submission. To make the document easier to read, annotate and comment on, I have included any published paper as a word-processed document in addition to the published proofs.

Table of Contents

List of Tables

List of Figures

List of Supplementary Tables

List of Supplementary Figures

Abbreviations

AKTH	Aminu Kano Teaching Hospital
CBHI	Community-based Health Insurance
CCR	Case-carrier ratio
CHE	Catastrophic Health Expenditure
GMC	Geometric mean concentration
HIC	High-income country
IPD	Invasive Pneumococcal Disease
LIC	Low-income country
LMIC	Low- or middle-income country
MMSH	Murtala Mohammed Specialist Hospital
NITAG	National Immunisation Technical Advisory Group
NP	Nasopharyngeal
NVT	Non-vaccine serotype
OOP	Out-of-pocket
PCV	Pneumococcal Conjugate Vaccine
PCV7	7-valent Pneumococcal Conjugate Vaccine
PCV10	10-valent Pneumococcal Conjugate Vaccine

PCV13	13-valent Pneumococcal Conjugate Vaccine
PPV	Pneumococcal Polysaccharide Vaccine
PR	Prevalence ratio
SII	Serum Institute of India
SRD	Serotype replacement disease
sSA	sub-Saharan Africa
VT	Vaccine serotype
WHO	World Health Organization

1 Background

1.1 Epidemiology of Pneumococcal Disease

Streptococcus pneumoniae (pneumococcus) is an important cause of morbidity and mortality, particularly in young children. It causes a spectrum of diseases that ranges from mild and localised syndromes such as sinusitis, otitis media and non-bacteraemic pneumonia to more severe and potentially fatal invasive pneumococcal disease (IPD), which includes bacteraemic pneumonia, meningitis and septicaemia.[1] In 2000, prior to widespread pneumococcal vaccination in children, pneumococcus was estimated to account for approximately 11% of deaths in children aged <5 years.[2] Although by 2015 these deaths were estimated to have declined by more than 50%, global models of invasive pneumococcal disease and pneumonia still estimated more than 9 million cases annually.[3]

The burden of pneumococcal disease varies across different settings. The disease burden is high in developing countries across South America, Africa and Asia.[4] The highest burden among children aged <5 years is in Africa. In 2015, it was estimated that out of the nearly 9.2 million cases and 320,000 deaths due to pneumococcal disease that occurred globally, >2.4 million cases and >160,000 deaths occurred in Africa.[3] Moreover, about half of the pneumococcal deaths in 2015 occurred in just four countries (India, Nigeria, the Democratic Republic of Congo and Pakistan).[3] Nigeria alone was estimated to account for over 1 million pneumococcal disease cases and 49,000 pneumococcal deaths in 2015.[3] The incidence of IPD varies with age, being highest among young children aged <5 years.[2] The incidence of IPD also

increases in the elderly, among whom case fatality has been shown to be as high as and, in some settings, even higher than that in young children.[5]

1.2 Pneumococcal carriage dynamics

The pneumococcus colonises the nasopharynx without eliciting symptoms in the host, and it is usually cleared within days to weeks.[6,7] Colonisation or carriage is transient and ends when the initial colonising strain is eliminated by an immune response, dies out spontaneously or is displaced by a different strain.[8] The dynamics of pneumococcal colonisation in a population depends on how frequently it is acquired, how fast it is cleared and how resistant or susceptible it is to displacement by competing strains.[9] Colonisation can, therefore, be prolonged when host immune responses are impaired, when strains elicit a poor immune response and evade clearance, or when strains have a competitive advantage and resist displacement.[10]Though largely assumed to be asymptomatic, a conflicting body of work argues rather that colonisation initiates an inflammatory process.[11] This inflammation, on the one hand, provides epithelial access that can potentially facilitate invasion and, on the other hand, gives access to inflammatory mediators and cells that speed adaptive immune responses. The colonisation stage is, therefore, not entirely asymptomatic, as evidenced by mild suppurative rhinitis. The colonisation-induced inflammation is also thought to be associated with increased pneumococcal shedding and host-to-host spread.[12] Pneumococcal adherence to the upper respiratory tract compromises the integrity of the epithelium, providing an inflammatory environment that is nutrient-enriched, advantageous for viral co-infection, and associated with higher susceptibility to acquisition and increased

density of colonising pneumococcus. Inflammation can also compromise the epithelial barrier and permit invasion in the absence of adequate mucosal immunity. Thus, colonisation can be complicated by direct pneumococcal seeding, which results in occult bacteraemia, particularly in young children.[11,13]

Pneumococcal colonisation can occasionally result in clinical disease when the pneumococcus extends into contiguous areas of the respiratory tract (sinuses, lung, middle ear) or penetrates the mucosa of the nasopharynx (or respiratory tract) to reach the systemic circulation and invade sterile sites (bloodstream, meninges, joints).[8,14] Nasopharyngeal colonisation is therefore thought to be an essential step in the progression of infection to pneumococcal disease. It is also the principal source of spread to others via nasal secretions/droplets.[14,15]

Nasopharyngeal pneumococcal carriage is common worldwide, though carriage prevalence is higher in low-income settings than in middle-income and high-income settings, irrespective of age.[16–19] In low-income settings, factors such as overcrowding, indoor air pollution, and poor hygiene facilitate effective contacts for transmission.[20,21] Comorbidities that impair non-specific immune responses and compromise the respiratory tract mucosa (undernutrition, viral respiratory infections) are also more prevalent in these settings.[8,22] Additionally, factors that impair humoral and cell-mediated immunity against the pneumococcus, such as sickle cell anaemia, undernutrition, and HIV, are more common in these settings.[23–26] Regardless of how frequent pneumococcal carriage is in a population, its prevalence declines with age due to immune maturation that increases clearance rate and reduces carriage density.[6,27–31] Furthermore, effective social contacts decrease

with increasing age, reducing opportunities for acquisition.[20] However, adults exposed to young children (such as day-care workers and parents of day-care attendees) have an increased risk of carriage acquisition.[32] Similarly, adults residing in confined spaces, such as military training camps, nursing homes, and prisons, where interpersonal contacts are frequent, are also at increased risk of carriage acquisition.[33–35]

One hundred pneumococcal serotypes have been identified based on the chemical structure of the polysaccharide capsule attached to the bacterial surface.[36] This capsule is an important contributor to pneumococcal virulence and immunogenicity. The key host immune factor that protects against pneumococcal infection is opsonin-dependent phagocytosis, opsonophagocytosis.[14] Anti-capsular antibodies initiate opsonisation and activate the classical complement pathway.[37] The pneumococcal capsule, however, blocks access of phagocytes to complement fixed on the underlying bacterial cell surface.[38] The capsule also limits mechanical clearance by mucus and facilitates adhesion to host cells through physiochemical mechanisms to enable colonisation.[15] Non-specific host immune factors such as the intact respiratory tract mucosa, mucus, ciliated cells, bactericidal peptides, and alveolar macrophages also contribute to immunity by inhibiting local pneumococcal spread, by limiting multiplication, and by eliminating pneumococci when invasion occurs.[15,37]

Colonisation induces serotype-specific anti-capsular antibody-mediated and capsule-independent T cell-mediated (Th17 CD4+ cells) immune responses that protect against re-colonisation and enhance pneumococcal clearance. [27,39–42]

To optimise survival, a pneumococcal strain needs to evade host clearance and be successfully transmitted to a new host. Encapsulated strains are able to transit from mucus and efficiently adhere to the epithelial cell surface during colonisation and initiate inflammatory responses that permit invasion.[11,43] Non-encapsulated pneumococcal strains colonise poorly and rarely cause invasive disease.[11,44] The encapsulated pneumococcus may, on occasion, up- or down-regulate capsule production, and this affects its survival dynamics. The up- or down-regulation of pneumococcal capsule production during intimate contact with host epithelial cells can be both beneficial and detrimental. Increased capsular expression assists with evading opsonisation during the invasion phase, while reduced expression is associated with better access of host antibodies and complement factors to the pneumococcal surface but is considered a necessary step for more efficient colonisation, as it allows greater exposure to the epithelial surface and better adherence.[45,46] It is also plausible that reduced capsular expression may be disadvantageous for effective serotype-specific anti-capsular immune response. Therefore, the conversion from heavily encapsulated to less encapsulated pneumococci and vice versa has to be delicately regulated to enable the pathogen to more efficiently colonise, be transmitted, evade host clearance, and cause invasive disease.

Independent of capsule expression, pneumococcal strains also vary reversibly between two forms during pathogenesis due to modification of the cell wall structure. This variation manifests as an alteration in the opacity of colonies in culture, resulting in two distinct phenotypes, the transparent and opaque phenotypes, which provide

selective advantages for survival during the different stages of pneumococcal pathogenesis. [47,48] Transparent variants are able to colonise the nasopharynx more efficiently than opaque variants by greater expression of surface proteins and cell wall structures but are relatively avirulent. Opaque variants are inefficient colonisers but are highly virulent and show improved survival in the blood. This is probably related to higher quantities of capsular polysaccharide and variations in cell wall polysaccharides and proteins that facilitate evasion of antibody, complement and phagocytes leading to diminished clearance.[37,49]

From the perspectives of both host and pathogen, invasive disease is detrimental. Thus, pneumococci are adapted for colonisation, where they can be transmitted from host to host. Carriage duration and degree of encapsulation can determine the epidemiological characteristics of serotypes. Serotypes with thicker capsules are associated with longer carriage duration in young children, and evasion of neutrophil-mediated killing compared to thinner capsules.[28] Prevalent serotypes with long duration of carriage (6, 19 and 23) do not elicit inflammatory reactions and evade host immune responses.[50] For such indolent serotypes, concomitant viral infection that induces inflammatory responses provides the opportunity for shedding, transmission, and invasion, and when they invade, they tend to be highly virulent. In contrast, serotypes with short duration of carriage (1, 4, 5) tend to be highly invasive and outbreak-prone but usually less virulent. Because of their short duration of carriage, these highly invasive serotypes may be adapted to elicit inflammatory responses that will permit shedding and transmission but inadvertently invade. Thus,

for both groups of pneumococci, invasion may be an inadvertent consequence of conditions that facilitate shedding and transmission.

The prevalence of carriage in a population is a function of acquisition and clearance rates. The nasopharyngeal acquisition and clearance rates vary by serotype and by age. Low clearance rates increase the mean duration of carriage, and serotypes that colonise the nasopharynx for a longer duration (6A, 6B, 19F, 23F) are more likely to be identified in prevalence studies.[6,7,51–54] More prevalent serotypes are, in turn, more likely to be transmitted and are therefore more frequently acquired.[6,7,54] Epidemiological evidence indicates there is protection against the acquisition of heterologous serotypes, mediated by serotype-independent responses,[29] and protection against re-infection with homologous serotypes, mediated by serotype-specific immune responses.[27] In early infancy, protection is thought to be mediated primarily by non-specific immune responses due to the immaturity of capsular-mediated immunity. Serotype-specific immunity takes over in older children and young adults.[27,41]

Two factors mediate immunity – age and experience, i.e., prior exposure. Natural immunity following colonisation is not very effective in young children because it does not protect against successive acquisition or reduced carriage duration of homologous serotypes.[28] With increasing age, adaptive immunity matures and can respond to serotypes with or without prior exposure. Carriage density and duration reduce with age throughout childhood, adolescence, and early adulthood, and this is likely mediated by non-specific, serotype-dependent and serotype-independent immune responses.[31,55] With prior exposure, immunity develops in response to

infection with a particular serotype, and the resultant immune responses reduce the future likelihood of being infected with that serotype. Repeated carriage is essential to develop natural immunity against colonisation.[42,56]

Interactions between pneumococcal strains also influence carriage dynamics. Serotypes differ in their susceptibility to competition. Competition can be postulated as either resistance to displacement of the resident serotype or competitive displacement by the invading serotype. Mathematical models that specify competition as resistance to displacement rather than competitive displacement generally provide a better fit to the epidemiological data.[7] Therefore, once established in the nasopharynx, a serotype with competitive advantage reduces the probability of acquisition of less competitive serotypes.[7,9,28,57] More prevalent ('paediatric') serotypes have a fitness advantage in children due to more frequent acquisition and slower clearance. However, with increasing age, immunity develops and immunological mechanisms that increase clearance and serotype-specific responses that reduce acquisition mature.[6,7,41] Co-colonisation by more than one serotype has also been documented, although standard methods are not very sensitive at detecting multiple colonisation.[58–64] Interaction is not always competitive. For instance, the presence of serotype 1 induces an inflammatory response akin to a viral infection that increases the opportunity for multiplication of co-colonising serotypes.[65] Unmasking may occur due to detection bias from common serotyping techniques that are largely restricted to detecting single serotypes. Thus, when predominant serotypes are eliminated, for instance, by vaccination, detecting less

predominant serotypes becomes easier even though there may have been no actual increase in their absolute carriage prevalence.[66]

1.3 Relationship between pneumococcal carriage and disease

The pneumococcus is a commensal with the capacity to become pathogenic depending on bacterial, host and environmental factors.[12] Nasopharyngeal carriage of the pneumococcus is thought to be a necessary precondition for pneumococcal disease. Evidence for the link between pneumococcal carriage and disease has been supported in different types of studies. Some prospective studies have shown a direct temporal association between acquisition of carriage of a serotype and subsequent disease by the same serotype, although this is restricted to otitis media as a manifestation of disease.[67,68] At an ecological level, the association between age and geographical location for both carriage and disease also supports the argument for a relationship between pneumococcal carriage and disease. Pneumococcal colonisation acquisition and prevalence are highest among children aged <5 years, and the age of peak IPD incidence coincides with the peak age of carriage.[15] In regions and among populations where carriage prevalence is high, acquisition occurs at earlier ages, and accordingly, the incidence of IPD is higher than in regions with lower carriage prevalence.[17,69–71] Vaccine impact studies that demonstrate a reduction in VT-IPD alongside a concomitant decrease in the prevalence of VT carriage lend the strongest credence to this relationship.[72,73] The indirect population-level effect of decrease in VT-IPD incidence associated with decreased VT carriage prevalence observed among unvaccinated persons also supports this relationship.[74]

The incidence of IPD caused by a particular serotype can be expressed as the product of its frequency in carriage and its inherent capacity to cause invasive disease following colonisation, invasiveness.[75–77] Some serotypes seldom cause disease despite being frequently found in carriage. In contrast, other serotypes (1, 5 and 7F) that are rarely found in nasopharyngeal carriage cause a disproportionately large fraction of IPD, indicating a higher propensity for invasion.[78] Invasiveness has been measured in a number of ways by combining contemporaneous colonisation and disease data. A common approach is the invasiveness odds ratio, calculated as the ratio of odds of serotype-specific carriage and disease to either a reference serotype or all other serotypes [75,79] or odds ratio comparing serotype proportions causing IPD in children to proportional carriage in the community.[80] However, odds ratios are relative and cannot be used to translate carriage prevalence into disease risk. This requires an absolute measure of serotype invasiveness such as the attack rate, calculated as the ratio of serotype-specific IPD incidence and serotype-specific acquisition rates [76] or the case--carrier ratio, calculated as the ratio of serotype-specific IPD incidence to serotype-specific carriage prevalence.[77,81] If the risk of invasion is higher shortly after acquisition, as earlier presumed, then attack rates will more accurately represent invasive capacity. However, if the risk of invasion is similar throughout the carriage episode, then attack rates will underestimate the invasiveness of serotypes with long carriage duration. In such a scenario, the case-carrier ratio which utilises carriage prevalence would be a more accurate measure of invasiveness.

Invasiveness measures are assumed to be stable and unique to serotypes, which some evidence has supported.[79,82] Still, variations in relative serotype distribution in

IPD by age and geographic location have been documented.[83,84] Host and environmental factors which affect susceptibility to disease risk or ascertainment of disease can modify the relationship between carriage acquisition or prevalence and invasive disease or the size of calculated invasiveness. The distribution of host factors such as age, HIV and malnutrition can vary in different populations and may influence serotype distribution in IPD and calculated invasiveness.[15] Variation in the robustness of the IPD surveillance system can influence its sensitivity for IPD ascertainment and lead to differences in invasiveness across settings. For instance, invasiveness measured from surveillance systems that underestimate IPD incidence will underestimate invasiveness.

Other clinical outcomes, like mortality and QALY, as proxies for disease severity have been used as measures of serotype invasiveness.[85–87] However, these measures are more likely to be affected by non-bacterial host and environmental factors.

1.4 Serotype epidemiology in IPD

The varying polysaccharide capsule structure of the 100 immunologically distinct pneumococcal serotypes have been described based on the serologic properties of their capsular polysaccharides, and the serotypes are further classified into serogroups.[88] Prior to the pneumococcal conjugate vaccine era, only a few serogroups (1, 5, 14, 6, 19 and 23) were responsible for most cases of IPD, with some variation in ranking and frequency by age and location.[84,89,90] Due to variations in incidence, serogroups were proposed to be considered epidemiologically distinct pathogens. Serogroups comprise serotypes that are immunologically cross-reactive. With this cross-reactivity, it was presumed that serotype-specific immune responses to

a serotype would be extended to other serotypes within the same serogroup. Observed impact of vaccines containing serotype 6B (but not 6A) on serotype 6A IPD incidence and the small or absent impact of PCVs containing serotype 19F (but not 19A) on serotype 19A IPD incidence shows that cross-protection within serogroups is not consistent.[91,92] From the vaccine manufacturing and licensing perspective, serotypes are treated as separate organisms for selection of vaccine serotype candidates, during development, and for demonstration of immunological responses. However, from the epidemiological perspective of assessment of clinical impact, grouping serotypes into those included in the vaccine or not is more reasonable.

Serotype 14 was the most common serotype identified in cases of invasive disease globally.[93] However, there were some differences in the ranking of serotypes across and within regions. In high-income settings such as the USA, Canada and Europe, serogroups 18 and 9 were relatively more frequent causes of IPD. Additionally, in these settings, serogroups more prevalent in carriage (14, 6, 19) were commonly isolated in disease.[89,93] In North America, serotype 4 was relatively more common as a cause of disease compared to Europe, particularly in older children and adults.[83] In Africa, Asia and Latin America, serotypes 1 and 5 were important causes of IPD despite their very low prevalence in carriage studies.[83,94] However, interpreting IPD serotype distributions can be confounded by temporal changes and regional differences in reporting and diagnosis.[66,90] For example, IPD surveillance data from low- and middle-income countries (LMICs) are limited, and serotype distribution data from these settings are likely under-represented in the global data.[83,84] External factors such as poor access to early treatment and higher risk of

transmission from IPD cases may cause variation in relative burden of serotypes between regions. Additionally, regional differences and secular changes in the indications for blood culture may contribute to variations in observed serotype distribution. And because serotypes vary in their ability to cause mild or severe disease, comparing serotype distribution between sites with different blood culture indications may be inappropriate. For instance, in the US, blood cultures are obtained for outpatients with presumed mild disease, while in many other settings, culture is largely limited to inpatients with potentially more severe disease, i.e. bacteraemia.[95,96]

The serotype distribution in disease also varies by age and syndrome.[44] The number of different serotypes causing IPD increases with age. The relative burden of IPD caused by the paediatric serotypes declines with age. The age-related decline in serotype-specific IPD incidence evinced by paediatric serotypes is not as evident for serotypes 1 and 5 [44,97], probably because of the absence of acquired immunity because humans lack the stimulation of prolonged exposure in carriage. Among elderly persons aged ≥65 years, an increase in the incidence of IPD due to common childhood serotypes has been observed[98]. This is possibly related to increased contacts with younger children, as grandparents, combined with an age-related decline in immunity.[44]

Serotypes 1 and 14 show a predilection for blood, serogroups 6, 23 and 19 are preferentially isolated in the cerebrospinal fluid (CSF), while serotype 1 is associated with pneumococcal pneumonia and peritonitis.[99–101] Though highly invasive, serotype 1 has a lower case fatality ratio than less invasive serogroups, such as 19 and

23, suggesting a lower disease severity.[44,102] Serotypes with longer carriage duration are associated with antimicrobial-resistant IPD.[44,101] Prolonged carriage likely provides the opportunity for the exchange of genetic material between serotypes, including resistance genes.[14] Outbreaks of pneumococcal disease are relatively more commonly attributable to 1 and 5 than to other serotypes. [97,103–109] In the meningitis belt of Africa, serotype 1 has often caused meningitis outbreaks.[105,106,109] To a lesser extent than serotypes 1 and 5, serotypes 4 and 12F have also been observed in outbreaks.[35,110,111]

Currently licensed pneumococcal vaccines are all serotype-dependent. Until serotype-independent vaccines become licensed, surveillance of serotypes causing disease will continue to be beneficial as it guides selection of serotypes to include in future vaccines and interventions to optimise current vaccination strategies. In the post-vaccination era, surveillance has shown variations in serotype distribution in IPD. [112–116] Unlike the pre-vaccination period, however, these variations are heterogeneous across populations and settings.[96,117] The heterogeneity is likely driven by differences in type, schedule, and duration of vaccine used, vaccine coverage, age structure, IPD surveillance systems, underlying serotype distribution in carriage, and factors that influence transmission potential or vulnerability to invasive disease.

1.5 Health economic burden of IPD

In the absence of vaccination, the control of pneumococcal disease largely depends on early diagnosis and successful treatment of infected symptomatic persons. Treatment of IPD is costly to both the healthcare system and households and families. In

addition to the direct medical costs incurred from drugs, investigations and use of hospital resources related to a hospital stay or visit, households and families also bear out-of-pocket, non-medical and indirect costs related to transportation, feeding, and accommodation for the patient, and the costs of loss of income and productivity for the carers.[118–121] Out-of-pocket (OOP) costs are health expenses individuals or families directly pay for at the moment they need healthcare.[122] These costs can be significant, particularly in settings with poor healthcare access, and are potentially catastrophic in settings of poverty.[123,124]Catastrophic health expenses can reduce the availability of household income for other household expenditure such as food and housing and potentially further impoverish families.[125,126]

Treatment costs vary by disease syndrome, disease severity, age, setting and level of care.[118–121,127–132] Costs per episode are higher for meningitis than for other pneumococcal clinical syndromes, and this varies by region; differences are more pronounced in middle and high-income countries compared to countries in sub-Saharan Africa (sSA).[118–121,127–129,131,133]. Moreover, patients with meningitis incur extra costs from long-term sequelae.[130,134] Treatment costs, irrespective of pneumococcal syndrome, are significantly higher in high-income countries (HICs) compared to low and middle-income countries (LMICs).[119–121,127,131,132] In contrast to high and middle-income settings where healthcare financing is through insurance or state schemes, financing in LMICs is largely via direct payments, such that OOP costs tend to contribute to a higher proportion of overall costs. These OOP costs represent a substantial fraction of household income

and expenditure.[118,121,127,133] Adults also incur higher treatment costs than children, probably related to underlying co-morbid disease.[135,136]

1.6 Pneumococcal Conjugate Vaccine (PCV)

Historical efforts for pneumococcal vaccine development and testing date back to the early 20th century, and these efforts have been reviewed in the past few decades.[137–139] Initial efforts to prevent pneumococcal disease by vaccination were focused on whole-cell killed pneumococcal vaccines that were tested between 1911 and 1916 among South African gold miners, a population with high incidence and mortality from pneumococcal disease, and also between 1918 and 1919 among US military. Though initially not serotype-specific, whole-cell vaccines showed some evidence of a short-lived reduction in pneumonia incidence but no change in case fatality. With the realisation of the serotype-specificity of pneumococcal disease and identification of more serotypes, later whole-cell vaccines specific to three, four, and eight serotypes reduced pneumonia incidence due to these serotypes. The lack of serotype-specificity of the killed vaccines, low rigour of epidemiological design of the studies, and absence of appropriate bacteriological techniques to assess and compare serotype-specific disease contributed to the uncertainty of the protective effectiveness of the whole-cell vaccines. However, a re-analysis in 2010, of the data from the 1918-1919 US trials using modern epidemiological methods confirmed significant vaccine efficacy between 34% and 59% against pneumonia and between 42% and 70% against case fatality.[140]

The next class of pneumococcal vaccines to be developed were the pneumococcal capsular polysaccharide vaccines. This followed the recognition that the composition

of the pneumococcal capsule was a polysaccharide and not protein, as had been earlier postulated.[137] Scientists showed that the capsular polysaccharide was responsible for the different pneumococcal types (serotypes), the antibody immune response that produced the agglutination reaction, and also had immunising capacity against pneumococcal infection. Between 1933 and 1944, a series of bivalent (serotypes 1 and 2) and tetravalent (serotypes 1, 2, 5 and 7) polysaccharide vaccines were developed and tested among US civilian corps and military and demonstrated efficacy against disease caused by the homologous serotypes. The discovery of penicillin as a highly effective treatment for pneumococcal pneumonia stalled interest in pneumococcal vaccines, but early mortality among treated individuals renewed interest in pneumonia prevention.

Pneumococcal polysaccharide vaccines (PPV) containing six and 13 serotypes tested among South African miners in 1972 showed vaccine efficacy of 79% against serotype-specific pneumococcal pneumonia and 80% against pneumococcal bacteraemia.[141] PPVs containing 14 and later 23 serotypes were licensed in 1977 and 1983, respectively.[142,143] A recent meta-analysis of trials and observational studies of PPV in adults showed a vaccine efficacy against IPD of 74% and 42%, respectively.[144] However, PPVs were poorly immunogenic in children aged <2 years and among adults with chronic illness, who are most at risk of invasive disease.[145,146]In addition, because they do not elicit serotype-specific memory B cells, protection induced by unconjugated polysaccharide vaccines is only short-term.

The pneumococcal conjugate vaccines (PCVs) that contain capsular polysaccharides from the ‘vaccine-type’ serotypes conjugated (chemically linked) to one or more

protein carrier(s) were the next pneumococcal vaccines to be developed.[147] Conjugation of carbohydrate antigen to a carrier protein had been shown to elicit immune responses via saccharide-specific antibodies in the 1930s.[148] Polysaccharide vaccines rely largely on the B-cell immune response. In contrast, polysaccharide conjugate vaccines elicit a T-cell-dependent antibody response.[149–151] Bacterial surface carbohydrates, such as polysaccharides of the pneumococcal capsule, are classified as T-cell independent antigens. These antigens consist of repeated units that lead to the cross-linking of B-cell receptors and the activation of B cells without requiring T helper cells. As a result, the antibodies generated have low affinity, are predominantly of the IgM isotype, and have limited switching to IgG and IgA. Besides, the response is associated with diminished development of memory B cells. Consequently, T-cell-independent antigens are poorly immunogenic and have poor memory, particularly among young infants who are most at risk and whose B-cell responses are immature.

Conjugation of polysaccharide antigens to a protein enables their uptake by antigen-presenting cells.[150,151] These cells present the protein peptides to T helper cells via the surface major histocompatibility complex Class II molecules, leading to the stimulation of polysaccharide-specific B cells to mature into antibody-producing plasma cells or memory cells. This process elicits a long-lasting T-cell memory response associated with the differentiation of polysaccharide-specific B-cells to plasma cells and the switching of IgM to IgG. Subsequent exposure to the antigen then results in plasma cell proliferation and maturation, leading to the production of protective high-affinity antibodies.

PCVs induce serotype-specific immunity that reduces carriage acquisition in the nasopharynx and protects against invasive pneumococcal disease caused by serotypes included in the vaccine. The conjugation, however, is challenging from the manufacturer's perspective: the complexity of the conjugation technique creates technical limitations to the inclusion of all serotypes in a single vaccine.[152] Production of a conjugate vaccine involves many steps, and to be successful, each step should not alter the eventual immunogenicity of the vaccine.[153–155] In brief, the polysaccharide is purified and chemically activated by synthesising an oligosaccharide resembling the capsular polysaccharide and selecting the minimum epitope that would maximise protection. These steps should not alter or degrade the polysaccharide size. The choice of the carrier protein is also crucial as it should be immunogenic, i.e., include a T-cell epitope. Protein carriers also require cold chain maintenance, which contributes to current PCV costs. The chemical method used to link polysaccharide to protein should not degrade or reduce polysaccharide size and should retain the immunogenic epitope structure and result in an adequate yield of the conjugate. The conjugate is also tested for stability and immunogenicity. Theoretically, in developing polyvalent vaccines, each component can be conceptualised as an individual vaccine, as each distinct serotype has to be prepared and conjugated separately.[138] This process can affect vaccine efficacy in a number of ways.[156,157] Firstly, from the manufacturing process and quality control perspective, unsuccessful conjugation of any single serotype effectively results in a failed lot that has to be discarded, and the risk of this increases with each added serotype. Secondly, the conjugation technique can also affect the immunogenicity of individual serotypes. Differences in the capacity to elicit opsonophagocytic antibodies

resulted in lower cross-reactivity of 19F to 19A in techniques using amination compared to cyanylation.[156] Finally, the use of the same carrier protein for multiple serotypes carries a risk of immune tolerance or suppression of carrier epitopes with repeated stimulation.

The seven-valent PCV (PCV7) was the first conjugate pneumococcal vaccine to be licensed in 2000.[158] PCV7 comprised serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, which were the serotypes most frequently isolated from the blood or CSF of children aged <6 years (ranked in decreasing order of frequency - 14, 6B, 19F, 18C, 23F, 4, and 9V) in the US and accounted for 80% of invasive disease.[158] These serotypes clearly contrast those included in the earlier bivalent (1 and 2) and tetravalent (1, 2, 5, and 7) polysaccharide vaccines, which were tested mainly among outbreak-prone populations. PCV7 introduction in 2000 in the USA and Europe resulted in a 76% decline in vaccine type (VT) IPD incidence rates among children aged <5 years within the first year of introduction, and this was sustained up to 7 years post-PCV introduction.[158–160] Indirect protection against VT-IPD was also observed among unvaccinated persons,[74,159] contributing a substantial fraction of the total burden of disease prevented.[159,161,162] Indeed, in the US, indirect effects were estimated to be at least twice the direct effects.[161] Unfortunately, following the elimination of these VTs, non-vaccine serotypes (NVTs) soon replaced the ecological niche in the nasopharynx vacated by these VTs, and this resulted in an increase in non-VT IPD incidence (i.e. serotype replacement disease – SRD)[66] that diminished the overall impact of the vaccination programme.[113,159,160,163] However, the increase in NVT-IPD incidence has always been smaller than reduction in VT-IPD incidence

following vaccine introduction. Thus, the PCV programme has always resulted in a net benefit. Additionally, PCV7 did not include serotypes (1 and 5) and was, therefore, unlikely to provide a substantial benefit in LMICs where these serotypes account for >20% of all IPD.[84] Because of the problem of SRD in high in high-income countries and the absence of cover for serotypes 1 and 5 in low-income countries, PCV7 was replaced with higher valency formulations with 10 or 13 serotypes.[147]

Following the switch from PCV7 to PCV10/13, varying levels of SRD have been reported from high-income settings. A significant increase in non-PCV13 SRD among adults ≥45 years, particularly with serotypes 8, 12F and 9N was reported from England and Wales.[113] In Norway, a modest increase in SRD (23B, 15A and 22F) was also reported in adults ≥65 years.[164] By contrast, in the US, SRD has not been observed in all ages. Following long-term use of PCV10 and PCV13, the serotype distribution in IPD has shifted to non-vaccine serotypes, but vaccine serotypes still persist. In a global systematic analysis of 87,341 IPD cases from 54 surveillance sites across 41 countries with a mature PCV programme (5-7 years post-PCV), serotypes 3 and 19A and vaccine-related serotype 6C were among the top causes of IPD among children aged <5 years.[165] In surveillance sites where PCV10 was introduced, 10% and 16% of IPD in children and adults were caused by PCV10 serotypes. In sites where PCV13 was introduced, 26% and 30% of IPD were caused by PCV13 serotypes, respectively.

The recently licensed PCV manufactured by the Serum Institute of India (SII-PCV) is another 10-valent PCV that replaces serotypes 4 and 18C in the original PCV10 with

6A and 19A. Additional PCVs containing 15 and 20 serotypes initially licensed for use in adults were extended to children in the US.[166] PCV15 contains PCV13 serotypes plus 22F and 33F. PCV20 contains PCV15 serotypes plus 8, 10A, 11A, 12F and 15B. A global systematic analysis of remaining serotypes in IPD reported the top non-vaccine serotypes (not covered by PCV13) were serotypes 8, 9N, 11A,12F, 15A, 15BC, 22F, 23A, 23B, 24F. PCV15 serotypes were estimated to contribute to about 50% of IPD in children and adults in PCV10 settings and 45% in PCV13 settings, while PCV20 serotypes were estimated to cause 60% of IPD across both settings. [165] However, in PCV10 settings, the proportions of IPD attributable to PCV13 and PCV15 serotypes did not differ much. Despite the preponderance of NVTs in the post PCV-10/13 era, SRD has been substantially smaller than direct protection against VT-IPD. In many settings, indirect protection against VT-IPD has also been larger than SRD, resulting in net benefit among the non-vaccine target population. An exception is in the UK, where SRD surpassed indirect protection against VT-IPD among persons aged ≥65 years.[113]

1.6.1 PCV formulations, schedules, and immunogenicity

The PCVs widely used are the 10-valent (PCV10) and 13-valent (PCV13) vaccines. PCV10 contains polysaccharides of serotypes 1, 4, 5, 6B, 7F, 9V, 14 and 23F conjugated to protein D derived from non-typeable *Haemophilus influenzae* (NTHi); 18C conjugated to tetanus toxoid; and 19F conjugated to diphtheria toxoid.[147] PCV13 contains polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F conjugated to CRM197, a non-toxic protein derived from *Corynebacterium diphtheriae.*[147] The two formulations also differ in the dose of

polysaccharide included and in the conjugation technique.[1,147] These vaccines are recommended to infants in three primary doses without a booster (3p+0) or in two primary doses with an additional booster dose (2p+1) by the WHO and three primary doses with an additional booster (3p+1) by the US.[1,158,167]

Unlike PCV7, which was licensed on the basis of proven clinical efficacy in several individually randomised controlled trials [168,169], PCV10 and PCV13 were licensed on the basis of non-inferiority of immune responses compared to PCV7. For the purpose of licensure, a correlate of protection (IgG ≥0.35 g/mL) for pooled PCV7 serotypes was estimated from the dispersion of the reverse cumulative distribution curves of vaccinated and unvaccinated children and the vaccine efficacy of the same vaccine (PCV7) in clinical endpoint trials.[170] Efficacy data for IPD were pooled from three trials with the assumption that the estimated correlate of protection was applicable to all serotypes. PCV10 and PCV13 stimulated proportions of children with antibody levels above the correlate of protection that were non-inferior to the same proportions vaccinated with PCV7 for the shared serotypes [171,172], except for serotypes 19F and 23F for the PCV10 trial.[171] PCV15 and PCV20 were licensed based on evidence of non-inferiority of immunogenicity to PCV13.[173,174]Because there are no established correlates of protection for adults, the criteria for immunogenicity used for PCV15 and PCV20 were serotype-specific opsonophagocytic activity (OPA) GMTs.

Most serotypes elicited higher antibody concentrations after three primary doses (3p+0) compared to 2 primary doses (2p+0).[175] The WHO initially recommended a 3p+0 schedule given in infancy. However, later evidence also showed that two

primary doses with a booster dose (2p+1) elicited high antibody concentrations and, therefore, was accepted as an alternate schedule.[176] Following the considerable success of PCV13 in reducing the risk of VT-IPD, particularly in infants, the benefit of multiple primary doses in infancy was questioned. Hence, a trial in the UK, comparing 2p+1 to 1p+1 schedule, the post-booster serotype-specific antibody (IgG) geometric mean concentrations (GMCs) were significantly higher for four serotypes (1, 4, 14 and 19F) among children who received one primary dose (1p+1), significantly higher for four serotypes (6A, 6B, 18C and 23F) among children who received two (2p+1), indistinguishable between the two groups in the remaining five serotypes (3, 5, 7F, 9V, and 19A).[177] The proportions of children who achieved antibody levels above the correlate of protection (≥0.35μg/ml) were similar across the two groups for all 13 serotypes. This finding prompted the switch to a 1p+1 schedule in the UK in January 2020, which also coincided with the beginning of the COVID-19 lockdown.[178] As with other respiratory diseases, IPD incidence declined during the lockdown period, and increased to pre-COVID levels after restrictions were removed. Three years following the schedule switch, surveillance data revealed an increase in overall IPD incidence among children aged 1-4 years, primarily driven by increase in NVT-IPD incidence, but with an increase in proportion of IPD attributable to PCV13 serotypes, in particular serotypes 3, 19A, and 19F.[179] More importantly, there was no evidence of breakthrough infections or vaccine failure among children eligible for the 1p+1 schedule. However, these findings are most likely confounded by effects of the lockdown, particularly on disruption of ecology of respiratory pathogens.

1.7 PCV efficacy against IPD and carriage

PCVs elicit circulating serotype-specific antibodies that protect against invasive disease and carriage acquisition. PCV-elicited protection against pneumococcal disease occurs at two levels (see Figure 1).[180] Firstly, PCV induces serotype-specific circulating antibodies that protect against VT invasion following nasopharyngeal colonisation. This level of protection is direct and only experienced by the vaccinees, and it is a strong component of the vaccine's protection against IPD in that person. Secondly, PCV protects against nasopharyngeal acquisition of VT pneumococci. This level of protection against VT acquisition is experienced by vaccinated and unvaccinated persons in the population where PCV is used. This protection against acquisition reduces carriage prevalence among vaccinees, which also reduces person-person transmission, leading to herd protection best observed among non-vaccinees but present in the whole population. Protection against disease via the second level is additionally mediated indirectly through protection against VT acquisition and reduced transmission. The first level directly protects vaccinated individuals, whereas the latter level benefits the whole community, whether vaccinated or unvaccinated.

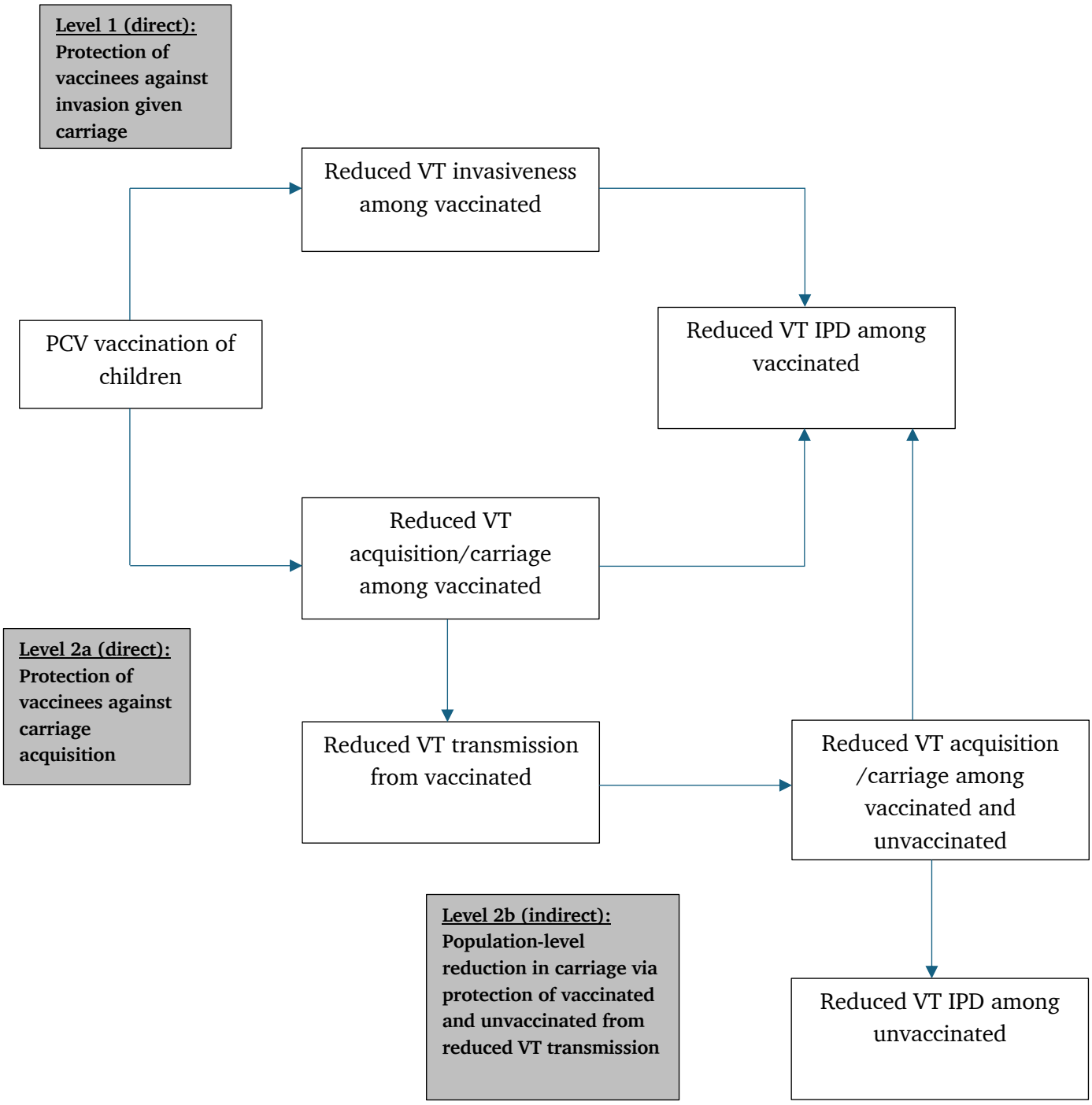

Figure 1.1: Conceptual diagram for mode of protection by PCVs against invasive disease

For vaccinated individuals, the vaccine efficacy (VE) against IPD (VE_{IPD}) is, therefore, a function of VE against carriage acquisition (VE_{acq}) and VE against invasion (VE_{inv}). VE_{IPD} and VE_{acq} can be inferred from clinical trials; therefore, VE_{inv} can be calculated from the relationship below.

$$VE_{IPD} = 1 - (1 - VE_{inv}) \times (1 - VE_{acq})$$

Alternatively, VE_{acq} can be estimated from carriage prevalence odds [181], where the acquisition rates the carriage prevalence odds have the following relationship:

$$Carriage\ odds\ \left(\frac{carr\ prev\ (P)}{1 - carr\ pev(P)}\right) = acquistion\ rate(\lambda) \times carriage\ duration(d)$$

Assuming mean carriage duration is similar among vaccinated and unvaccinated individuals, i.e., vaccination has no effect on carriage duration, then acquisition rate ratios and carriage prevalence odds VE_{acq} approximate, and the relationship is expressed as:

$$VE_{acq} = 1 - \left(\frac{\lambda_{vacc} \times d}{\lambda_{unvacc} \times d}\right) = 1 - \left(\frac{\lambda_{vacc}}{\lambda_{unvacc}}\right) = 1 - (\frac{carriage\ odds_{vacc}}{carriage\ odds_{unvacc}})$$

There are also differences in levels of protection by vaccine type, schedule, and serotype. PCV13 may provide more protection against carriage for shared serotypes than PCV10 [182], while three primary doses may offer more protection than two primary doses.[183] And despite being immunogenic for serotype 3, PCV13 did not significantly protect against serotype 3 IPD.[1,184] Cross-protection against carriage

and IPD between serotypes within serogroups has also been reported. For example, for PCV10, which contains serotypes 6B and 19F, studies indicate evidence of direct protection against IPD caused by serotypes 6A and 19A, although they are not included in the vaccine.[1,180,185,186] In contrast, cross-protection against carriage is less clear-cut. There is evidence of direct cross-protection against carriage of serotype 6A with PCV10, while for serotype 19A, studies demonstrated either no evidence of cross-protection or even an increase in 19A carriage following PCV10 vaccination.[1,180,186–188]. Regardless of schedule, both PCV10 and PCV13 are associated with indirect protection at a population level against VT-carriage and therefore VT-IPD.[72,116,162,189,190] Evidence also indicates some level of indirect cross-protection at a population level against serotype 6A IPD for PCV10 but no cross-protection against 19A.[180] PCV13 has also been shown to have some cross-protection against carriage and disease of serotype 6C.[180]

PCV10 is used in routine immunisation programmes by far fewer countries compared to PCV13.[186,191] A few countries have experience of using both vaccine products. Clinical trials and post-marketing studies have all demonstrated a significant reduction in VT-IPD as well as overall IPD, irrespective of the setting or schedule in use. The vaccine efficacy (VE) of PCV10 has been demonstrated in two trials in South America and Finland against different pneumococcal disease syndromes. VE was highest for VT IPD (100%) and overall IPD (ranging between 66% and 93%) and modest for pneumonia ranging between 18% to 45%.[192,193]

1.8 PCV impact

The vaccine efficacy determines the proportion of all disease that PCVs can avert in ideal conditions. Vaccine efficacy is measured by comparing disease occurrence in vaccinated and unvaccinated persons from the same populations. Vaccine impact measures the relative reduction in disease occurrence at a population level attributable to the vaccination programme. Vaccine impact is measured in observational studies by comparing disease occurrence in the same population before and after the vaccine programme or by comparing disease occurrence in vaccinated clusters (comprising vaccinated and unvaccinated) to unvaccinated clusters in cluster randomised trials.[194,195] The impact of introducing a vaccine programme occurs at different levels, directly due to protection against disease from being vaccinated and indirectly due to population-level protection that results in reduced transmission from widespread vaccination.[194] In a post-vaccine population, vaccinated persons benefit from combined direct and indirect effects (total effects), while unvaccinated persons benefit from indirect effects.[194,195] And the overall vaccine impact is the sum of the total effects among the vaccinated and the indirect effects among the unvaccinated.

In addition to the vaccine efficacy, the impact of the PCV programme will be influenced by the proportion of target children vaccinated (coverage), the vaccine schedule, including whether or not a booster dose is included or whether catch-up is offered, the time since PCV was introduced, and the background relative burden of VTs in IPD and carriage which local/contextual dynamics or trends can influence.[196]

An overarching factor influencing the size of PCV10 impact, whether direct or indirect, and the eventual success of PCV programmes is the coverage, i.e., the proportion of target children vaccinated. Coverage determines the levels of direct protection and additional indirect protection from reduced carriage acquisition and onward transmission among vaccinated children. Direct protection in the population is 'linearly' related to uptake. Among vaccinated individuals, direct protection is a function of the vaccine efficacy and vaccine coverage [194,197]:

$$Vaccine\ impact = Vaccine\ efficacy \times Vaccine\ coverage$$

Thus, ignoring indirect protection, the impact of direct protection of a PCV with vaccine efficacy of ~90% against IPD [193], in a population with 50% coverage will be 45%.

Indirect vaccine effects (protection unvaccinated people receive from reduced transmission of VTs at a population level) in the population are non-linear. At the start, when only a small fraction of the target population is vaccinated, the indirect effects are likely to be very small, but as the vaccine coverage increases, fewer contacts between people lead to transmission, and these effects are exponential, leading to a rapid increase in indirect protection.[198,199] Once herd protection is 'established', particularly if this leads to elimination of VT transmission, the exponential increase in impact with coverage tails off as the effect saturates and asymptotes towards 100%.[198] In Australia, a modelling study quantifying the estimated degree of indirect effects for under-vaccinated (≤1 dose in infancy) children at varying coverage levels, estimated that PCV coverage of 50% among

children aged <5 years would prevent 81.4% (95% CI 71.2-88.0) of PCV7-type IPD, while 70% coverage prevents 90.5% (95% CI 82.5–94.9).[198] The marginal increase in preventable VT-IPD was minimal (<3%) beyond 70% PCV coverage, even when the analysis was restricted to unvaccinated children. This brings into question the benefits of efforts to achieve coverage beyond the point that herd protection is established.

It follows, therefore, that as successive cohorts of infants are vaccinated and high coverage is maintained, direct protection is sustained in this at-risk group. But as the vaccinated infants age into the toddlers and pre-schoolers, the main drivers of transmission, the indirect protection becomes more robust, and its effects surpass that of direct effects, negating the necessity of repeated primary doses in infancy and indicating an advantage of booster doses post-infancy.[197] In the population, there are both direct and indirect effects, and as coverage rises, the evaluation of the overall effect must take into account both the linear effect (direct) and the non-linear effect (indirect) combined.

The time since PCV was introduced, i.e., the duration of PCV use in a setting, is another key factor influencing PCV impact. Population immunity accumulates with increased coverage of the target age group, and if the vaccine is introduced at birth, it will take five years to reach all children aged <5 years, at which point direct effects are maximal. National PCV programmes primarily target infants and young children who are at most risk of pneumococcal disease. At the initial post-introduction stage, PCV-induced decline in IPD is rapid among these vaccine-target age groups because direct effect is immediate.[162] This age-related differential impact disappears as

indirect effect comes to fruition and becomes the main driver of protection. Direct vaccine-induced protection wanes over time, so as the PCV programme matures, persons vaccinated as infants do not have additional benefits over those who are unvaccinated because both benefit similarly from indirect protection.[200][201]

Booster dose beyond infancy and catch-up vaccination to children outside the eligibility age, in theory, provide a way to rapidly build up overall vaccine effects (total + indirect) in the population. In a meta-analysis of indirect effects from 242 studies, a comparison of studies with and without booster indicated a larger impact for schedules with 2p+1 or 3p+1 compared to 3p+0, but with overlapping intervals. However, it is important to note that 80% of the studies were from North America and Europe, only 4% were from middle-income countries and no LMIC was included, the only sSA country was South Africa, and only two studies reported using 3p+0. Head-to-head comparison from Israel, however, clearly supported the larger impact of booster dose given post-infancy in driving indirect effects compared to primary infant series.[197] Pneumococcal colonisation and invasive disease epidemiology in LMICs may favour a preference for more primary doses early in infancy. Although there is no direct comparison, VT-IPD among infants too young to be vaccinated was eliminated within two years of the introduction of PCV10 with a catch-up in Kilifi, Kenya and within five years led to a similar decline (91%) as observed with eight years of PCV use in the Gambia among children aged <5 years.[72,202]

Baseline serotype distribution is another factor that affects the size of PCV impact. The relative burden of VTs in IPD determines how much disease PCV can potentially avert. Analysis of serotype distribution in IPD in the pre-PCV period revealed regional

variation in potential coverage of PCV7, PCV10 and PCV13.[84] Due to the absence of serotypes 1 and 5, which were estimated to account for >20% of IPD in sub-Saharan Africa (sSA), PCV7 was estimated to cover only 49% of IPD in sSA, in contrast to North America and Europe, where PCV7 covered ≥72% of IPD. Whereas PCV10 and PCV13 that included these serotypes had >70% coverage in sSA.

1.8.1 Serotype replacement disease

An unintended negative effect of PCVs is the potential of serotypes not included in the vaccine to replace vaccine serotypes in the nasopharynx and invade the mucosa to reach normally sterile sites, leading to serotype replacement disease. Serotype replacement in disease is not proportional to serotype replacement in carriage because NVTs are, on average, less invasive than VTs. As a result the complete replacement observed in nasopharyngeal pneumococcal carriage prevalence has not been reflected in invasive disease incidence.[73] There has been heterogeneity in the magnitude of reported serotype replacement in disease following the use of PCV10/13, however, the net benefit has generally been positive because the protective impact on the incidence of VT disease has been larger than the disadvantageous rise in NVT incidence. The only setting where SRD has exceeded the (indirect) benefits attributable to reduced VT IPD incidence is among persons aged ≥65 years in the UK, where SRD incidence nearly increased more than VT incidence decreased.[113] In this age group, non-PCV13 IPD incidence (per 100,000 persons) increased from 9.55 in the pre-PCV7 period to 22.68 eight years after the switch from PCV7 to PCV13, whereas PCV13 IPD incidence only declined from 6.94 to 5.52, respectively. Additionally, there is an increase in diversity of serotype distribution in

replacement disease following PCV10/13 use with no distinct serotype(s) clearly dominating post-PCV.[117]

PCV10 has been accompanied by varied levels of serotype replacement in disease across different settings. Non-vaccine factors may explain some of this phenomenon. First, biases in surveillance from differences in culturing practices, disease severity, and clinical syndromes can lead to differential sampling criteria across settings.[66,96] As such, variations of disease severity across and between surveillance populations can lead to differences in the observed serotype distribution and reported magnitude of serotype replacement disease. Serotypes have a predilection for site and are associated with severity of disease, therefore, the site and nature of the surveillance can influence the serotypes 'observed'. For instance, restriction of surveillance to hospitalised (severe) disease or inclusion of out-patient (non-severe) disease can lead to differences in the serotypes identified. Second, the local serotype distribution prior to PCV use can give a competitive advantage to more prevalent NVTs. Third, the magnitude of antimicrobial use can determine the pre-PCV burden of resistance among NVTs and select for resistant strains among NVTs post-PCV. Fourth, the age structure and contact pattern of the population can determine the size of the vulnerable elderly population and affect the magnitude of indirect protection and serotype replacement. Fifth, the distribution of risk factors for invasive disease in the population can affect the magnitude and distribution of serotype replacement disease.[96,203]

1.9 PCV introduction and financing in Africa and Nigeria

PCV7 was introduced into the routine childhood immunisation programme in the USA in 2000, but the first countries to introduce PCVs in Africa (South Africa, Rwanda and The Gambia) did so in 2009.[204–206] This lag in introduction was mainly caused by the high cost of the vaccine. For instance, in 2010, the per-dose cost of PCV13 in the USA was $92 [207], which was four times the cost of all the vaccine antigens in the whole routine childhood immunisation programme in Nigeria in 2007 ($22.30) and 2013 ($24). [208,209] In 2011, Gavi, The Vaccine Alliance, offered support to low-income countries to introduce PCVs, and this led to a rapid expansion in the number of children offered the vaccine in LMICs. Gavi overcame the challenge of vaccine costs in two ways. [210,211] Firstly, it used donor funding to subsidise the purchase costs on a graduated scale pegged to the size of each country's economy. For countries with a per capita Gross National Income of ≤$1,580 in the previous three years, Gavi supplied PCV10 or PCV13 at approximately 20-30 cents. Secondly, Gavi reduced the purchase price of the vaccine by guaranteeing a future market to manufacturers through its 'Advanced Market Commitment' (AMC). By committing to sustained demand from LMICs, Gavi was able to encourage manufacturers to invest in high-volume manufacturing plants that could supply a sufficient volume of doses at contractually agreed prices. A key point to note regarding the first mechanism is that it was transitory; as soon as a country's economy passed the threshold identified, Gavi required the government to increase its contribution to the subsidized prices until, after 5-10 years, it was supporting the full cost. [212] Nevertheless, because of the AMC, the 'full cost' of vaccine for Gavi-ineligible middle-income countries will still be reduced to within the range of $2.00-3.00, i.e., the 'tail price'.

Nigeria applied for Gavi support to introduce PCV in 2011 and successfully introduced PCV10 in 3 annual phases across its states between 2014 and 2016.[213] Along with other routine vaccines, PCV is given in 3 primary doses at 6, 10 and 14 weeks, and there was no catch-up vaccination for older children at the time of introduction. UNICEF was able to further negotiate a discount from GSK, the manufacturer of PCV10, and this effectively brought the net cost from $3.50 to $3.05 per dose of PCV10 for Gavi-supported countries.[214] Nigeria currently pays $0.30 per dose, while Gavi bears the remaining cost. Originally, Nigeria planned to move to the accelerated transition phase in 2021, steadily increasing its financial contribution to vaccine costs to the point of full financing over five years.[214] This transition would have steadily increased PCV co-payments from $24.9 million to $45.8 million over these five years, representing >50% of the total annual costs of vaccines the country paid in 2011.[215] However, in 2018, Gavi board made the exceptional decision to extend its support to the country through to 2028.[216] This extension, a departure from the usual five-year transition period, was driven by some unique underlying factors.[216] First, poor immunisation coverage and considerable inequalities in immunisation coverage in the country were of major concern. Second, Gavi's commitment to sustainability led it to support the country to develop a robust 10-year plan to strengthen immunisation and primary healthcare in line with the Sustainable Development Goals, "National Strategy for Immunisation and PHC System Strategy 2018-2028" (NSIPSS). Third, this extended support would also allow the introduction of new vaccines to the Nigerian schedule (second measles dose, Rotavirus and HPV) and for Gavi to have a multi-layered approach for the Federal and state-level support provided. Fourth, a key precondition for this extended support

was the refund of misused funds and the country's commitment to an enhanced accountability framework and mobilising resources from different funds. Finally, the extended support provided additional funds for vaccine financing and health system strengthening.

1.10 Maximising PCV impact

Given the significant costs of PCV, even at the Gavi tail price, various efforts are being made to reduce the cost of the vaccine programme without reducing its effectiveness. These efforts include improved coverage, reduced dose schedules and fractionated doses. In addition, the demand from HICs has driven the development of higher-valency PCVs with 15, 20 [166] or more serotypes; if these are incorporated into the GAVI mechanism at similar prices, they would increase the cost-effectiveness of the programme.

As earlier discussed, high coverage is important for both direct and indirect effects. Therefore, achieving a high vaccine coverage is the first step in making the PCV programme cost-effective. Effective high coverage can be attained over time as coverage accumulates or more rapidly with catch-up vaccination.

As the PCV programme matures and VT transmission and disease are controlled, the low background risk of VT acquisition obviates the necessity to achieve high levels of direct protection in young infants via multiple primary doses.[217] Therefore, reduced dose schedules become possible, as was done in the UK. [177,178,218] Reduced dose schedules are also being contemplated in LMICs. In South Africa, a trial comparing the effects of a reduced dose schedule for both PCV10 and PCV13 showed

that reduction in VT carriage prevalence for the 1p+1 schedule was non-inferior to 2p+1 .[219] In The Gambia, a trial is also underway to evaluate whether a 1p+1 schedule is clinically non-inferior to a 3p+0 schedule of PCV13, where VT carriage prevalence in children with clinical pneumonia is the primary trial outcome.[220]

Reduced schedules may, therefore, be an efficient option for LMICs that have achieved and sustained high vaccine coverage, leading to the elimination of VT transmission.[217,221] The key challenge here is control of VT transmission to a point where the risk of exposure is so small that the reduction in direct protection achieved by a single primary dose compared to two primary doses is negligible. A second important consideration is to give the primary dose at an age when the immune system is sufficiently mature to mount adequate responses that maximise the impact of a booster dose.[222] For instance, in the South Africa trial, a delayed first dose (14 weeks) was associated with a larger reduction in VT carriage compared to an earlier first dose (6 weeks).[219]

Another strategy to increase PCV cost-effectiveness being evaluated is the administration of fractionated doses. Trials are underway in Kenya and Niger to evaluate the non-inferiority of fractionated doses (20% and 40%) of PCV10 and PCV13 compared to a full dose to reduce vaccine costs.[223,224] Preliminary results show fractionated PCV10 and PCV13 at 40% were non-inferior to a full PCV10 post-prime, but only PCV13 was non-inferior post-booster.[225]In Niger, the trial also evaluated the impact of mass PCV campaigns in children aged 1-9 years in accelerating herd immunity.[226]

Finally, PCVs with a different serotype composition, or with more serotypes, are under consideration. The SII-PCV supplied through GAVI at $2.00/dose will be much more affordable for LMIC PCV programmes. A trial in Gambia demonstrated that the immunogenicity of SII-PCV was non-inferior to PCV10 using the standard non-inferiority margins required for licensure of new PCVs.[227] Higher-valency vaccines (PCV15 and PCV20) have also been licensed in the US for use in children and adults [166] and more are in the pipeline.

1.11 Options for assessment of PCV impact

1.11.1 Pneumococcal disease surveillance

The ultimate goal of a PCV programme is to reduce the burden of morbidity and mortality from pneumococcal disease. The ideal approach would be to evaluate long-term trends in pneumococcal disease using well-established population-based surveillance systems with comprehensive and consistent clinical and laboratory components. Pneumococcal disease comprises a wide range of non-invasive (mucosal) and invasive clinical syndromes that are preventable by PCV. From a surveillance perspective, the key validity indicators of diagnostic criteria of any clinical syndrome are sensitivity and positive predictive value. While sensitivity depends solely on the clinical (or laboratory) definition, positive predictive value depends on the specificity, prevalence and the true aetiologic burden of *S. pneumoniae* in the respective clinical syndromes.

Non-IPD syndromes occur more frequently than invasive forms, making them theoretically attractive endpoints for assessing PCV impact due to the potential for

high statistical power. However, a number of factors limit the utility of non-IPD endpoints for PCV impact assessment. Firstly, non-invasive syndromes are usually mild, have non-specific clinical presentation, and often only require outpatient medical care. Therefore, they are more likely to be affected by healthcare utilisation behaviours. Secondly, non-invasive syndromes are also frequently caused by non-PCV serotypes, viruses and other non-pneumococcal bacteria.[228] Non-IPD endpoints will have poor positive predictive value and poor PCV coverage. Thirdly, immunological criteria by which new PCV products are licensed are predominantly applicable to IPD but not to any of the non-IPD end points, including colonisation. Thus, post-licensure studies more commonly report pneumonia and invasive forms of pneumococcal disease as outcomes.

Given that the pneumococcus is a leading cause of pneumonia and pneumonia is a major cause of death, clinically and radiologically-confirmed pneumonia have been used as measures of pneumococcal pneumonia and pneumococcal disease burden, respectively, as they are less laboratory dependent.[229,230] Using pneumonia as an endpoint was based on the premise that *Streptococcus pneumoniae* was the leading cause of pneumonia morbidity and mortality in children.[231,232] However, these estimates are based on models relying on assumptions of the accuracy of vital registries, published verbal autopsy and surveillance data, and estimation of aetiologic attributable fraction using a vaccine probe approach.[233] The benefit of pneumonia as an endpoint will depend what fraction of pneumonia is attributable to pneumococcus and what fraction of that is attributable to VTs. The Gambia PCV9 trial showed low vaccine efficacy of 7% and 12% for non-severe and severe clinical

pneumonia, 35% and 37% for severe and non-severe radiological pneumonia, 15% for hospitalisation and 16% for mortality.[229] These small values also had wide 95% CIs, implying inadequate power to detect small effects. In summary, the low positive predictive value of non-IPD endpoints will underestimate the vaccine impact. The validity of using all-cause or radiologically-confirmed pneumonia as a disease end-point for pneumococcal disease will be dependent on the true aetiologic burden of pneumococcus in pneumonia.

IPD endpoint is, therefore, a more pragmatic option for PCV impact assessment via population or hospital-based surveillance. A major challenge in IPD surveillance is choosing the appropriate syndrome to investigate. Conclusive diagnosis of pneumococcal disease hinges upon having access to confirmatory tests, which in turn rely on laboratory capacity. For instance, diagnosis of pneumococcal meningitis requires access to a health care facility with skills for lumbar puncture to obtain and culture cerebrospinal fluid (CSF); diagnosis of bacteraemic pneumococcal pneumonia or septicaemia requires a health facility with blood culturing facilities. Both require adequate laboratory procedures to isolate pneumococcus from the body fluids as well as serotyping capability.

Pneumonia presents an even greater diagnostic challenge. Isolating the pneumococcus from sputum specimens has a poor sensitivity and, moreover, they are difficult to obtain, particularly in young children, and like other culture samples, findings can be affected by antimicrobial use. Lung/tracheal aspirates are more sensitive but require more technical skills and are, therefore, practised rarely.[234] Rapid urinary antigen test (*BinaxNow*), which tests for the presence of pneumococcal

C polysaccharide antigen in the urine of patients with pneumonia, showed some promise with moderate sensitivity and high specificity in adults.[235] *BinaxNow* has two distinct limitations. Firstly, it does not distinguish between serotypes. Secondly, in young children, high carriage prevalence leads to false positives because colonisation can also lead to the appearance of the antigen in urine.[236] Therefore, *BinaxNow* will have low positive predictive value for VT disease and bias the size of the estimated impact downwards. More recently, a multiplex Urinary Antigen Detection (UAD) test based on Luminex technology has been shown to simultaneously detect multiple serotypes (initially 13, now up to 24).[237,238] UAD captures serotype-specific pneumococcal polysaccharides secreted in human urine with serotype-specific monoclonal antibodies. Thus, UAD would more accurately measure VT disease compared to non-serotype-specific *BinaxNow* but limited to included serotypes. Another challenge with the urinary antigen tests is the risk of false positives due to persistence of pneumococcal antigens in the urine weeks after the clinical episode has resolved or following pneumococcal vaccination.[238,239]

1.11.2 Modelling the burden of IPD using pneumococcal carriage prevalence data

IPD surveillance requires the integration of a large team of specialists, including clinicians, laboratory staff, porters, data managers and epidemiologists. It has proven too costly to establish in LMICs. For instance, in The Gambia, setting up a population-based IPD surveillance in a population of <140,000 cost $500,000 with additional annual costs of US$1.3 million for maintenance.[205] Hospital-based surveillance is

less expensive than population-based surveillance, but it is biased by variable access to hospital care.

Consequently, data on IPD incidence are rare in sSA. For instance, in 2006, prior to PCV introduction, only three countries, Kenya, Gambia and Mali, reported population-based IPD estimates.[4] Following the increasing uptake of PCV across sub-Saharan Africa, a few additional countries have reported hospital-based surveillance vaccine impact introduction.[240] Only two countries in sSA (Kenya and Mozambique) have reported the impact of PCV10 on disease (IPD or pneumonia).[72,230,241–243] In Nigeria, no study has assessed the impact of PCV on IPD incidence, except for studies that reported serotypes in a few IPD isolates.[244–246]

An inexpensive alternative to surveillance for IPD is surveillance for pneumococcal carriage. Carriage data are more difficult to interpret because of the complex relationship between carriage and disease. However, there are three scientific approaches that can be marshalled to overcome this limitation: dynamic (mathematical) modelling, statistical modelling, and application of the case-carrier ratios (CCRs).

1.11.2.1 Dynamic models

Transmission dynamic models have been used extensively to predict vaccine impact on carriage and IPD.[241,247,248] Due to minor temporal fluctuations, particularly of serotype-specific carriage, collecting several years' worth of data, both pre- and post-vaccine introduction, may be necessary to obtain representative prevalence

estimates.[249] A major advantage of dynamic models is that parameters such as birth rate, serotype-specific force of infection, intra-nasal competition between strains, age-structured contact pattern, waning immunity, and herd immunity can be incorporated to better capture real-life scenarios and inform predictions.[241,247,250] Dynamic models are, therefore, computationally complex and time-consuming to run, and because they are not intuitive, they are not widely understood. Additionally, their reliance on a wide range of parameters undermines the advantage or simplicity of parsimony. Data sources for the input parameters are scarce, and the underlying assumptions required for external data are potentially inappropriate for local epidemiology.

1.11.2.2 Statistical models

Statistical models can also generate evidence that can be used to inform policy. These models are generally simpler, require fewer assumptions and depend on fewer data inputs than transmission dynamic models.

Since the overall population-level impact of vaccination relies substantially on protection against colonisation, changes in the distribution of carriage prevalence of circulating serotypes can be used to predict changes in IPD incidence.[15] It is expected that, following vaccination, a reduction in carriage prevalence of a particular serotype will result in a proportionate reduction in IPD incidence caused by the serotype. A number of models have been suggested, validated, and proposed for use in populations that lack IPD surveillance data.[116,241,251,252]

1.11.2.3 Application of Case-Carrier Ratios (CCRs)

As previously described, the case-carrier ratio (CCR) for any serotype is the ratio of IPD incidence of that serotype to carriage prevalence among healthy individuals of the same serotype within the same population. CCRs give a measure of how invasive a serotype is, given its frequency of colonisation. Findings from studies that show the similarity, across settings, in ranking serotypes based on their invasiveness indicate that CCR is an intrinsic serotype characteristic and, in general, can be comparable.[79,82] Still, host and environmental factors can modify the relationship between carriage and IPD, resulting in variations in the serotype-specific CCR estimates across population subgroups. For instance, variations estimated CCRs may be indicative of differences in the relative serotype distribution in IPD by age and geographic location [83,84] and not necessarily a variation in intrinsic serotype invasiveness. In addition to providing insight into pneumococcal serotype epidemiology, the CCR can be a valuable tool to assess vaccine impact.[77,241,253] When applied to carriage prevalence data, the CCR gives an estimate of the IPD incidence. Thus, in settings that lack IPD surveillance data, CCRs offer a reasonable option to translate carriage prevalence data to IPD incidence. Even though much of the PCV effect is mediated by preventing carriage acquisition and reducing transmission, it is important to note that, in theory, CCR may be affected by vaccination, i.e., individuals who have been vaccinated and are carriers of a VT serotype are less likely to develop disease than individuals who have been unvaccinated and are carriers of that same serotype.

Relying on the premise that the cross-cutting determinant of invasiveness is a characteristic of the pneumococcal capsule, i.e., the serotype, and that the influence of other factors on invasiveness can be measured, CCRs estimated from similar settings ca be applied to carriage prevalence data to estimate IPD incidence and vaccine impact. CCR estimates can be adjusted to account for the effect of other factors, such as age and sensitivity of the IPD surveillance from which CCRs were calculated. Alternatively, stratified CCRs can be calculated and applied as was done in previous meta-analysis.[82,253]

2 Study Rationale and Objectives

2.1 Study rationale

To generate evidence of vaccine impact in the absence of IPD data, nasopharyngeal carriage studies and statistical/mathematical models have been proposed as an alternative. Nasopharyngeal pneumococcal colonisation is more frequent compared to pneumococcal disease, and carriage prevalence studies are less expensive than invasive disease surveillance. Methods for obtaining nasopharyngeal swabs; transporting and storing samples; culturing isolates; and serotyping have also been standardised to reduce study variability and to facilitate unbiased interpretations.[254] Statistical models that utilise changes in carriage with reasonable assumptions to estimate vaccine impact on IPD have been developed and validated in both high and low-income settings.[86,116,251]

The intended purpose of this study was to generate local evidence of vaccine impact to guide vaccine policy in Nigeria. In vaccine impact studies, disease endpoints are preferred to non-disease endpoints to guide decision-making. However, because of its high cost, disease surveillance is not a practical option for many LMICs. Therefore, for this PhD, I propose to evaluate the utility of carriage data and statistical models in place of disease end-point data and to measure the costs of treatment of invasive pneumococcal disease to provide evidence of vaccine impact to support decisions in PCV policy in Nigeria.

2.2 Aim & Objectives

2.2.1 Aim

The overall aim of this study is to use vaccine-induced changes in pneumococcal carriage prevalence to assess the impact of PCV10 introduction in Nigeria.

2.2.2 Specific Objectives

1. To estimate the impact of PCV10 introduction against nasopharyngeal carriage of vaccine-serotype (VT) and non-vaccine-serotype (NVT) pneumococci in vaccine-target and non-target populations in rural and urban Nigerian settings
2. To evaluate the applicability of different statistical models of carriage prevalence in estimating the impact of the 10-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in Nigeria
3. To assess the economic cost of treating IPD among children aged < 5 years in Nigeria.

2.3 Structure of the Thesis

The thesis is divided into chapters based on the specific objectives in a 'research paper' style. The methodology for each study is presented in the respective chapter.

In **Chapter 1,** I have given an overview of the epidemiology of pneumococcal disease and carriage, relationship between carriage and disease, economic burden of IPD, impact of PCV and options for PCV impact assessment. In **Chapter 2,** I have provided a justification for the study and thesis aim, objectives, and structure. In **Chapter 3**, I have presented the manuscript for Objective 1 of the thesis and reported the

population-level impact of introduction of PCV10 on pneumococcal carriage in a rural and urban setting in Nigeria. In **Chapter 4**, I have presented the manuscript for Objective 2 of the thesis. In this manuscript I have evaluated statistical models of carriage prevalence and their predictions for PCV10 impact on IPD, using carriage prevalence data collected in Nigeria. In **Chapter 5**, I have presented the manuscript for Objective 3 of the thesis which reports the economic costs of treatment of IPD among children aged <5 years. In **Chapter 6**, I have synthesised the findings and discuss their implications, as well as the strengths and limitations of the methodology, and areas of further research.

3 The impact of the introduction of the 10-valent pneumococcal conjugate vaccine on pneumococcal carriage in Nigeria (PhD Objective 1)

3.1 Preamble

In this chapter I present the findings of the serial carriage and vaccine coverage surveys I conducted during my PhD. Between 2017 and 2020 I conducted seven carriage and five PCV10 coverage surveys in the post-PCV period. The surveys were conducted in the sites the baseline surveys were conducted. I compare the changes in carriage at the population level – vaccine-target (children aged <5 years) and non-vaccine target (persons ≥5 years) and explore the relationship between PCV10 coverage and population-level changes in VT carriage.

I have presented a poster from this analysis at the following conference:

12th International Symposium on Pneumococci and Pneumococcal Diseases, 19th-23rd June 2022.

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SECTION A – Student Details

Student ID Number	382943	**Title**	Dr
First Name(s)	Aishatu		
Surname/Family Name	Adamu		
Thesis Title	Assessing the impact of a 10-valent pneumococcal conjugate vaccine (PCV10) in the absence of pneumococcal disease surveillance data in Nigeria		
Primary Supervisor	Prof. Anthony Scott		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Nature Communications		
When was the work published?	April 2023		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Yes

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Where is the work intended to be published?	

Please list the paper's authors in the intended authorship order:	
Stage of publication	**Published**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I together with IA Adetifa and JAG Scott designed the carriage and coverage surveys. I participated in obtaining study IRB approvals. I led and coordinated the fieldwork and sample and data collection. I participated in coordinating sample transport logistics. I conducted data cleaning and analysis with input from IA Adetifa, JAG Scott and J Ojal. I wrote first draft of the manuscript. I incorporated suggestions from peer review and responded to reviewers' comments with input from IA Adetifa and JAG Scott.

SECTION E

Student Signature	
Date	24/06/2022

Supervisor Signature	
Date	22/02/2024

3.2 Author contributions

I, together with IA Adetifa and JAG Scott designed the carriage and coverage surveys. I participated in obtaining study IRB approvals. D Akech led the survey preparation logistics. I led and coordinated the fieldwork and sample and data collection. I participated in coordinating sample transport logistics. A Karani led the laboratory analysis and sample storage. I conducted data cleaning and analysis with input from IA Adetifa, JAG Scott and J Ojal. I wrote first draft of the manuscript. I incorporated suggestions from peer review and responded to reviewers' comments with input from IA Adetifa and JAG Scott. All authors approved the original and reviewed versions of the manuscript before submission.

3.3 Title page

The impact of the introduction of the 10-valent pneumococcal conjugate vaccine on pneumococcal carriage in Nigeria

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3.4 Abstract

Pneumococcal conjugate vaccines (PCVs) protect against invasive pneumococcal disease (IPD) among vaccinees. However, at population level, this protection is driven by indirect effects. PCVs prevent nasopharyngeal acquisition of vaccine-serotype (VT) pneumococci, reducing onward transmission. Each disease episode is preceded by infection from a carrier, so vaccine impacts on carriage provide a minimum estimate of disease reduction in settings lacking expensive IPD surveillance. We documented carriage prevalence and vaccine coverage in two settings in Nigeria annually (2016-2020) following PCV10 introduction in 2016. Among 4,684 rural participants, VT carriage prevalence fell from 21% to 12% as childhood (<5 years) vaccine coverage rose from 7% to 84%. Among 2,135 urban participants, VT carriage prevalence fell from 16% to 9% as uptake rose from 15% to 94%. Within these ranges, carriage prevalence declined with uptake. Increasing PCV10 coverage reduced pneumococcal infection at all ages, implying at least a comparable reduction in IPD.

3.5 Introduction

In 2015, pneumococcal disease was estimated to cause approximately 300,000 deaths globally among children aged 1-59 months. Over 50% of these deaths occurred in Africa, and Nigeria alone accounted for nearly 50,000 of these pneumococcal deaths.[3] Between 2014 and 2016, in three geographically distinct phases, Nigeria introduced the 10-valent Pneumococcal Conjugate Vaccine (PCV10) in a three-dose schedule for infants aged 6, 10 and 14 weeks, without a catch-up campaign. Although PCV is the most expensive vaccine programme in the Nigerian portfolio, the country could not evaluate the impact of the vaccine programme on invasive disease or pneumonia due to lack of surveillance data.

Every episode of pneumococcal disease is preceded by infection from another infected person, normally a nasopharyngeal carrier.[15] Young children are the main reservoirs for carriage and have the highest number of effective contacts.[255,256] Consequently, a reduction in carriage prevalence among young children is likely to reduce onward transmission and the incidence of disease proportionately across the population. Among vaccinated children, PCVs provide direct protection against both acquiring carriage and progressing to invasive disease following carriage of vaccine-serotypes (VTs).[15] At the population level, PCVs provide indirect protection, regardless of vaccine status, by reducing everyone's exposure to new infections from VTs. This indirect effect is driven by the direct protection against carriage among vaccinees.[74,180] As vaccine coverage increases, VT carriage prevalence declines linearly due to direct protection among vaccinees and non-linearly due to indirect

protection from the consequences of reduced VT transmission in the whole population.[15,74]

In real-world settings, the indirect effects of PCVs account for most of the vaccine programme impact.[15,162] Consequently, some countries have tailored their PCV schedules to maximise indirect effects of a booster dose at the expense of marginal direct effects of additional primary doses in infancy. For example, in the UK, population protection is being achieved with only a single dose in infancy and a booster dose at 12 months.[178] A disadvantage of PCV introduction is replacement carriage by non-vaccine serotypes (NVTs) leading, to a varying extent, to serotype replacement disease.[159,191] However, in most settings, any increase in serotype replacement disease is small compared to the reduction in vaccine-type disease because non-vaccine types are generally less invasive.[159]

In the absence of robust IPD surveillance and given the strong anticipation of indirect protection following PCV10 introduction, we set out to evaluate the impact of the Nigerian PCV programme using carriage prevalence as an endpoint.[257] In Nigeria, among children aged <5 years who were studied immediately after PCV10 introduction, from a rural and an urban setting, VT pneumococci accounted for 52% and 64% of all carriage, respectively.[258] We conducted annual carriage and vaccination coverage surveys in these same two sites, for four years following PCV10 introduction. We assessed changes in the prevalence of overall carriage (i.e. all pneumococci), and VT and NVT carriage separately and explored the relationship between changes in vaccination uptake and changes in VT carriage prevalence.

3.6 Methods

3.6.1 Study design and participants

We conducted annual cross-sectional carriage surveys in Kumbotso, Kano State and Pakoto, Ogun State (Figure 3.1). The sites were purposively selected to represent a rural and urban setting, respectively. We did four surveys (2017-2020) in the rural site and three (2018-2020) in the urban site. PCV10 was introduced in Kumbotso in July 2016 and in Pakoto in October 2016 with a schedule of three primary doses (3p+0) at ages 6, 10 and 14 weeks and no booster. There was no formal catch-up campaign for children aged ≥12 months. From 2018 onwards, we conducted annual vaccine coverage surveys in both sites simultaneously with all carriage surveys. The target population for the carriage and vaccine coverage surveys was defined as residents living within 10km of the Kumbotso and Pakoto Comprehensive Primary Health Care Centres, respectively. Baseline carriage surveys were conducted in December 2016 (rural) and February 2017 (urban), four to five months after PCV10 was introduced, and have already been published.[258] They are included in this analysis as the reference baseline.

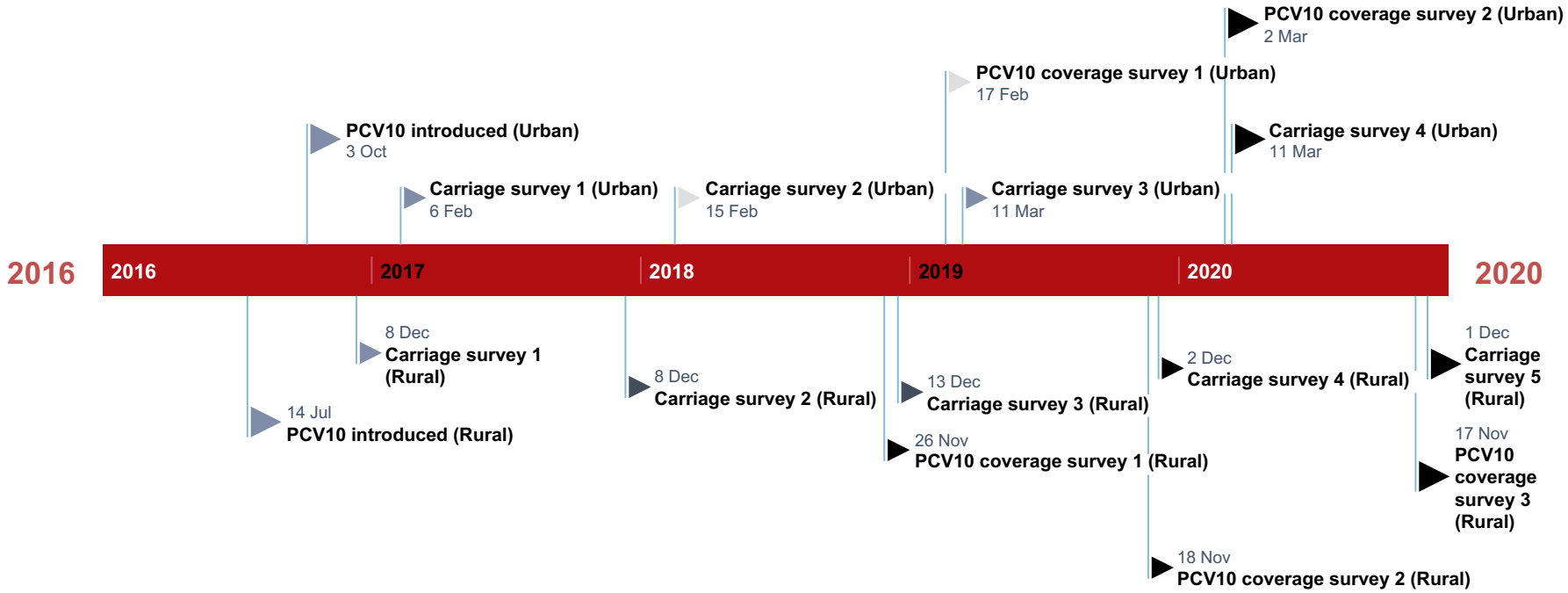


Figure 3.1: Timelines for surveys in the two sites.

Carriage surveys were seasonally restricted at each site; November/December for four years (2017-2020) in the rural site and February/March for three years (2018-2020) in the urban site (Figure 3.1). Carriage surveys targeted all ages, and each annual sample was independent of all other samples. PCV10 coverage surveys targeted children aged <5 years who were age-eligible to have received PCV10 at the date of the baseline carriage survey. Each annual PCV10 coverage sample was selected independently of prior samples.

Having selected representative study areas, we used a two-stage sampling design. In the first stage, we selected households using simple random sampling. To obtain a sampling frame, we conducted a census of all households in the catchment area before each survey. We selected separate samples of households for the carriage and PCV10 coverage surveys. If the household was known to be occupied, but there was no one at home, we revisited it later. If the house was non-residential, unoccupied, or empty, we chose the next household on the list.

In the second stage of sampling for the carriage surveys, we randomly selected one participant per household drawn from a specific age-stratum. We recruited participants in ten age strata (<1, 1-2, 3-4, 5-9, 10-14, 15-19, 20-39, 40-49, 50-59, and ≥ 60 years), starting with the lowest and moving upwards, from household to household, until we had recruited one participant per age group and then we restarted the process. If there was no participant in a particular age group in the household or if the targeted individual declined to participate, we selected the next age group in sequence and then looked for the missed age group in the next household.

The baseline surveys sampled the same defined catchment areas at all ages using a convenience sample of volunteers, recruited at the two health centres, recruited by community outreach [258]. For the baseline carriage surveys (2016/2017)[258], the sample size was set at 1000 participants to achieve a desired precision; given a VT carriage prevalence of 22-26% in this survey, we estimated a prevalence reduction of 50% could be detected with a power of 0.90 if the follow-up surveys were also 1000 in size. Therefore, we targeted to recruit 100 participants in each of the ten age groups.

In the second stage of sampling for the PCV10 coverage survey, we recruited all eligible children per selected household. A sample size of at least 639 children per site per survey was sufficient to estimate coverage of the second dose of PCV of 50% with a 5% precision (i.e., a coverage of 45-55%), assuming at least two eligible children per household, an intra-class coefficient (ICC) of 0.33 (as recommended by WHO[259]) and an 80% probability of response or participation.[260] Targeting a vaccination coverage of 50% allowed the estimation of the largest possible sample size required.

3.6.2 Procedure

Sociodemographic and clinical information was obtained from carriage survey participants using an interviewer-administered questionnaire. Nasopharyngeal swabbing, transport, storage and culture were done according to WHO-recommended standards.[254] We collected one swab specimen per participant from the posterior wall of the nasopharynx using nylon-tipped flexible flocked swabs (*FloQSwabs*®).

Swabs were transported to the laboratory within 8 hours of collection in skimmed milk-tryptone-glucose-glycerin (STGG) on ice packs in a cold box and were stored at -80°C to -55°C before shipping on dry ice to the KEMRI-Wellcome Trust Research Programme (KWTRP), Kilifi, Kenya. In Kilifi, swabs were stored at -80°C until they were thawed and cultured on blood agar with 5µg/ml gentamicin.

We identified pneumococci by α-haemolysis and optochin sensitivity testing. For optochin-resistant isolates (zone of inhibition <14mm diameter), we used bile solubility testing to confirm *S. pneumoniae*. For serotyping, we selected one colony per plate from the dominant colony morphology. We identified serotypes using latex agglutination confirmed by Quellung Reaction. For isolates with inconclusive serotyping, we confirmed species and serotype by polymerase chain reaction (PCR) for autolysin (*lytA*) and capsular locus genes, respectively.[254]

For the PCV10 coverage survey, we obtained the PCV10 vaccination status of each child in the household, including doses and dates received from the vaccination cards or caregiver recall, through household interviews of caregivers.

3.6.3 Statistical analysis

3.6.3.1 Carriage surveys

We calculated the total (all ages) and age-stratified prevalence of overall carriage (all pneumococci), VT pneumococci, and NVT pneumococci for each survey year. Vaccine serotypes (VT) were those contained in the vaccine introduced locally (PCV10 – serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F). Any other serotype, including non-typeable isolates, was classified as NVT. We recalculated VT prevalence for four

other commercially-licensed PCVs. We standardised crude prevalence estimates to the population age structure of Kumbotso (for rural) and Ifo and Ado-Ota (for urban) Local Government Areas (LGAs). These were obtained from 2019 population models of the 2016 Nigerian census data.[261]

We assessed changes in carriage prevalence across the survey years using Chi-square test for trend. To derive prevalence ratios (PRs) comparing the last survey with the first, we modelled carriage prevalence using log-binomial regression or Poisson regression with robust standard errors when the models failed to converge. We adjusted PRs for exposure variables independently associated with carriage and survey year at $p < 0.1$ which included: living with children aged <5 years and a history of cough and runny nose in the preceding two weeks. We also adjusted for the stratified sampling method by (probability) weighting age-specific PRs by the local population age structure, as above, obtained from the Nigerian census data.[261] We calculated PRs for the total population (all ages), for children aged <5 years and for persons aged ≥5 years.

3.6.3.2 Vaccination coverage surveys

The purpose of the coverage survey was to infer population immunity, not to evaluate programme effectiveness. Therefore, we estimated PCV10 coverage in each survey year (2018-2020) as the proportion of children aged <5 years (regardless of age-eligibility) who received two doses of PCV10 irrespective of timing and age of receipt. In addition, because we did not conduct PCV10 coverage surveys in the early period (2016-2017), we used a birth cohort analysis to estimate the PCV10 coverage of children aged <5 years retrospectively from the data collected in 2018-2020.

3.6.4 Relationship between PCV10 coverage and VT carriage

Within the range of vaccine coverage observed, we analysed a simple ecological association between population-level PCV10 coverage in children aged <5 years and VT carriage, in both children aged <5 years and persons aged ≥5 years, using linear regression. We considered a non-linear relationship between PCV10 coverage and VT carriage using a log-linear model and compared the fit of linear to the log-linear model graphically. We also examined this non-linear relationship by comparing the models using the Akaike Information Criterion (AIC). A lower value of AIC is a better fit model. To allow direct comparison of AIC values from the linear and log-transformed model, we adjusted the AIC of the log-linear model by adding the following quantity[262]:

$$2 \times \text{sum}(\log(\text{VT carriage})) \qquad [3.1]$$

We did all the analysis separately for each site with Stata® version 15.1(College Station, Texas, United States).

Sensitivity analysis

In a sensitivity analysis, we compare vaccine coverage estimated using 1) card alone among cardholders; 2) card alone among all children; and 3) card plus caregiver recall (card+history). We also assess the relationship between VT carriage prevalence and PCV10 coverage among under-fives assessed using the three approaches.

Ethics

Written informed consent was obtained from participants/guardians. Ethics approval for study was granted by the Research Ethics Committees of Aminu Kano Teaching Hospital (NHREC/21/08/2008/AKTH/EC/2165), Kano State Ministry of Health (MOH/OFF/797/T.I/596), Lagos University Teaching Hospital (ADM/DCST/HREC/APP/10300); the Kenya Medical Research Institute's Scientific and Ethical Review Unit (SERU 3350); and by the London School of Hygiene and Tropical Medicine Observational/Interventions Research Ethics Committee (Ref 11670).

3.7 Results

Including the baseline survey, reported above,[258] we conducted five annual carriage surveys in the rural and four in the urban sites (Figure 3.1) and recruited 4,684 and 3,653 participants, respectively. In the rural and urban sites, the proportion of eligible residents who consented to participate varied from 60-98% and 63-99%, respectively, across the sampling age groups and surveys (Supplementary Fig. 3.1 and Supplementary Table. 3.1).

Participants in the rural site resided in larger households and more commonly reported living with ≥2 children aged <5 years, using solid fuel for cooking, and having a cough or runny nose in the preceding two weeks compared to their counterparts in the urban site (Table 3.1).

Table 3.1: Background characteristics of study participants of the carriage surveys

	N (%)	N (%)	N (%)	N (%)	N (%)
Kumbotso (rural)					
	Survey 1 (2016)	**Survey 2 (2017)**	**Survey 3 (2018)**	**Survey 4 (2019)**	**Survey 5 (2020)**
Total sample	878	879	999	973	954
Clinical history[1]					
Runny nose	714 (81%)	681 (77%)	900 (90%)	843 (87%)	727 (76%)
Cough	450 (51%)	551 (63%)	687 (69%)	558 (57%)	487 (51%)
Antibiotic use	65 (7%)	431 (49%)	510 (51%)	233 (24%)	202 (21%)
Household composition					
Living with ≥2 aged <5 years	645 (73%)	469 (53%)	555 (56%)	619 (64%)	748 (78%)
Sharing bed with ≥2 persons	729 (83%)	704 (80%)	882 (88%)	795 (82%)	857 (90%)
Household cooking fuel					
Solid fuel	833 (95%)	795 (90%)	959 (96%)	892 (92%)	850 (89%)
Gas	12 (1%)	19 (2%)	18 (2%)	38 (4%)	51 (5%)
Kerosene	16 (2%)	18 (2%)	5 (0.5%)	66 (0.6%)	3 (0.3%)
Others	17 (2%)	47 (5%)	17 (2%)	40 (4%)	46 (5%)
Household size[2]					
All persons, median (IQR)	9 (7-13)	6 (3-10)	6 (4-9)	8 (6-10)	9 (7-12)
Pakoto (urban)					
	Survey 1 (2017)	**Survey 2 (2018)**	**Survey 3 (2019)**	**Survey 4 (2020)**	
Total sample	924	943	932	854	N/A
Clinical history[1]					
Runny nose	238 (26%)	163 (17%)	106 (11%)	51 (6%)	N/A
Cough	216 (23%)	122 (13%)	75 (8%)	32 (4%)	N/A
Antibiotic use	145 (16%)	76 (8%)	39 (4%)	10 (1%)	N/A
Household composition					
Living with ≥2 aged <5 years	95 (10%)	81 (9%)	69 (7%)	53 (6%)	N/A
Sharing bed with ≥2 persons	185 (20%)	212 (23%)	121 (13%)	121 (14%)	N/A
Household cooking fuel					
Solid fuel	58 (6%)	38 (4%)	35 (4%)	11 (1%)	N/A
Gas	326 (35%)	584 (62%)	713 (76%)	775 (91%)	N/A
Kerosene	515 (56%)	238 (25%)	155 (17%)	29 (3%)	N/A
Others	25 (3%)	83 (8%)	29 (3%)	39(5%)	N/A
Household size[2]					
All persons, median (IQR)	4 (3-5)	5 (4-6)	5 (4-6)	5 (4-6)	N/A

[1] History of any of the symptoms in the two weeks preceding the interview date
[2] Including the participant

3.7.1 Carriage prevalence

Table 2 shows the crude and age-standardised carriage prevalence stratified by survey. Among the age-standardised results, overall pneumococcal carriage prevalence was consistently high across all ages in all surveys at the rural site. At both sites, overall pneumococcal carriage prevalence and NVT carriage prevalence were higher in children aged <5 years compared to persons aged ≥5 years; VT carriage prevalence was also higher in children aged <5 years in the baseline surveys at both sites. The crude carriage prevalence (by sampled ages) is also illustrated in Supplementary Fig. 2.

3.7.2 Changes in carriage prevalence

Overall carriage prevalence in the total population (all ages combined) remained unchanged across the surveys, in both settings (Tables 3.2 and 3.3). However, in the rural site (Table 3.2), overall carriage prevalence increased significantly among persons aged ≥5 years (Chi-squared test for trend, p =0·004), and in the urban site (Table 3.3), overall carriage prevalence declined significantly among children <5 years (Chi-squared test for trend, p <0·0001).

Table 3.2: Crude and age-standardised* prevalence (and 95% CI) of overall, non-vaccine serotype (NVT) and vaccine serotype (VT) pneumococcal carriage stratified by age group and survey in the rural site.

			Overall carriage		VT carriage		NVT carriage	
	Survey	N	Crude	Age-standardised	Crude	Age-standardised	Crude	Age-standardised
				Kumbotso (rural)				
All ages								
	Survey 1 (2016)	872	74 (71-77)	68 (65-71)	26 (22-28)	21 (18-24)	48 (45-52)	47 (43-51)
	Survey 2 (2017)	879	74 (71-77)	71 (67-74)	18 (16-21)	16 (14-19)	55 (52-59)	54 (51-58)
	Survey 3 (2018)	999	77 (74-80)	77 (74-79)	16 (14-19)	16 (13-18)	60 (57-64)	61 (58-64)
	Survey 4 (2019)	976	77 (74-79)	74 (71-77)	15 (13-17)	13 (11-15)	61 (59-65)	60 (57-64)
	Survey 5 (2020)	953	78 (75-80)	74 (71-77)	14 (12-17)	12 (10-14)	63 (61-67)	61 (58-65)
<5 years								
	Survey 1 (2016)	296	92 (88-94)	91 (88-94)	42 (37-48)	41 (35-46)	50 (44-56)	50 (45-56)
	Survey 2 (2017)	264	93 (89-95)	92 (89-96)	30 (25-36)	30 (25-36)	63 (57-68)	62 (56-68)
	Survey 3 (2018)	304	93 (89-95)	92 (90-95)	25 (21-30)	25 (20-30)	68 (62-73)	67 (62-72)
	Survey 4 (2019)	365	91 (88-94)	91 (88-94)	21 (17-26)	22 (17-26)	70 (65-75)	69 (64-74)
	Survey 5 (2020)	333	89 (85-92)	88 (84-91)	22 (18-27)	22 (18-27)	67 (61-72)	65 (60-71)
>5 years								
	Survey 1 (2016)	576	65 (60-68)	62 (58-66)	17 (14-20)	16 (13-19)	48 (43-52)	46 (42-50)
	Survey 2 (2017)	615	66 (62-64)	65 (61-69)	13 (11-16)	13 (10-16)	53 (49-56)	52 (48-56)
	Survey 3 (2018)	695	70 (67-74)	73 (69-76)	13 (10-15)	13 (11-16)	57 (54-61)	59 (55-63)
	Survey 4 (2019)	611	68 (64-71)	69 (66-73)	11 (9-14)	11 (9-14)	57 (53-61)	58 (54-62)
	Survey 5 (2020)	620	72 (69-76)	70 (66-74)	10 (8-13)	9 (7-11)	62 (58-66)	61 (57-64)

* Standardised using the respective population structures of the two study sites taken from population models of the Nigerian census[261]

Table 3.3: Crude and age-standardised* prevalence of overall, non-vaccine serotype (NVT) and vaccine serotype (VT) pneumococcal carriage stratified by age group and survey in the urban site.

			Overall carriage		VT carriage		NVT carriage	
	Survey	**N**	**Crude**	**Age-standardised**	**Crude**	**Age-standardised**	**Crude**	**Age-standardised**
					Pakoto (urban)			
All ages								
	Survey 1 (2017)	919	50 (47-53)	40 (36-43)	22 (19-24)	16 (13-18)	29 (25-31)	24 (21-27)
	Survey 2 (2018)	941	52 (49-55)	51 (47-54)	15 (13-18)	14 (12-17)	37 (34-40)	36 (33-39)
	Survey 3 (2019)	932	47 (44-50)	44 (41-48)	12 (10-14)	11 (9-14)	35 (32-38)	33 (30-36)
	Survey 4 (2020)	851	40 (36-43)	39 (36-42)	9 (7-11)	9 (6-10)	31 (28-34)	31 (28-34)
<5 years								
	Survey 1 (2017)	335	78 (73-82)	77 (72-81)	38 (33-43)	36 (31-42)	40 (35-45)	40 (35-45)
	Survey 2 (2018)	244	70 (64-76)	70 (65-76)	23 (18-29)	23 (18-29)	47 (41-53)	47 (41-54)
	Survey 3 (2019)	243	70 (64-75)	69 (63-75)	19 (15-25)	19 (14-24)	51 (44-57)	50 (43-56)
	Survey 4 (2020)	185	52 (45-59)	53 (46-61)	12 (8-17)	12 (7-17)	40 (33-47)	41 (34-49)
≥5 years								
	Survey 1 (2017)	584	34 (31-38)	32 (28-36)	13 (10-15)	12 (9-15)	22 (19-25)	20 (17-24)
	Survey 2 (2018)	697	46 (42-50)	47 (43-50)	12 (10-15)	13 (10-15)	34 (30-37)	34 (30-38)
	Survey 3 (2019)	689	39 (36-43)	40 (36-43)	9 (7-12)	10 (8-12)	30 (26-33)	29 (26-33)
	Survey 4 (2020)	666	36 (33-40)	36 (33-39)	8 (6-10)	7 (5-9)	29 (25-32)	29 (25-32)

* Standardised using the respective population structures of the two study sites taken from population models of the Nigerian census [261]

In the total population VT carriage prevalence steadily declined from 21% to 12% (Chi-squared test for trend, p <0·001) in the rural site and from 16% to 9% (Chi-squared test for trend, p <0·001) in the urban site. Among the total population sample, there was a significant trend for an increase in NVT carriage over the survey years in the rural site (Chi squared test for trend p<0.001) and but not in the urban site (Chi squared test for trend p =0.36).

For both age groups, VT carriage declined significantly across surveys in at each site (Chi-squared test for trend, p <0·001 for all 4 trends). NVT carriage prevalence increased significantly in both age groups across surveys but only at the rural site (Chi-squared test for trend, p <0·001).

Compared to the baseline survey, the adjusted age-standardised PR for VT carriage prevalence in the final survey was 0.52 and 0.53 (Table 3.4) among children <5 years and older persons, respectively, in Kumbotso (rural). The adjusted PRs were 0.31 and 0.60 among children <5 years and older persons, respectively, in Pakoto (urban). NVT carriage increased significantly in both age groups in Kumbotso, with adjusted PRs of 1.34 and 1.26 in children aged <5 years and persons ≥5 years, respectively. In Pakoto, serotype replacement carriage was significant only in those aged ≥5 years (adjusted PR 1.36, Table 3.4).

Table 3.4: Prevalence ratios (PR), and 95% CI, showing changes in overall, non-vaccine serotype (NVT), and vaccine serotype (VT) carriage stratified by age and site.

	Overall carriage		**VT carriage**		**NVT carriage**	
	Crude PR	**Adjusted age-standardised PR[1]**	**Crude PR**	**Adjusted age-standardised PR[1]**	**Crude PR**	**Adjusted age-standardised PR[1]**
	PR for carriage in the final survey compared to the baseline survey[2]					
Kumbotso (rural)[3]						
All ages	1·06 (1·00-1·11)	1·00 (0·95-1·05)	0·55 (0·45-0·67)	0·52 (0·43-0·64)	1·32 (1·22-1·44)	1·30 (1·19-1·42)
<5 years	0·97 (0·82-1·14)	0·97 (0·92-1·02)	0·52 (0·41-0·67)	0·52 (0·41-0·67)	1·34 (1·17-1·54)	1·34 (1·17-1·54)
≥5 years	1·12 (0·97-1·28)	1·06 (0·97-1·14)	0·58 (0·43-0·78)	0·53 (0·39-0·72)	1·31 (1·18-1·46)	1·26 (1·12-1·40)
Pakoto (urban)[4]						
All ages	0·79 (0·71-0·88)	0·72 (0·65-0·80)	0·40 (0·31-0·51)	0·34 (0·26-0·45)	1·09 (0·95-1·26)	1·03 (0·89-1·20)
<5 years	0·67 (0·58-0·78)	0·68 (0·58-0·79)	0·32 (0·21-0·48)	0·31 (0·20-0·48)	1·01 (0·81-1·25)	1·02 (0·82-1·28)
≥5 years	1·05 (0·91-1·22)	1·07 (0·90-1·28)	0·61 (0·44-0·86)	0·60 (0·41-0·87)	1·30 (1·07-1·58)	1·36 (1·10-1·69)

[1] adjusted for symptoms of upper respiratory tract infection in past two weeks, living with≥2 children aged <5 years, and age-standardised to the respective age distribution of study sites; [2] PR=prevalence ratios comparing each survey compared to the baseline (first) survey; [3] Five surveys (2016-2020); [4] Four surveys (2017-2020).

For children aged <5 years, the individual serotypes with the highest age-standardised prevalence in the final surveys were 6A (11·4%), 19F (5·5%) and 19A (5·4%), 11A (4·7%), 14, (4.4%) 16F (4·4%), and 23F (3·7%) in the rural site (Figure 3.2 and Supplementary Table 3.2); and 19A (7·4%), 15B (4·6%), 6B (4·0%), 19F (3·9%), and 16F (3·7%) in the urban site (Figure 3.2 and Supplementary Table 3.3). Among persons aged ≥5 years, in the rural site (Supplementary Table 3.4), the most prevalent serotypes in the final surveys were 3, 34, 11A, 16F and 10A; in the urban site, the most prevalent serotypes were 11A, 3, 19A, 4, 23B and 38 (Figure 3.2 and (Supplementary Table 3.5).

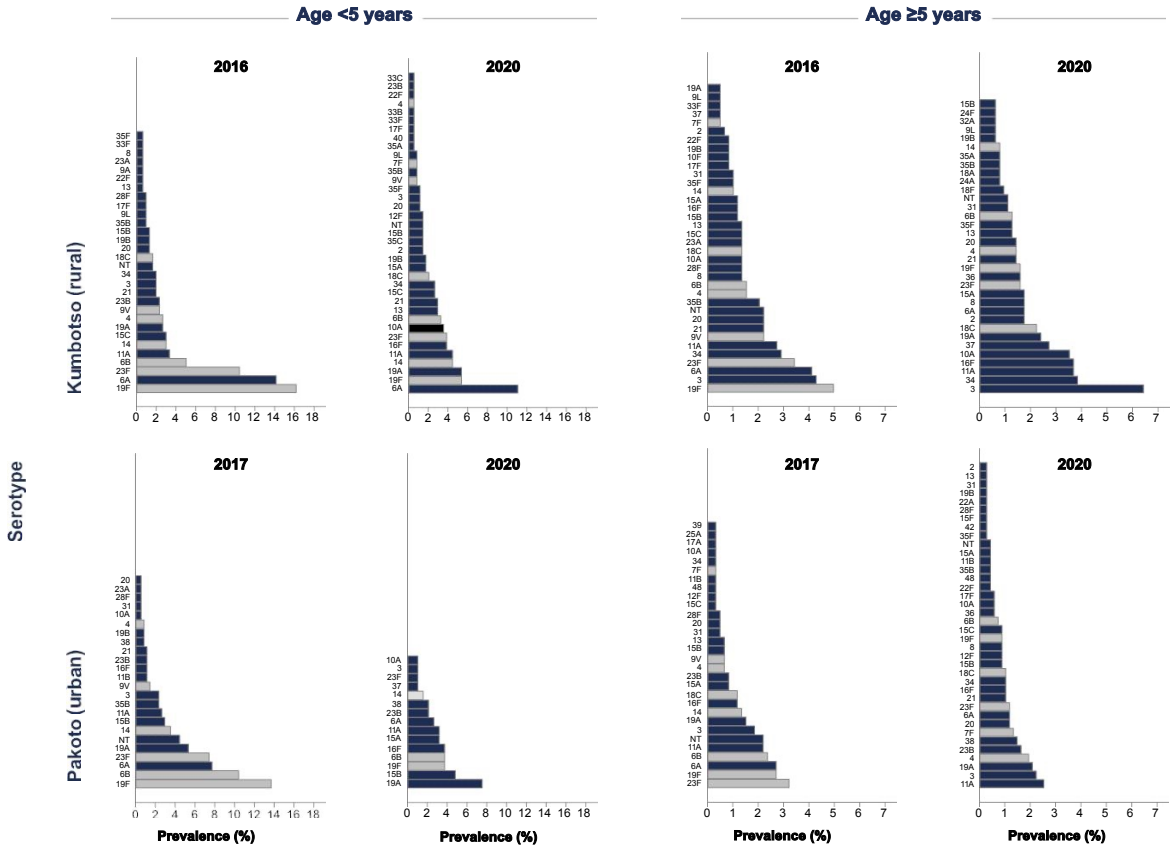


Figure 3.2: Distribution and ranking of serotypes in carriage (serotypes with >1 isolate) among children aged <5 years and persons ≥5 years by vaccine-type (grey bars – vaccine-serotypes, blue bars – non-vaccine serotypes) in the baseline and final surveys.

Note the differences in scale in graphs by age.

In the rural site (Supplementary Tables 3.2 and 3.4), significantly increased prevalence odds (final vs baseline survey) were observed for serotypes 16F (OR 12.6) and 10A (11.6), among children aged <5 years, and for serotypes 19A (4.4), 16F (2.9), 10A (2.4), and 37(5.0) for persons aged ≥5 years. In the urban site ("Supplementary Tables 3 and 5"), NVT replacement was significant for serotypes 19A (OR 2.3), 15B (2.6) and 16F (5.0) in children aged <5 years; there was no significant increases in individual NVTs among persons aged ≥5 years.

We compared the carriage prevalence of serotypes included in different PCV formulations (Supplementary Table 3.7) in the final survey among children <5 years old. The total carriage prevalence of all serotypes contained in the Serum Institute of India 10-valent PCV (SII-PCV), 13-valent PCV (PCV13), 15-valent PCV (PCV15) and 20-valent PCV (PCV20) were 54%, 61%, 62%, and 68%, respectively, in the rural site and 50%, 53%, 53%, and 60%, respectively, in the urban site.

3.7.3 PCV10 vaccine coverage

We assessed the PCV10 vaccination status of 2,165 children (aged <5 years) in the rural site and 1,313 children in the urban site. We accepted either written evidence of vaccination or the caregiver's recall. The average proportion of children for whom the caregivers had retained their vaccination card was 70% in the rural site (52% in 2018; 77% in 2019; and 90% in 2020) and 80% in the urban site (70% in 2019 and 91% in 2020). Figure 3.3A shows the annual proportions of children aged <5 years who had received at least two doses of PCV10. PCV10 coverage (≥2 doses) increased

steadily from 7% in 2016 to 84% in 2020, in the rural site; and from 15% in 2017 to 94% in 2020, in the urban site.

3.7.4 Relationship between PCV10 coverage and VT carriage

Within the range of PCV10 coverage observed in children, the ecological relationship between PCV10 coverage and the prevalence of VT carriage (Figure 3.3B) shows a linear decline for older persons aged ≥5 years in both settings (gradient -0.09 (95% CI -0.13- -0.04) in Kumbotso; -0.07 (95% CI -0.10- -0.04) in Pakoto. For children aged <5 years, a log-linear model had a better fit to the data (Supplementary Fig. 3.3) which show a steep decline in VT carriage prevalence associated with a small increase in PCV coverage towards 20% followed by slower gains as coverage increases further.

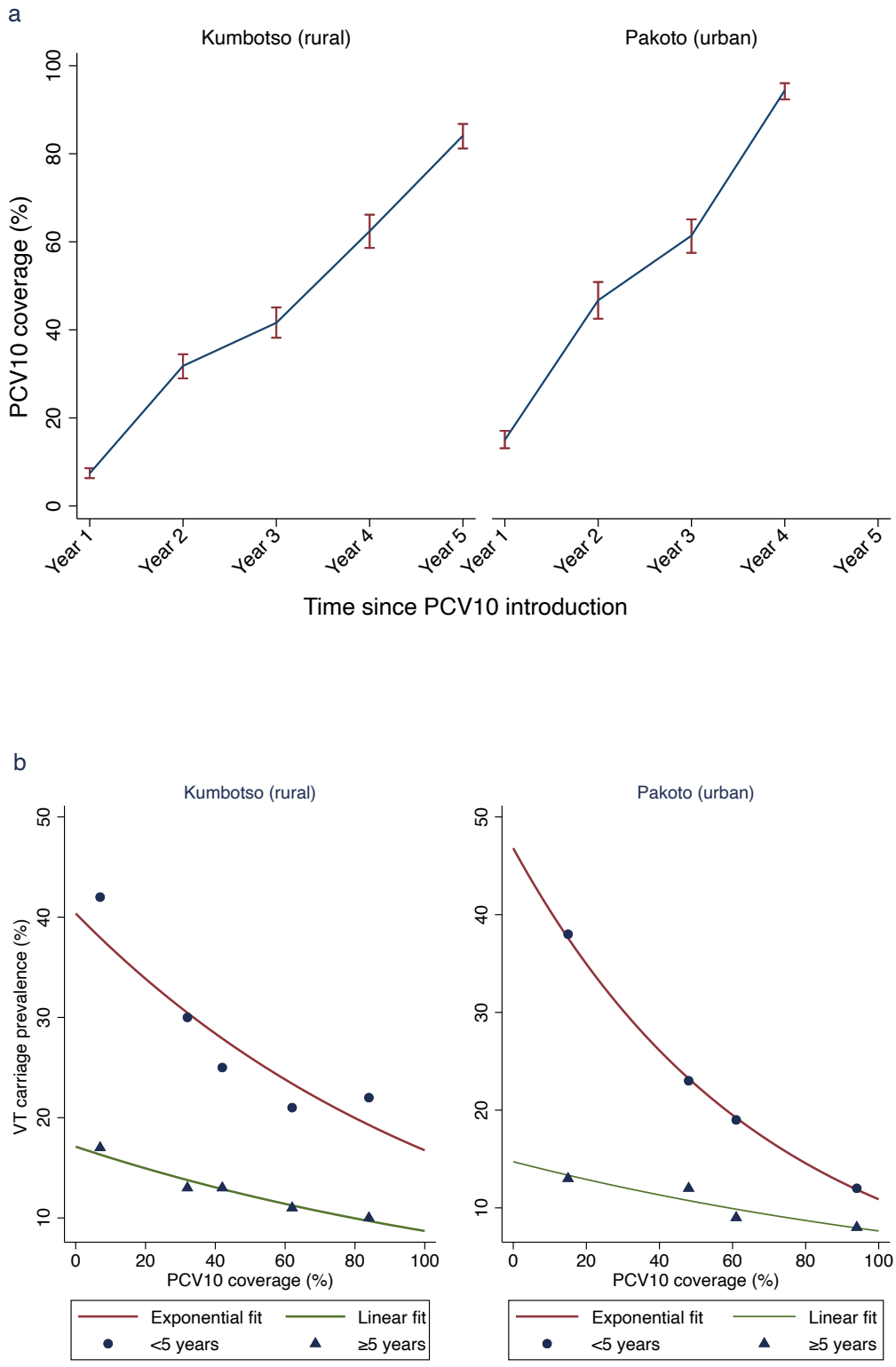


Figure 3.3: Annual Coverage of two doses of PCV10 among children aged <5 years and Relationship between Vaccine serotype (VT) carriage prevalence and PCV10 coverage.

3a (top). Annual Coverage of two doses of PCV10 among children aged <5 years.
Year 1 represents the year of PCV10 introduction. PCV10 coverage values for Year 3 to Year 5 were assessed directly among 817, 655 and 693 children in Kumbotso, and for Year 3 and 4 among 652 and 661 children in Pakoto. PCV10 coverage values for Year 1 and Year 2 were estimated using a birth-cohort analysis of children observed during Years 3-5 (among 2,165 and 1140 children in Kumbotso, and 1,313 and 568 children in Pakoto). Error bar = 95% confidence interval CI).
3b (bottom). Relationship between Vaccine serotype (VT) carriage prevalence and PCV10 coverage. Scatter graph of log-linear regression among children aged <5 years and linear regression among persons ≥5 years of VT carriage prevalence against PCV10 coverage for each of the 9 surveys, stratified by age of carrier and shown separately for the Kumbotso (rural) site and Pakoto (urban) site. The lines for children (aged <5 years) are exponential fits (log-linear regression) and the lines for the older persons (age ≥5 years) are arithmetic (linear regression). Values from the log-linear regression among children are exponentiated and shown here on the non-log (arithmetic) scale.

3.7.5 Sensitivity analysis

Including vaccine receipt reported by card only among cardholders, PCV10 coverage (≥2 doses) increased from 8% in 2016 to 92% in 2020 in the rural site and from 14% in 2017 to 96% in 2020 in the urban site (Figure 3.4). Including vaccine receipt by card only among all children assessed, PCV10 coverage increased from 3% to 82% in the rural site and from 4% to 72% in the urban site. PCV10 coverage levels assessed by 'card only' analyses among cardholders were mostly higher than those assessed among all children, regardless of whether the source was card only or card plus history, with some overlap in the confidence intervals for some years. The confidence intervals for PCV10 coverage levels assessed by 'card only' among cardholders and by 'card+history' overlapped for the earlier years where we assessed PCV10 coverage indirectly through birth cohort analysis (Years 1 to 2) in both sites. For the later years that we assessed PCV coverage directly i.e., years 3 to 5), the confidence intervals did not overlap except for the final survey (Year 4) in the urban site.

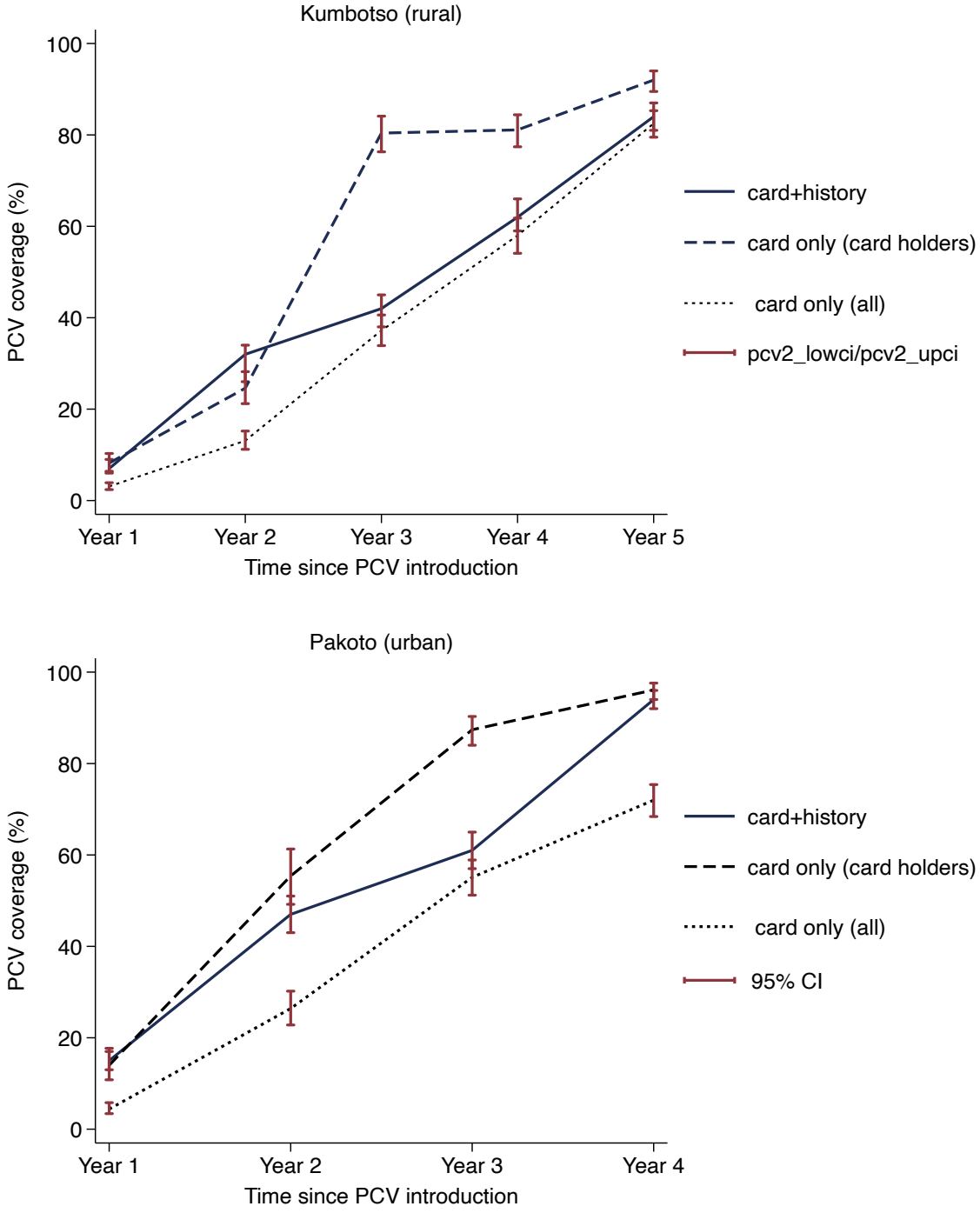


Figure 3.4: Comparison of annual coverage of two doses of PCV10 vaccination coverage among children aged <5 years reported by card+history among all participants (black line), by card only among cardholders (black dash), and by card only among all participants (black dot) in the rural (top) and urban (bottom).

PCV10 coverage values for Year 3 to Year 5 were assessed directly among cardholders (all) in 423 (817), 502 (655), and 622 (693) children in Kumbotso, and for Year 3 and 4 among 453 (652), and 508 (661) children in Pakoto. PCV10 coverage values for Year 1 and Year 2 were estimated using a birth-cohort analysis of children observed during Years 3-5 among cardholders (all) in 816 (2,165) and 606 (1,140) children in Kumbotso, and 421 (1,313) and 271 (568) children in Pakoto). Error bar = 95% confidence interval CI).

Within the range of PCV10 coverage observed in children aged <5 years and persons aged ≥5 years in both sites, we observe a linear decline in VT carriage prevalence with increase in PCV10 coverage measured by card and history (Figure 3.5) by card only among cardholders, and by card only among all children. The confidence intervals of the gradients for the linear relationship were significantly less than the null, except for the relationship in children aged <5 years in the rural site which included the null value for vaccine coverage assessed by card only analysis among all children (Table 3.5) The gradients for the linear regression models were higher for 'card +history' analysis compared to 'card only' analysis among cardholders, but the confidence intervals of the gradients using all three approaches overlapped.

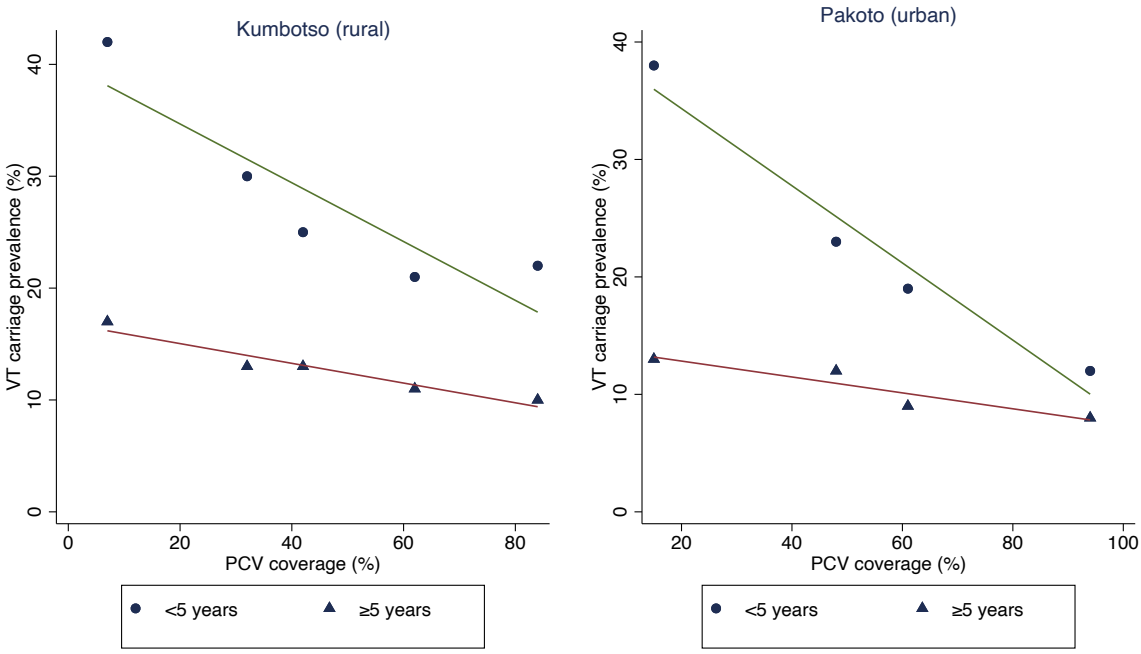


Figure 3.5: Scatter graph of linear regression among persons ≥5 years of VT carriage prevalence against base PCV10 coverage (card+history) for each of the 9 surveys, stratified by age of carrier and shown separately for the Kumbotso (rural) site and Pakoto (urban) site.

Table 3.5: Comparison of Gradients with 95% Confidence Intervals of linear relationship between PCV10 coverage and VT carriage prevalence with PCV10 coverage assessed using card+history analysis, card only analysis among cardholders, and card only analysis among all children stratified by age and site.

PCV coverage assessment approach	<5 years			≥5 years		
	Gradient	95% CI	R-squared	Gradient	95% CI	R-squared
			Rural			
Card+history	-0.26	-0.50,-0.03	0.73	-0.09	-0.13,-0.04	0.93
Card only (cardholders)	-0.21	-0.37,-0.04	0.84	-0.06	-0.13,-0.01	0.77
Card only (all)	-0.22	-0.48, 0.03	0.72	-0.07	-0.14, -0.01	0.8
			Urban			
Card+history	-0.33	-0.54,-0.11	0.8	-0.07	-0.10,-0.04	0.97
Card only (cardholders)	-0.29	-0.48,-0.09	0.96	-0.06	-0.12,-0.02	0.76
Card only (all)	-0.35	-0.67,-0.03	0.91	-0.08	-0.11,-0.04	0.97

3.8 Discussion

The aim of this study was to evaluate the introduction of a new, expensive vaccine programme in Nigeria using an inexpensive proxy measure of impact, vaccine-type nasopharyngeal carriage. Over five years, in a rural setting (Kumbotso) in northern Nigeria, the proportion of children aged <5 years who were vaccinated increased from 7% to 84%. During the same period, the age-standardised population prevalence of VT carriage fell from 21% to 12%, giving an adjusted prevalence ratio of 0.52 or a VT carriage reduction of 48%. Over three years, in an urban setting (Pakoto) in southern Nigeria, the proportion of children vaccinated increased from 15% to 94%. During the same period, the age-standardised population prevalence of VT carriage fell from 16% to 9%, giving an adjusted PR of 0.34 or a reduction in carriage of 66%. In both settings, we observed a decrease in VT carriage prevalence among children and older persons as vaccine coverage among children <5 years accumulated over time. For older persons (aged ≥5 years) this relationship was approximately linear representing a reduction in VT carriage prevalence of 1.4-1.5% for every 20% increase in vaccine coverage among children in the same setting.

Although carriage is only a proxy, we can use it to infer the impact of PCV10 on disease rates in these settings. A reduction in carriage prevalence will produce a proportionate reduction in the number of carriers each person contacts, reducing the incidence of carriage acquisition and the incidence of all pneumococcal diseases commensurately. A reduction in VT carriage prevalence of 66% at all ages in Pakoto is likely to translate into a reduction in the incidence of all VT pneumococcal disease of at least 66% at all ages. This estimate considers only the indirect effect of the

programme, but it is, in itself, a very significant public health gain. Direct effects cannot be estimated from these surveys, but in an individually-randomised controlled trial of PCV9 in The Gambia, vaccine efficacy against VT IPD was 77%.[229] Therefore, even among the 34% of new pneumococcal infections that have not been potentially averted by indirect effects in Pakoto, the risk of developing disease will still be attenuated (by 77%) if the infected child has been vaccinated with PCV10, as most have.

This concept of additional gains from indirect vaccine effects is substantiated by the results from other settings. In Kilifi, Kenya, for example, a 74% decline in VT carriage prevalence among children aged <5 years was associated with a 92% decline in VT IPD in this age group.[72] In Sao Paulo, Brazil, a 91% decline in VT carriage prevalence among toddlers aged 12-23 months was associated with an 83-87% decline in VT IPD in children across the whole age range <5 years.[263,264]

The decline in VT carriage prevalence in Nigeria was accompanied by an increase in NVT carriage prevalence among children in Kumbotso (rural) and among older persons in both settings, with adjusted prevalence ratios of 1.26-1.34. In Kenya, the 74% decline in VT carriage prevalence was accompanied by a 1.71-fold increase in NVT carriage prevalence, though there was no significant rise in serotype replacement disease.[72] Non-vaccine serotypes with high frequency in the final surveys in children <5 years were 6A, 19A, 11A, 15B, and 16F. The first two are contained in the alternative PCV10 manufactured by Serum Institute of India, and 11A and 15B are contained in the PCV20 recently licensed for adult use.[166,265] This NVT distribution suggests that if serotype replacement disease becomes

problematic, it may be controlled by wider valency vaccines. However, the relevance of serotype replacement carriage is dependent on the inherent invasiveness of the serotypes increasing in prevalence[66,81,266] which can only be ascertained from linked studies of carriage and IPD.[72,73,266]

The study findings need to be interpreted in light of several practical constraints. The study began more than four months after PCV10 introduction, and at the baseline survey, an estimated 7%-15% of children aged <5 years had already been vaccinated. Had the baseline survey pre-dated PCV10 introduction, the measured impact may have been larger. The evaluation is a 'before-after' study which is susceptible to confounding by secular trends in VT carriage prevalence. It is difficult to control for this possibility in retrospect. Nonetheless, it is unlikely that secular trends alone could account for so large an effect size on VT carriage. The study design did, however, control for seasonal variation in pneumococcal carriage [267], as the surveys were done at the same time each year.

Vaccination coverage surveys were only introduced in 2018, and we inferred the coverage estimates for young children prior to 2018 from the coverage results among older children. Despite random selection and a study of adequate size, the coverage data contain internal inconsistencies; for example, in Pakoto, the rise in coverage in Year 3 (2019) was >40% and yet only approximately 20% of children aged <5 years were eligible to be vaccinated in that year. This may implicate poor recall of vaccination among caregivers of older children sampled in 2019. Vaccination coverage is notoriously difficult to ascertain.[268] Therefore, the ecological

relationship we observe between coverage and VT carriage in older persons should be interpreted with some caution.

In the absence of vaccine cards, relying on caregiver recall to estimate vaccine coverage may be associated with several biases. Caregivers may report having taken their child for vaccination (but not retaining the card) simply because they believe that this is the response desired by the interviewer (social desirability bias); this would bias vaccine coverage upwards. Conversely, caregivers may experience recall bias, particularly for older children, as they may not fully remember events several years in the past; forgetting a vaccine truly given would bias vaccine coverage downwards.

Although cards are more objective, relying on cards alone to assess vaccine status can also introduce biases, particularly in settings with low vaccine coverage. The primary point of contact for caregivers to receive vaccine cards is when they attend for vaccination. If they do not attend to get their child vaccinated, they will not have a card. Therefore, restricting the analysis to cardholders alone in such settings will exclude truly unvaccinated children from the coverage survey, resulting in an upward bias in vaccine coverage. We believe that relying exclusively on cards will be associated with more extreme biases to the vaccine coverage estimates, while relying on both sources will be associated with a more conservative bias hence, our decision to use both recall and card as valid sources for vaccination status.

Our data shows that a substantial proportion (72% in the rural and 71% in the urban site) of unvaccinated children did not have vaccine cards. Hence, non-vaccination was

more likely reported by caregiver recall than by card. Thus, assessing vaccination status among cardholders alone has excluded the majority of the unvaccinated children, and this has resulted in an upward bias of vaccine coverage. An alternative approach to reduce this bias is to rely on cards as an objective measure of vaccine receipt and include all children assessed in the denominator. This approach resulted in PCV coverage levels lower than estimated using the other two approaches. It has probably underestimated the coverage because, by the third year of PCV10 introduction, the PCV10 coverage using this approach only reached 37% and 55% compared to 42% and 61% using the card+history approach.

In the sensitivity analysis, coverage estimates using card only among cardholders exceeded coverage estimates using card+history by up to 15% in the urban site and 33% in the rural site. For instance, using card alone, a vaccine coverage of 80% and 87% among under-fives will be impossible by the third year of PCV10 introduction. At that point, only 60% of children aged <5 years were eligible for PCV10. Because catch-up was not offered, the highest possibility for coverage was 60%, indicating a bias of at least 1.3-fold in the rural site and 1.4-fold in the urban site.

In the earlier periods, where we inferred PCV10 coverage indirectly through birth cohort analysis, the coverage levels between the two approaches were more similar and had overlapping intervals. Therefore, it is unlikely that there will be a sudden huge difference in coverage between the two approaches in the later years. An annual increase in coverage of >20% will be highly improbable. For instance, using ‘card only’ analysis among cardholders, PCV10 coverage increased between Year 2 and

Year 3 by 55% in the rural site and by 32% in the urban site. This is compared to 10% and 14%, respectively, using ‘card+history ‘ analysis.

Nonetheless, restricting our analysis to cards alone, we still observed an ecological relationship between population-level PCV10 coverage (among children aged <5 years) and VT carriage prevalence among both children aged <5 years and persons aged ≥5 years in both settings. Although the gradient for the relationship was lower than observed for the relationship of coverage assessed using caregiver recall and card, the confidence intervals of the gradients using the three approaches overlapped.

For practical reasons we selected two markedly different sites to represent the broad environmental and socio-demographic differences in Nigeria. However, we do not consider these sites to be wholly representative of all settings in Nigeria. Households in the rural site (Kumbotso) from northern Nigeria were larger, had more children and generally used solid cooking fuel. Households in the urban site (Pakoto) from southern Nigeria were smaller, had substantially fewer children and generally used gas and kerosene for cooking. At baseline, VT carriage prevalence was higher in the rural setting at all ages but, paradoxically, vaccine impact was greater in the urban setting, at least among children <5 years old; adjusted prevalence ratios were 0.52 in Kumbotso and 0.31 in Pakoto. This differential impact may be attributable to the steeper rise in PCV10 coverage among children aged <5 years in Pakoto. Alternatively, the lower density of children in urban households may imply a lower force of infection. A high force of infection has been proposed as an important cause of residual VT carriage in mature vaccine programmes in Africa [269], and in

Kumbotso, VT carriage prevalence reaches its nadir at 22% in years 2019/2020, compared to 9% in Pakoto in 2020.

Hence, the impact of the vaccine on carriage prevalence is likely to be affected by several additional factors; the baseline serotype distribution, age-specific carriage prevalence, demography, the contact patterns of the community, the probability of transmission at each contact and the duration of carriage and of vaccine-induced immunity.[20,270,271] The age structure of the vaccinated population is also influential; for example, a catch-up campaign for children aged <5 years in Kenya elicited a 64-66% reduction in VT carriage prevalence at all ages within six months of PCV10 introduction.[272] The full interaction of these effects can only be understood within a formal framework, such as a dynamic transmission model. Even here, the accuracy of predicting disease depends on a clear understanding of the risk of disease per episode of carriage for both VTs and NVTs.[77,241] The full spectrum of data required to parameterise such a model is not currently available for Nigeria.

In addition to a lower VT carriage prevalence in the final survey compared to the baseline in Pakoto (as was observed in Kumbotso), we also found significantly lower overall and NVT carriage prevalence. This could indicate the possible influence of other non-PCV factors on the observed pneumococcal carriage prevalence. Non-PCV factors that can affect trends in carriage prevalence include use of antibiotics, reduced exposure to indoor air pollution, improvement in personal hygiene, living conditions, and health status, changes in risk of viral respiratory infections, and changes in household and population age structure and contact patterns.[21,255,273,274]

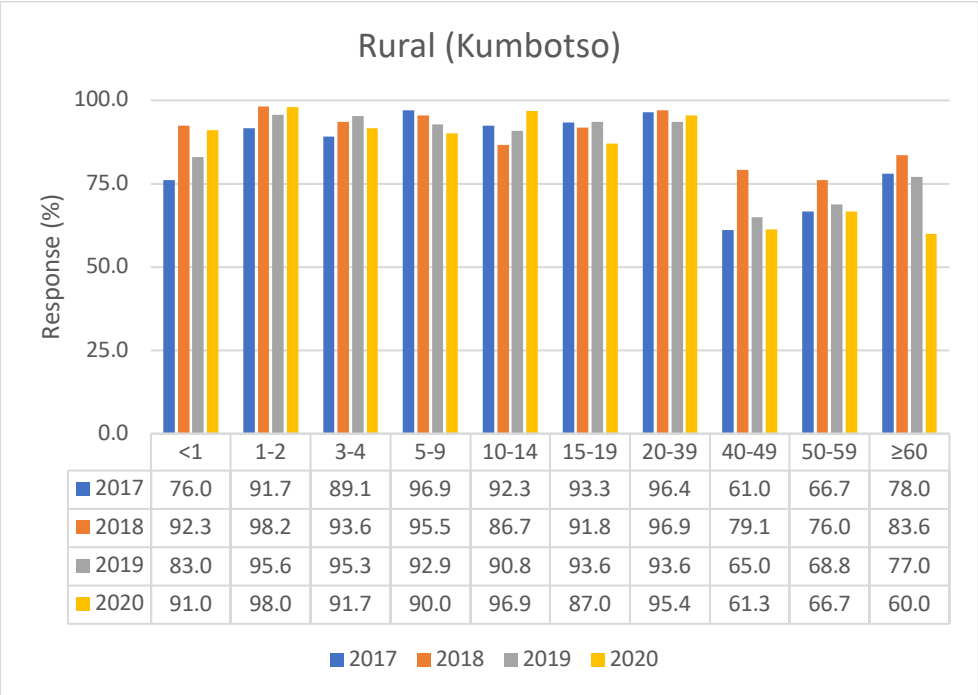
Among children, we found that VT carriage declines exponentially with a large reduction in VT carriage prevalence observed at low levels of increasing PCV10 uptake. In an ecological analysis in Australia, 73% of VT-IPD cases were estimated to have been prevented by approximately 50% vaccine uptake of PCV7 [32], which lends credence to the hypothesis that indirect effects may begin at relatively low levels of uptake. It is also possible that our data are capturing the dynamic stage of a complex polynomial effect, and the exponential fit works only within the coverage range we explored. Although both direct and indirect effects are expected in children, changes are mostly driven by the latter, which supports the non-linear effect observed. Given that the impact on adult carriage is entirely attributable to indirect effects, we would expect the same function should be observed in older people. The arithmetic decline we observed in this population is, therefore, difficult to explain.

We restricted our study to detect a single serotype in each swab despite abundant evidence supporting multiple serotype colonisation in children.[62] The dynamics and clinical importance of multiple serotypes in nasopharyngeal carriage are not fully understood.[66,203] Nonetheless, sampling a single strain per child provides a valid estimate of the distribution of serotypes colonising the population of children in these areas.

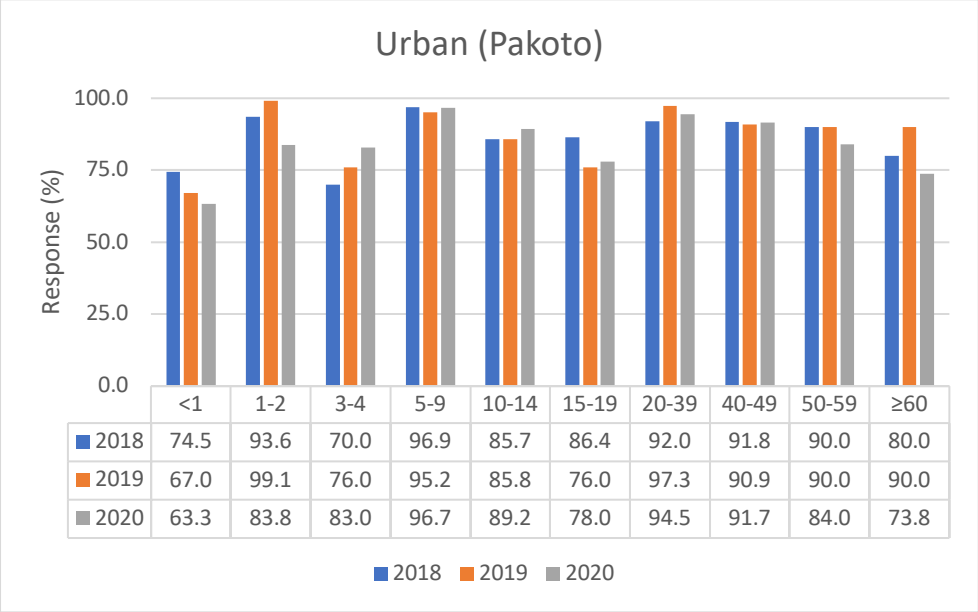
The measurable impact on VT carriage reported here should reassure immunisation policymakers and service providers in Nigeria that, in settings with similar baseline epidemiology and comparable vaccine coverage across the country, PCV10 is bringing about population protection through its indirect effect. This protection is likely to have reduced the incidence of pneumococcal disease among all ages by 48-66%,

depending on the setting. Among the majority of children aged <5 years who have now received a course of PCV10, this indirect effect will have been augmented by direct effects that are likely to be very strong. The decline in VT carriage prevalence as PCV10 coverage increases among children <5 years suggests that, in settings with sub-optimal coverage, efforts to improve coverage will yield significant reductions in carriage and transmission and, therefore, disease incidence.

3.9 Supplement to Research paper 1



	<1	1-2	3-4	5-9	10-14	15-19	20-39	40-49	50-59	≥60
2017	76.0	91.7	89.1	96.9	92.3	93.3	96.4	61.0	66.7	78.0
2018	92.3	98.2	93.6	95.5	86.7	91.8	96.9	79.1	76.0	83.6
2019	83.0	95.6	95.3	92.9	90.8	93.6	93.6	65.0	68.8	77.0
2020	91.0	98.0	91.7	90.0	96.9	87.0	95.4	61.3	66.7	60.0



	<1	1-2	3-4	5-9	10-14	15-19	20-39	40-49	50-59	≥60
2018	74.5	93.6	70.0	96.9	85.7	86.4	92.0	91.8	90.0	80.0
2019	67.0	99.1	76.0	95.2	85.8	76.0	97.3	90.9	90.0	90.0
2020	63.3	83.8	83.0	96.7	89.2	78.0	94.5	91.7	84.0	73.8

Supplementary Figure 3.1: Annual participation in carriage surveys.

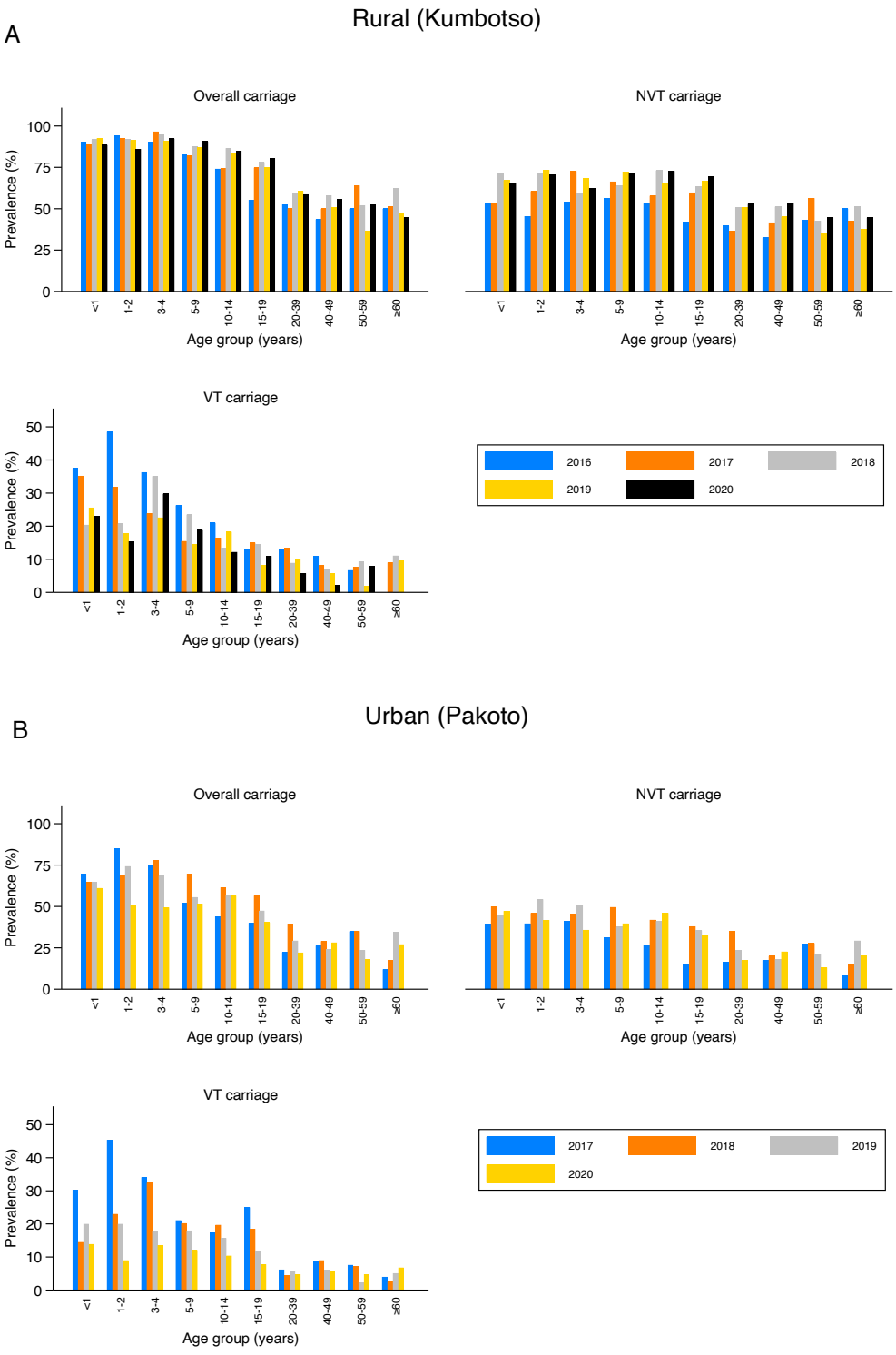
Proportion of invited participants in sampled age groups that consented to be swabbed by survey year in the rural and urban sites.

Supplementary Table 3.1: Numbers of participants invited*, consented, and swabbed in each carriage survey in the rural site.

Age group	swabbed	invited	consented	swabbed	invited	consented	swabbed	invited	consented	swabbed	invited	consented	swabbed
	2016**		2017			2018			2019			2020	
Kumbotso (rural)													
<1	73	100	76	71	130	120	108	100	83	82	100	91	89
1-2	132	120	110	105	110	108	101	160	153	147	150	147	141
3-4	91	110	98	88	110	103	95	150	143	133	120	110	106
5-9	191	130	126	116	110	105	102	140	130	124	140	126	120
10-14	81	130	120	110	150	130	119	120	109	106	160	155	149
15-19	38	120	112	107	110	101	97	110	103	96	100	87	85
20-39	154	110	106	104	130	126	125	110	103	101	130	124	122
40-49	46	100	61	61	110	87	87	80	52	52	80	49	47
50-59	30	60	40	39	100	76	75	80	55	55	60	40	40
≥60	36	100	78	78	110	92	90	100	77	76	100	60	58
Total	872	1,080	927	879	1,170	1048	999	1,150	1,008	972	1,140	989	957
Pakoto (urban)													
	2017**		2018			2019			2020				
<1	109	110	82	76	100	67	65	60	38	37			
1-2	141	110	103	100	110	109	105	80	67	67			
3-4	85	100	70	68	100	76	73	100	83	81			
5-9	161	130	126	119	125	119	117	120	116	116			
10-14	75	140	120	117	120	103	102	130	116	115			
15-19	20	110	95	92	100	76	76	100	78	78			
20-39	130	100	92	91	110	107	106	110	104	104			
40-49	57	110	101	100	110	100	99	120	110	110			
50-59	66	110	99	98	100	90	90	100	84	84			
≥60	75	100	80	80	110	99	99	80	59	59			
Total	919	1120	968	941	1085	946	932	1000	855	851			

* Age groups (school-aged children and young adolescents) with poor participation due to 'apprehension' about the swab procedure were oversampled to improve response. Participants or their caregivers occasionally made errors in reporting ages at the time of invitation. Such participants had to be reclassified to

their correct age groups at the time of interview and the wrongfully assigned age group had to be resampled. ** Sampling technique was not age-stratified in this year. This was a convenient sample volunteers and results of this survey have been published. [258]



Supplementary Figure 3.2: Age-stratified annual pneumococcal carriage prevalence. Carriage prevalence of overall, NVT and VT across sampled age groups by survey year in the rural site Note scales for VT carriage are from 0-50%.

Supplementary Table 3.2: Annual crude serotype-specific carriage prevalence and crude odds ratio (OR) and 95% CI from logistic regression comparing carriage in the final survey (Year 5) to the baseline survey (year 1) among children aged <5 year the rural site

Children aged <5 years in Kumbotso (rural)							
Serotype	**Prevalence (95% CI)**						
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Crude OR (95% CI)**	**P value***
19F	16.2 (12.0,21.5)	9.9 (6.4,14.4)	6.6 (4.0,10.2)	4.9 (2.9,7.8)	5.4 (3.2,8.5)	**0.3 (0.2,0.54)**	**<0.0001**
23F	10.5 (7.1,14.9)	9.9 (6.4,14.4)	4.9 (2.8,8.1)	6.9 (4.4,10.1)	3.9 (2.1,6.7)	**0.3 (0.2,0.7)**	**0.003**
6B	5.1 (2.8,8.4)	3.4 (1.6,6.5)	3.3 (1.6,6.1)	3.8 (2.1,6.4)	3.3 (1.7,5.9)	0.7 (0.3,1.5)	0.33
14	3.0 (1.4,5.8)	1.9 (0.6,4.4)	2.3 (0.9,4.7)	1.1 (0.3,2.8)	4.5 (2.5,7.4)	1.6 (0.7,3.7)	0.29
4	2.7 (1.2,5.3)	1.1 (0.2,3.3)	0.7 (0.1,2.4)	0.8 (0.2,2.4)	0.6 (0.1,2.2)	0.2 (0.5,1.1)	0.06
9V	2.4 (1.0,4.9)	2.7 (1.1,5.5)	2.6 (1.1,5.2)	0.0 (0.0,0.0)	0.9 (0.2,2.6)	0.4 (0.1,1.5)	0.18
18C	1.7 (0.6,3.9)	1.1 (0.2,3.3)	2.0 (0.7,4.3)	3.0 (1.5,5.4)	2.1 (0.9,4.3)	1.3 (0.4,4.2)	0.65
5	0.3 (0.01,1.9)	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.0 (0.0,0.0)	-**	-**
1	0.0 (0.0,0.0)	0.0 (0.0,0.0)	1.0 (0.2,2.9)	0.6 (0.1,2.0)	0.0 (0.0,0.0)	-**	-**
7F	0.0 (0.0,0.0)	0.0 (0.0,0.0)	1.6 (0.5,3.8)	0.0 (0.0,0.0)	0.9 (0.2,2.3)	-**	-**
6A	14.2 (10.2,19.2)	9.5 (6.1,14.0)	8.6 (5.6,12.5)	10.7 (7.6,14.6)	11.1 (7.8,15.3)	0.8 (0.5,1.3)	0.34
19A	2.7 (1.2,5.3)	6.4 (3.8,10.3)	7.6 (4.8,11.4)	6.9 (4.4,10.1)	5.4 (3.2,8.5)	2.2 (0.9,5.1)	0.08
3	2.0 (0.7,4.4)	2.3 (0.8,5.0)	3.0 (1.5,5.6)	1.9 (0.8,4.0)	1.2 (0.3,3.1)	0.6 (0.2,2.2)	0.45
16F	0.3 (0.01,1.9)	6.1 (3.5,9.8)	3.3 (1.6,6.1)	5.8 (3.6,8.8)	3.9 (2.1,6.7)	**12.6 (1.6,97.3)**	**0.015**
10A	0.3 (0.01,1.9)	1.1 (0.2,3.3)	3.6 (1.8,6.5)	1.1 (0.3,2.8)	3.6 (1.9,6.3)	**11.6 (1.5,90.0)**	**0.02**
15A	0.3 (0.01,1.9)	1.1 (0.2,3.3)	3.0 (1.4,5.6)	3.0 (1.5,5.4)	1.8 (0.7,3.9)	5.7 (0.7,47.6)	0.11
15B	1.4 (04,3.5)	1.5 (0.4,3.9)	2.3 (0.9,4.7)	3.0 (1.0,5.4)	1.5 (0.5,3.5)	1.2 (0.3,4.4)	0.82
13	0.7 (0.1,2.4)	3.0 (1.3,6.0)	2.6 (1.1,5.2)	1.4 (0.4,3.2)	3.0 (1.4,5.5)	**4.8 (1.0,22.1)**	**0.05**
11A	3.4 (1.6,6.2)	4.2 (2.1,7.5)	4.0 (2.0,6.9)	5.8 (3.6,8.8)	4.5 (2.5,7.4)	1.4 (0.6,3.2)	0.4
21	2.0 (0.7,4.4)	2.7 (1.1,5.5)	2.6 (1.1,5.2)	2.5 (1.1,4.7)	3.0 (1.4,5.5)	1.6 (0.6,4.4)	0.39

Children aged <5 years in Kumbotso (rural)							
Serotype	**Prevalence (95% CI)**						
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Crude OR (95% CI)**	**P value***
34	2.0 (0.7,4.4)	3.8 (1.8,7.0)	6.3 (3.8,9.8)	1.9 (0.8,4.0)	2.7 (1.2,5.1)	1.4 (0.5,4.0)	0.52
20	1.4 (0.4,3.5)	3.8 (1.8,7.0)	0.7 (0.1,2.4)	1.6 (0.6,3.6)	1.2 (0.3,3.1)	0.9 (0.2,3.8)	0.92
8	0.7 (0.1,2.4)	1.5 (0.4,3.9)	4.0 (2.0,6.9)	0.8 (0.2,2.4)	0.0 (0.0,0.0)		
33F	0.7 (0.1,2.4)	1.1 (0.2,3.3)	0.7 (0.08,2.38)	0.6 (0.1,2.0)	0.6 (0.1,2.2)	0.9 (0.1,6.7)	0.94
22F	0.7 (0.1,2.4)	0.4 (0.01,2.1)	1.0 (0.2,2.9)	0.3 (0.01,1.5)	0.6 (0.1,2.2)	0.9 (0.1,67)	0.94

* P values are for crude differences in the serotype-specific carriage prevalence in the final survey (Year 5 - 2020) compared to the baseline survey (Year 1 - 2016) using Chi square test. P values for bolded ORs are <0.05 and are two-sided. **ORs could not be calculated because carriage was not observed for these serotypes in either Year 1 or Year 5 or both. VTs and the commonest NVTs.

Supplementary Table 3.3: Annual serotype-specific carriage prevalence and crude odds ratio (OR) and 95% CI from logistic regression comparing carriage in the final survey (Year 4) to the baseline survey (year 1) among children aged <5 years in the urban site.

Children aged <5 years in Pakoto (urban)						
	Prevalence (95% CI)					
Serotype	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Crude OR (95% CI)**	**P value***
19F	13.7 (10.1,18.3)	4.5 (2.3,8.1)	7.0 (4.1,11.2)	3.8 (1.5,7.8)	**0.37 (0.16,0.84)**	**0.018**
6B	10.5 (7.3,14.5)	7.8 (4.7,12.2)	6.6 (3.8,10.7)	3.8 (1.5,7.8)	0.51 (0.22,1.18)	0.12
23F	7.5 (4.8,11.0)	4.1 (2.0,7.5)	2.1 (0.7,4.8)	1.1 (0.1,3.9)	**0.20 (0.05,0.86)**	**0.03**
14	3.6 (1.9,6.3)	0.8 (0.1,3.0)	0.8 (0.1,3.0)	1.6 (0.3,4.7)	0.67 (0.18,2.42)	0.54
9V	1.5 (0.5,3.5)	1.6 (0.5,4.2)	0.4 (0.01,2.29)	0.5 (0.01,3.0)	0.54 (0.06,4.66)	0.57
4	0.9 (0.2,2.62)	1.2 (0.3,3.6)	0.0 (0.0,0.0)	0.5 (0.01,3.0)	0.90 (0.09,8.79)	0.93
18C	0.0 (0.0,0.0)	2.9 (1.2,5.9)	2.5 (0.9,5.4)	0.5 (0.01,3.0)	-**	-**
6A	7.8 (5.1,11.4)	11.5 (7.6,16.6)	7.4 (4.4,11.7)	2.7 (0.9,6.3)	0.49 (0.18,1.33)	0.16
19A	5.4 (3.2,8.5)	8.6 (5.3,13.2)	7.8 (4.7,12.2)	7.6 (4.1,12.7)	**2.30 (1.09,4.82)**	**0.03**
3	2.4 (1.0,4.7)	1.6 (0.5,4.2)	1.7 (0.5,4.2)	1.1 (0.1,3.9)	0.67 (0.14,3.22)	0.62
15B	3.0 (1.4,5.5)	4.1 (2.0,7.5)	4.5 (2.3,8.1)	4.9 (2.2,9.2)	**2.59 (1.02,6.58)**	**0.05**
16F	1.2 (0.3,3.1)	2.5 (0.9,5.4)	4.1 (2.0,7.6)	3.8 (1.5,7.8)	**5.03 (1.44,17.62)**	**0.01**
11A	2.7 (1.2,5.1)	2.5 (0.90,5.35)	5.8 (3.2,9.7)	3.2 (1.2,7.1)	1.86 (0.64,5.37)	0.25
15A	0.0 (0.0,0.0)	0.8 (0.1,3.0)	0.4 (0.01,3.0)	3.2 (1.2,7.1)	-**	-**
23B	1.2 (0.3,3.1)	0.0 (0.0,0.0)	0.4 (0.01,3.0)	2.2 (0.6,5.5)	2.78 (0.68,11.37)	0.15
38	0.9 (0.2,2.6)	0.4 (0.01,3.0)	0.0 (0.0,0.0)	2.2 (0.6,5.5)	3.72 (0.82,16.98)	0.09
10A	0.6 (0.1,2.2)	1.6 (0.5,4.2)	1.2 (0.3,3.6)	1.1 (0.1,3.9)	2.74 (0.38,19.79)	0.32
37	0.3 (0.01,1.7)	0.8 (0.10,3.0)	0.0 (0.0,0.0)	1.1 (0.1,3.1)	5.51 (0.49,61.62)	0.17
35B	2.4 (1.03,4.7)	0.4 (0.01,3.0)	0.4 (0.01,3.0)	0.5 (0.01,3.0)	0.33 (0.04,2.69)	0.30
20	0.6 (0.1,2.2)	0.4 (0.01,3.0)	1.2 (0.3,3.6)	0.5 (0.01,3.0)	1.36 (0.12,15.17)	0.80

Children aged <5 years in Pakoto (urban)						
	Prevalence (95% CI)					
Serotype	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Crude OR (95% CI)**	**P value***
12F	0.3 (0.01,1.7)	0.4 (0.01,3.0)	0.8 (0.1,3.0)	0.5 (0.01,3.0)	2.73 (0.17,44.11)	0.48
22F	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.5 (0.01,3.0)	-**	-**
15C	0.3 (0.01,1.7)	3.3 (1.4,6.5)	3.7 (1.7,7.0)	0.5 (0.01,3.0)	2.73 (0.17,44.11)	0.48
13	0.3 (0.01,1.7)	0.8 (0.1,3.0)	0.4 (0.01,3.0)	0.0 (0.0,0.0)	-**	-**
21	1.2 (0.3,3.1)	0.4 (0.01,2.3)	1.7 (0.5,4.2)	0.0 (0.0,0.0)	-**	-*8

* P values are for crude differences in the serotype-specific carriage prevalence in the final survey (Year 5 - 2020) compared to the baseline survey (Year 1 - 2017) using Chi square test. P values for bolded ORs are <0.05 and are two-sided. **ORs could not be calculated because carriage was not observed for these serotypes in either Year 1 or Year 4 or both. VTs and the commonest NVTs.

Supplementary Table 3.4: Annual crude serotype-specific carriage prevalence and crude odds ratio (OR) and 95% CI from logistic regression comparing carriage in the final survey (Year 5) to the baseline survey (year 1) among persons aged ≥5 years in the rural site.

Persons aged ≥5 years in Kumbotso (rural)							
	Prevalence (95% CI)						
Serotype	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Crude OR (95% CI)**	**P value***
19F	5.0 (3.3,7.2)	3.3 (2.0,5.0)	1.2 (0.5,2.3)	2.3 (1.3,3.8)	1.6 (0.8,3.0)	**0.3 (0.1,0.6)**	**0.001**
23F	3.4 (2.1,5.3)	2.4 (1.4,4.0)	2.9 (1.8,4.4)	2.5 (1.4,4.1)	1.6 (0.8,3.0)	**0.4 (0.2,0.9)**	**0.025**
9V	2.2 (1.2,3.8)	1.5 (0.7,2.8)	0.7 (0.2,1.7)	0.8 (0.3,1.9)	0.2 (0,0.9)	**0.1 (0.01,0.5)**	**0.008**
4	1.6 (0.7,2.9)	2.8 (1.6,4.4)	1.3 (0.6,2.5)	0.3 (0.04,1.2)	1.5 (0.7,2.8)	0.9 (0.3,2.2)	0.74
6B	1.6 (0.7,2.9)	1.6 (0.8,3.0)	1.3 (0.6,2.5)	1.0 (0.4,2.1)	1.3 (0.6,2.5)	0.8 (0.3,2.0)	0.57
18C	1.4 (0.6,2.7)	1.3 (0.6,2.6)	2.6 (1.5,4.1)	1.3 (0.6,2.6)	2.3 (1.2,3.8)	1.5 (0.6,3.6)	0.36
14	1.0 (0.4,2.2)	0.3 (0.04,1.2)	0.4 (0.1,1.3)	0.7 (0.2,1.7)	0.8 (0.3,1.9)	0.7 (0.2,2.3)	0.57
7F	0.5 (0.1,1.5)	0.0 (0.0,0.0)	0.9 (0.3,1.9)	0.8 (0.3,1.9)	0.5 (0.1,1.4)	0.9 (0.2,4.3)	0.85
1	0.3 (0.04,1.2)	0.0 (0.0,0.0)	1.2 (0.5,2.3)	1.2 (0.5,2.4)	0.0 (0.0,0.0)	-**	-**
5	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.3 (0.3,1.0)	0.0 (0.0,0.0)	0.0 (0.0,0.0)	-**	-**
3	4.3 (2.8,6.3)	5.0 (3.4,7.2)	3.6 (2.3,5.3)	3.1 (1.9,4.9)	6.4 (4.6,8.9)	1.4 (0.8,2.4)	0.20
6A	4.1 (2.6,6.1)	2.3 (1.2,3.8)	2.7 (1.7,4.3)	3.0 (1.8,4.7)	1.8 (0.88,3.2)	0.8 (0.3,2.0)	0.57
19A	0.5 (0.1,1.5)	1.3 (0.6,2.6)	2.2 (1.2,3.6)	1.9 (0.9,3.2)	2.4 (1.4,4.0)	**4.4 (1.3,15.3)**	**0.02**
34	2.9 (1.7,4.7)	3.3 (2.0,5.0)	3.2 (2.0,4.8)	2.6 (1.5,4.3)	3.9 (2.5,5.8)	1.2 (0.6,2.3)	0.54
11A	2.8 (1.6,4.5)	2.8 (1.6,4.4)	2.9 (1.8,4.4)	2.3 (13,3.8)	3.7 (2.4,5.6)	1.2 (0.7,2.4)	0.52
16F	1.2 (0.5,2.5)	2.4 (1.4,4.0)	3.3 (2.1,5.0)	3.1 (1.9,4.9)	3.7 (2.4,5.6)	**2.9 (1.2,6.9)**	**0.015**
10A	1.4 (0.6,2.7)	1.3 (0.6,2.6)	2.6 (1.5,4.1)	2.3 (1.3,3.8)	3.5 (2.2,5.4)	**2.4 (1.1,5.5)**	**0.035**
37	0.5 (0.1,1.5)	1.3 (0.6,2.6)	1.6 (0.8,2.8)	2.6 (1.5,4.3)	2.7 (1.6,4.4)	**5.0 (1.5,17.2)**	**0.011**
8	1.4 (0.6,2.7)	2.8 (1.6,4.4)	4.8 (3.3,6.7)	3.0 (1.8,4.7)	1.8 (0.9,3.2)	1.2 (0.5,3.0)	0.73
21	2.2 (1.2,3.8)	1.3 (0.6,2.6)	2.5 (1.4,3.9)	1.6 (0.8,3.01)	1.5 (0.7,2.8)	0.6 (0.3,1.4)	0.22

Persons aged ≥5 years in Kumbotso (rural)							
	Prevalence (95% CI)						
Serotype	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Crude OR (95% CI)**	**P value***
13	1.4 (0.6,2.7)	2.8 (1.6,4.4)	1.9 (1.0,3.2)	2.5 (1.4,4.1)	1.3 (0.6,2.5)	0.9 (0.3,2.3)	0.75
35B	2.1 (1.1,3.6)	0.0 (0.0,0.0)	0.1 (0.0,0.8)	0.8 (03,1.9)	0.8 (0.3,1.9)	**0.4 (0.1,1.0)**	**0.05**
15B	1.2 (0.5,2.5)	0.7 (0.2,1.7)	0.7 (0.2,1.7)	0.7 (0.2,1.7)	0.6 (0.2,1.7)	0.5 (0.1,1.7)	0.25
22F	0.9 (0.9,2.0)	1.0 (0.4,2.1)	0.9 (0.3,1.9)	0.5 (0.1,1.4)	0.5 (0.1,1.4)	0.5 (0.1,2.2)	0.36
33F	0.5 (0.1,1.5)	1.6 (0.8,3.0)	1.2 (0.5,2.3)	0.5 (0.1,1.4)	0.2 (0.0,0.9)	0.3 (0.03,2.7)	0.28

* P values are for crude differences in the serotype-specific carriage prevalence in the final survey (Year 5 - 2020) compared to the baseline survey (Year 1 - 2016) using Chi square test. P values for bolded ORs are <0.05 and are two-sided. **ORs could not be calculated because carriage was not observed for these serotypes in either Year 1 or Year 5 or both. VTs and the commonest NVTs

Supplementary Table 3.5: Annual serotype-specific carriage prevalence and crude odds ratio (OR) and 95% CI from logistic regression comparing carriage in the final survey (Year 4) to the baseline survey (year 1) among persons aged ≥5 years in the urban site.

	Persons aged ≥5 years in Pakoto (urban)					
	Prevalence (95% CI)					
Serotype	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Crude OR (95% CI)**	**P value***
23F	3.2 (1.9,5.0)	0.9 (0.3,1.9)	1.6 (0.80,2.86)	1.2 (0.52,2.37)	0.33 (0.14,0.78)	0.01
19F	2.7 (1.6,4.4)	3.0 (1.9,4.6)	2.6 (1.55,4.13)	0.9 (0.33,1.96)	0.30 (0.11,0.78)	0.01
6B	2.4 (1.3,4.0)	1.9 (1.0,3.2)	2.2 (1.22,3.59)	0.8 (0.24,1.75)	0.29 (0.10,0.81)	0.02
14	1.4 (0.6,2.7)	0.6 (0.2,1.5)	0.6 (0.16,1.49)	0.2 (0,0.84)	0.10 (0.01,0.82)	0.03
18C	1.2 (0.5,2.5)	3.2 (2.0,4.8)	1.5 (0.70,2.67)	1.1 (0.42,2.17)	0.84 (0.29,2.43)	0.74
9V	0.7 (0.2,1.7)	1.1 (0.5,2.3)	0.2 (0,0.81)	0.2 (0,0.84)	0.21 (0.02,1.87)	0.16
4	0.7 (0.2,1.7)	1.1 (0.5,2.3)	0.7 (0.24,1.69)	2.0 (1.04,3.34)	2.84 (0.91,8.84)	0.07
7F	0.3 (0.04,1.2)	0.3 (0.03,1.0)	0.2 (0,0.81)	1.4 (0.62,2.57)	3.90 (0.83,18.27)	0.08
5	0.0 (0.0,0.0)	0.1 (0.0,0.8)	0.0 (0.0,0.0)	0.2 (0,0.84)	-**	-**
1	0.0 (0.0,0.0)	0.1 (0.0,0.8)	0.0 (0.0,0.0)	0.0 (0.0,0.0)	-**	-**
6A	2.7 (1.6,4.4)	2.3 (1.3,3.7)	2.2 (1.2,3.6)	1.2 (0.5,2.4)	3.90 (0.83,18.27)	0.08
3	1.9 (0.9,3.3)	3.7 (2.4,5.5)	1.7 (0.9,3.0)	2.3 (1.3,3.7)	1.16 (0.52,2.58)	0.72
19A	1.5 (0.7,2.9)	1.6 (0.8,2.8)	2.3 (1.3,3.8)	2.1 (1.2,3.5)	1.33 (0.56,3.14)	0.52
11A	2.2 (1.2,3.8)	3.0 (1.9,4.6)	3.2 (2.0,4.8)	2.6 (1.5,4.1)	1.11 (0.53,2.34)	0.79
16F	1.2 (0.5,2.5)	3.2 (2.0,4.8)	2.9 (1.8,4.5)	1.1 (0.4,2.2)	0.84 (0.29,2.43)	0.74
23B	0.9 (0.3,20)	0.3 (0.03,1.0)	0.3 (0.04,1.1)	1.7 (0.8,3.0)	1.89 (0.65,5.55)	0.24
34	0.3 (0.04,1.2)	1.3 (0.6,2.4)	1.6 (0.8,2.9)	1.1 (0.4,2.2)	3.01 (0.62,14.65)	0.17
21	0.2 (0.01,1.0)	1.1 (0.5,2.3)	0.7 (0.2,1.7)	1.1 (0.4,2.2)	6.04 (0.74,49.58)	0.09
15B	0.7 (0.2,1.7)	2.4 (1.4,3.9)	1.0 (0.4,2.1)	0.9 (0.3,2.0)	1.27 (0.35,4.57)	0.71
12F	0.3 (0.04,1.2)	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.9 (0.3,2.0)	2.57 (0.51,12.88)	0.25

8	0.2 (0.01,1.0)	1.1 (0.5,2.3)	1.2 (0.5,2.3)	0.9 (0.3,2.0)	5.16 (0.62,43.24)	0.13
15C	0.3 (0.04,1.2)	1.1 (0.5,2.3)	0.3 (0.04,1.1)	0.9 (0.3,2.0)	2.57 (0.51,12.86)	0.25
10A	0.3 (0.04,1.2)	0.6 (0.2,1.5)	1.5 (0.7,2.7)	0.6 (0.2,1.5)	1.70 (0.31,9.36)	0.54
22F	0.2 (0.01,1.0)	0.1 (0.01,0.8)	0.3 (0.04,1.1)	0.5 (0.1,1.3)	2.55 (0.26,24.70)	0.42
13	0.7 (0.2,1.7)	2.2 (1.2,3.5)	0.9 (0.3,1.9)	0.3 (0.04,1.1)	0.42 (0.08,2.30)	0.32

* P values are for crude differences in the serotype-specific carriage prevalence in the final survey (Year 5 - 2020) compared to the baseline survey (Year 1 - 2017) using Chi square test. P values for bolded ORs are <0.05 and are two-sided. **ORs could not be calculated because carriage was not observed for these serotypes in either Year 1 or Year 4 or both. VTs and the commonest NVTs

Supplementary Table 3.6: Annual coverage of PCV10 among children aged <5 years.

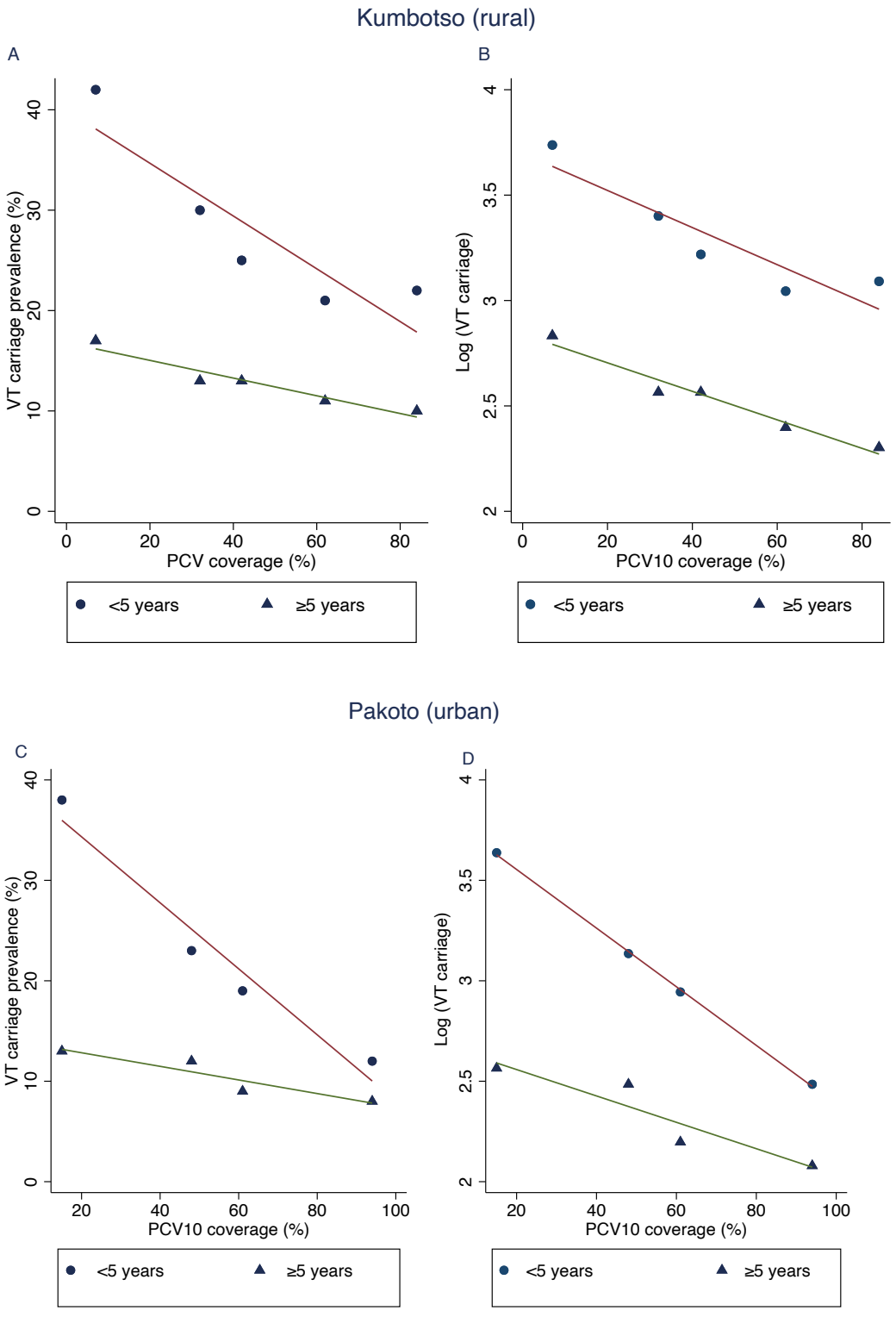
	PCV10 coverage					
Dose	**1 Dose**	**95% (CI)**	**2 Doses***	**95% (CI)**	**3 Doses**	**95% (CI)**
			Kumbotso (rural)			
Time since PCV10 introduction						
Year 1	8.04	6.89, 9.32	7.39	6.29, 8.63	6.56	5.52, 7.73
Year 2	34.3	28.10, 41.00	31.90	25.90, 38.5	27.90	22.30, 34.20
Year 3	47.37	43.5, 51.27	41.62	37.87, 45.46	34.64	31.10, 38.36
Year 4	70.38	66.79, 73.74	62.44	58.72, 66.03	54.20	50.45, 57.90
Year 5	90.33	87.88, 92.33	84.13	81.19, 86.68	76.33	73.02, 79.36
			Pakoto (urban)			
Time since PCV10 introduction						
Year 1	15.54	13.48, 17.82	15.00	12.98, 17.25	14.78	12.77, 17.01
Year 2	45.2	35.40, 54.80	48.00	39.30, 65.2	55.40	47.30, 63.20
Year 3	65.95	61.76, 69.91	61.35	57.10, 65.43	57.36	53.16, 61.46
Year 4	96.67	94.99, 97.8	94.40	92.3, 95.96	92.28	89.93, 94.13

Coverage for Year 1 and Year 2 were estimated using a birth cohort analysis of children observed between Year3 and Year 5 in Kumbotso, and Year 3 and Year 4 in Pakoto. * PCV10 coverage used in the analysis of relationship between VT carriage and PCV10 uptake in Figure 3 of the main text.

Supplementary Table 3.7: Carriage prevalence (95% CI) of serotypes contained in different PCV formulations in the baseline and final surveys among children aged <5 years and persons aged ≥5 years in the rural and urban sites.

		Kumbotso (rural)		Pakoto (urban)	
Formulation	**Age group**	**2016**	**2020**	**2017**	**2020**
PCV10 GSK[1]	<5 years	42.0 (36.5,47.8)	22.0 (17.8,26.8)	37.6 (32.6,42.9)	12.0 (8.0,17.5)
	≥5 years	17.0 (14.2,20.3)	9.9 (7.8,12.5)	12.6 (10.1,15.5)	7.7 (5.9,9.9)
PCV10 SII[2]	<5 years	54.4 (48.7,60.0)	35.4 (30.5,40.7)	21.1 (15.8,27.6)	53.1 (47.8,58.4)
	≥5 years	18.7 (15.8,22.1)	10.1 (8.0,12.8)	7.9 (6.1,10.3)	18.7 (15.7,22.0)
PCV13[3]	<5 years	60.8 (55.1,66.2)	39.3 (34.2,44.7)	53.1 (47.8,58.4)	23.2 (17.7,29.9)
	≥5 years	25.9 (22.5,29.7)	20.3 (17.3,23.6)	18.7 (15.7,22.0)	13.2 (10.8,16.0)
PCV15[4]	<5 years	62.2 (56.5,67.5)	40.5 (35.4,45.9)	53.1 (47.8,58.4)	23.8 (18.2,30.4)
	≥5 years	27.3 (23.8,31.1)	20.9 (17.9,24.3)	18.8 (15.9,22.2)	13.7 (11.3,16.5)
PCV20[5]	<5 years	67.9 (62.4,73.0)	51.7 (46.3,57.0)	59.7 (54.4,64.8)	34.1 (27.6,41.2)
	≥5 years	34.0 (30.3,38.0)	31.1 (27.6,34.8)	22.6 (19.4,26,1)	19.5 (16.7,22.7)

[1]GSK 10-valent PCV; [2]Serum Institute of India 10-valent PCV; [3]Pfizer 13-valent PCV; [4]Merck 15-valent PCV; [5]Pfizer 20-valent PCV



Supplementary Figure 3.3: Relationship between VT carriage and PCV10 coverage.

Graph comparing model fit of linear and non-linear (log-linear) relationship between changes in VT carriage and coverage with 2 doses of PCV10 in Kumbotso (A-B, top) and Pakoto (C-D, bottom). Using the Akaike Information Criterion (AIC), the non-linear model had a better fit for children aged <5 years compared to the linear model. AIC values for the linear and log-linear models in children

aged <5 years are -3.14 and -14.00 in Kumbotso and -3.98 and -17.68 in Pakoto. The respective AIC values for persons aged ≥5 years are -32.10 and -35.67 in Kumbotso and -23.69 and 12.61 in Pakoto. In Figure S3 (left), the gradient (95% CI) and R2 for each line of the linear regression are: Kumbotso age <5 years -0.26 (-0.50- -0.03), 0.73; Kumbotso age ≥5 years -0.09 (-0.13- -0.04), 0.93; Pakoto age <5 years -0.33 (-0.54- - 0.11), 0.80; Pakoto age ≥5 years -0.07 (-0.10- -0.04), 0.97.

In Figure S3 (right), the gradient (95% CI) and R2 for each line of the log-linear regression (on the log scale) are: Kumbotso age <5 years -0.0088 (-0.016- -0.0017), 0.83; Kumbotso age ≥5 years -0.0068 (-0.0093- -0.0042), 0.94; Pakoto age <5 years -0.0146 (-0.0157- - 0.013), 0.99; Pakoto age ≥5 years -0.066(-0.014- -0.013), 0.86.

Supplementary Table 3.8: Serotypes included in the different PCV formulations.

	Serotypes included																		
Formulation	**1**	**3**	**4**	**5**	**6A**	**6B**	**7F**	**8**	**9V**	**10A**	**11A**	**12F**	**14**	**15B**	**18C**	**19A**	**19F**	**22F**	**23F**	**33F**
PCV10[1]	●		●	●		●	●		●				●		●		●		●	
SII-PCV[2]	●			●	●	●	●		●				●			●	●		●	
PCV13[3]	●	●	●	●	●	●	●		●				●		●	●	●		●	
PCV15[4]	●	●	●	●	●	●	●		●				●		●	●	●	●	●	●
PCV20[5]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

[1]GSK 10-valent PCV; [2]Serum Institute of India 10-valent PCV; [3]Pfizer 13-valent PCV; [4]Merck 15-valent PCV; [5]Pfizer 20-valent PCV.
Dotted cells represent serotypes included in each vaccine.

Supplementary Table 3.9: Annual diversity of serotypes by site, age, and year of survey.

Age	Year of survey	Kumbotso (rural)		Pakoto (urban)	
		Simpson's diversity index	No. of serotypes identified	Simpson's diversity index	No. of serotypes identified
< 5 years					
	2016	0.976	41		
	2017	0.974	39	0.875	32
	2018	0.978	46	0.831	30
	2019	0.979	49	0.839	29
	2020	0.979	49	0.751	27
≥5 years					
	2016	0.982	55		
	2017	0.981	54	0.817	45
	2018	0.984	62	0.889	41
	2019	0.985	65	0.842	46
	2020	0.984	61	0.883	46

Strain (serotype) diversity was greater in Kumbotso (rural) than Pakoto (urban) and was marginally greater in older persons, but the diversity index did not vary substantially over time after introduction of the vaccine.

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The impact of introduction of the 10-valent pneumococcal conjugate vaccine on pneumococcal carriage in Nigeria

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Pneumococcal conjugate vaccines (PCVs) protect against invasive pneumococcal disease (IPD) among vaccinees. However, at population level, this protection is driven by indirect effects. PCVs prevent nasopharyngeal acquisition of vaccine-serotype (VT) pneumococci, reducing onward transmission. Each disease episode is preceded by infection from a carrier, so vaccine impacts on carriage provide a minimum estimate of disease reduction in settings lacking expensive IPD surveillance. We documented carriage prevalence and vaccine coverage in two settings in Nigeria annually (2016–2020) following PCV10 introduction in 2016. Among 4,684 rural participants, VT carriage prevalence fell from 21 to 12% as childhood (<5 years) vaccine coverage rose from 7 to 84%. Among 2,135 urban participants, VT carriage prevalence fell from 16 to 9% as uptake rose from 15 to 94%. Within these ranges, carriage prevalence declined with uptake. Increasing PCV10 coverage reduced pneumococcal infection at all ages, implying at least a comparable reduction in IPD.

In 2015, pneumococcal disease was estimated to cause ~300,000 deaths globally among children aged 1–59 months. Over 50% of these deaths occurred in Africa, and Nigeria alone accounted for nearly 50,000 of these pneumococcal deaths[1]. Between 2014 and 2016, in three geographically distinct phases, Nigeria introduced the 10-valent Pneumococcal Conjugate Vaccine (PCV10) in a three-dose schedule for infants aged 6, 10 and 14 weeks, without a catch-up campaign. Although PCV is the most expensive vaccine programme in the Nigerian portfolio, the country could not evaluate the impact of the vaccine programme on invasive disease or pneumonia due to lack of surveillance data.

Every episode of pneumococcal disease is preceded by infection from another infected person, normally a nasopharyngeal carrier[2]. Young children are the main reservoirs for carriage and have the highest number of effective contacts[3,4]. Consequently, a reduction in carriage prevalence among young children is likely to reduce onward transmission and the incidence of disease proportionately across the population. Among vaccinated children, PCVs provide direct protection against both acquiring carriage and progressing to invasive disease following carriage of vaccine-serotypes (VTs)[2]. At the population level, PCVs provide indirect protection, regardless of vaccine status, by reducing everyone's exposure to new infections from VTs. This indirect effect is driven by the direct protection against carriage among vaccinees[5,6]. As vaccine coverage increases, VT carriage prevalence declines linearly due to direct protection among vaccinees and non-linearly due to indirect protection from the consequences of reduced VT transmission in the whole population[2,5].

In real-world settings, the indirect effects of PCVs account for most of the vaccine programme impact[2,7]. Consequently, some countries have tailored their PCV schedules to maximise indirect effects of a

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booster dose at the expense of marginal direct effects of additional primary doses in infancy. For example, in the UK, population protection is being achieved with only a single dose in infancy and a booster dose at 12 months[8]. A disadvantage of PCV introduction is replacement carriage by non-vaccine serotypes (NVTs) leading, to a varying extent, to serotype replacement disease[9,10]. However, in most settings, any increase in serotype replacement disease is small compared to the reduction in vaccine-type disease because non-vaccine types are generally less invasive[10].

In the absence of robust IPD surveillance and given the strong anticipation of indirect protection following PCV10 introduction, we set out to evaluate the impact of the Nigerian PCV programme using carriage prevalence as an endpoint[11]. In Nigeria, among children aged <5 years who were studied immediately after PCV10 introduction, from a rural and an urban setting, VT pneumococci accounted for 52 and 64% of all carriage, respectively[12]. We conducted annual carriage and vaccination coverage surveys in these same two sites, for 4 years following PCV10 introduction. We assessed changes in the prevalence of overall carriage (i.e. all pneumococci), and VT and NVT carriage separately and explored the relationship between changes in vaccination uptake and changes in VT carriage prevalence.

Results

Including the baseline survey, reported above[12], we conducted five annual carriage surveys in the rural and four in the urban sites (Fig. 1) and recruited 4684 and 3653 participants, respectively. In the rural and urban sites, the proportion of eligible residents who consented to participate varied from 60–98% and 63–99%, respectively, across the sampling age groups and surveys (Supplementary Fig. 1 and Supplementary Table 1).

Participants in the rural site resided in larger households and more commonly reported living with ≥2 children aged <5 years, using solid fuel for cooking, and having a cough or runny nose in the preceding two weeks compared to their counterparts in the urban site (Table 1).

Carriage prevalence

Table 2 shows the crude and age-standardised carriage prevalence stratified by survey. Among the age-standardised results, overall pneumococcal carriage prevalence was consistently high across all ages in all surveys at the rural site. At both sites, overall pneumococcal carriage prevalence and NVT carriage prevalence were higher in children aged <5 years compared to persons aged ≥5 years; VT carriage prevalence was also higher in children aged <5 years in the baseline surveys at both sites. The crude carriage prevalence (by sampled ages) is also illustrated in Supplementary Fig. 2.

Changes in carriage prevalence

Overall carriage prevalence in the total population (all ages combined) remained unchanged across the surveys, in both settings (Tables 2 and 3). However, in the rural site (Table 2), overall carriage prevalence increased significantly among persons aged ≥5 years (χ^2 test for trend, $p = 0.004$), and in the urban site (Table 3), overall carriage prevalence declined significantly among children <5 years (χ^2 test for trend, $p < 0.0001$).

In the total population VT carriage prevalence steadily declined from 21 to 12% (χ^2 test for trend, $p < 0.001$) in the rural site and from 16 to 9% (χ^2 test for trend, $p < 0.001$) in the urban site. In the total population VT carriage prevalence steadily declined from 21 to 12% (χ^2 test for trend, $p < 0.001$) in the rural site and from 16 to 9% (χ^2 test for trend, $p < 0.001$) in the urban site. Among the total population sample, there was a significant trend for an increase in NVT carriage over the survey years in the rural site (Chi squared test for trend $p < 0.001$) and but not in the urban site (Chi squared test for trend $p = 0.36$).

For both age groups, VT carriage declined significantly across surveys in at each site (χ^2 test for trend, $p < 0.001$ for all 4 trends). NVT carriage prevalence increased significantly in both age groups across surveys but only at the rural site (χ^2 test for trend, $p < 0.001$).

Compared to the baseline survey, the adjusted age-standardised PR for VT carriage prevalence in the final survey was 0.52 and 0.53 (Table 4) among children <5 years and older persons, respectively, in Kumbotso (rural). The adjusted PRs were 0.31 and 0.60 among children <5 years and older persons, respectively, in Pakoto (urban). NVT carriage increased significantly in both age groups in Kumbotso, with adjusted PRs of 1.34 and 1.26 in children aged <5 years and persons ≥5 years, respectively. In Pakoto, serotype replacement carriage was significant only in those aged ≥5 years (adjusted PR 1.36, Table 4).

For children aged <5 years, the individual serotypes with the highest age-standardised prevalence in the final surveys were 6A (11.4%), 19F (5.5%) and 19A (5.4%), 11A (4.7%), 14, (4.4%) 16F (4.4%) and 23F (3.7%) in the rural site (Fig. 2 and Supplementary Table 2); and 19A (7.4%), 15B (4.6%), 6B (4.0%), 19F (3.9%), and 16F (3.7%) in the urban site (Fig. 2 and Supplementary Table 3). Among persons aged ≥5 years, in

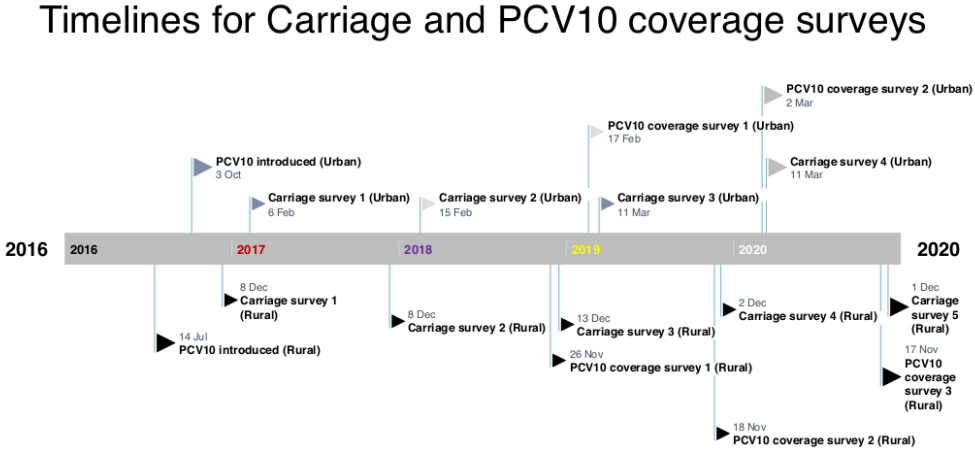

Fig. 1 | Timelines for surveys in the two sites. For each site, surveys were conducted around the same time. Note PCV10 coverage surveys started from 2018 onwards.

Table 1 | Background characteristics of study participants of the carriage surveys

Kumbotso (rural)	*N* (%) Survey 1 (2016)	*N* (%) Survey 2 (2017)	*N* (%) Survey 3 (2018)	*N* (%) Survey 4 (2019)	*N* (%) Survey 5 (2020)
Total sample	878	879	999	973	954
Clinical history[a]					
Runny nose (%)	714 (81)	681 (77)	900 (90)	843 (87)	727 (76)
Cough (%)	450 (51)	551 (63)	687 (69)	558 (57)	487 (51)
Antibiotic use (%)	65 (7)	431 (49)	510 (51)	233 (24)	202 (21)
Household composition					
Living with ≥2 aged <5 years (%)	645 (73)	469 (53)	555 (56)	619 (64)	748 (78)
Sharing bed with ≥2 persons (%)	729 (83)	704 (80)	882 (88)	795 (82)	857 (90)
Household cooking fuel					
Solid fuel (%)	833 (95%)	795 (90)	959 (96)	892 (92)	850 (89)
Gas (%)	12 (1%)	19 (2)	18 (2)	38 (4)	51 (5)
Kerosene (%)	16 (2%)	18 (2)	5 (0.5)	66 (0.6)	3 (0.3)
Others (%)	17 (2%)	47 (5)	17 (2)	40 (4)	46 (5)
Household size[b]					
All persons, median (IQR)	9 (7–13)	6 (3–10)	6 (4–9)	8 (6–10)	9 (7–12)
Pakoto (urban)	**Survey 1 (2017)**	**Survey 2 (2018)**	**Survey 3 (2019)**	**Survey 4 (2020)**	
Total sample	924	943	932	854	N/A
Clinical history[a]					
Runny nose (%)	238 (26)	163 (17)	106 (11)	51 (6)	N/A
Cough (%)	216 (23)	122 (13)	75 (8)	32 (4)	N/A
Antibiotic use (%)	145 (16)	76 (8)	39 (4)	10 (1%)	N/A
Household composition					
Living with ≥2 aged <5 years (%)	95 (10)	81 (9)	69 (7)	53 (6)	N/A
Sharing bed with ≥2 persons (%)	185 (20)	212 (23)	121 (13)	121 (14)	N/A
Household cooking fuel					
Solid fuel (%)	58 (6)	38 (4)	35 (4)	11 (1)	N/A
Gas (%)	326 (35)	584 (62)	713 (76)	775 (91)	N/A
Kerosene (%)	515 (56)	238 (25)	155 (17)	29 (3)	N/A
Others (%)	25 (3)	83 (8)	29 (3)	39(5)	N/A
Household size[b]					
All persons, median (IQR)	4 (3–5)	5 (4–6)	5 (4–6)	5 (4–6)	N/A

[a]History of any of the symptoms in the 2 weeks preceding the interview date.
[b]Including the participant.

the rural site (Supplementary Table 4), the most prevalent serotypes in the final surveys were 3, 34, 11A, 16F and 10A; in the urban site, the most prevalent serotypes were 11A, 3, 19A, 4, 23B and 38 (Fig. 2 and Supplementary Table 5).

In the rural site(Supplementary Tables 2 and 4), significantly increased prevalence odds (final vs baseline survey) were observed for serotypes 16F (OR 12.6) and 10A (11.6), among children aged <5 years, and for serotypes 19A (4.4), 16F (2.9), 10A (2.4), and 37(5.0) for persons aged ≥5 years. In the urban site (Supplementary Tables 3 and 5), NVT replacement was significant for serotypes 19A (OR 2.3), 15B (2.6) and 16F (5.0) in children aged <5 years; there was no significant increases in individual NVTs among persons aged ≥5 years.

We compared the carriage prevalence of serotypes included in different PCV formulations (Supplementary Table 7) in the final survey among children <5 years old. The total carriage prevalences of all serotypes contained in the Serum Institute of India 10-valent PCV (SII-PCV), 13-valent PCV (PCV13), 15-valent PCV (PCV15) and 20-valent PCV (PCV20) were 54%, 61%, 62% and 68%, respectively, in the rural site and 50%, 53%, 53% and 60%, respectively, in the urban site.

PCV10 vaccine coverage

We assessed the PCV10 vaccination status of 2165 children (aged <5 years) in the rural site and 1313 children in the urban site. We accepted either written evidence of vaccination or the caregiver's recall. The average proportion of children for whom the caregivers had retained their vaccination card was 70% in the rural site (52% in 2018; 77% in 2019; and 90% in 2020) and 80% in the urban site (70% in 2019 and 91% in 2020). Figure 3A shows the annual proportions of children aged <5 years who had received at least two doses of PCV10. PCV10 coverage (≥2 doses) increased steadily from 7% in 2016 to 84% in 2020, in the rural site; and from 15% in 2017 to 94% in 2020, in the urban site.

Relationship between PCV10 coverage and VT carriage

Within the range of PCV10 coverage observed in children, the ecological relationship between PCV10 coverage and the prevalence of VT carriage (Fig. 3B) shows a linear decline for older persons aged ≥5 years in both settings (gradient −0.09 (95% CI −0.13 to −0.04) in Kumbotso; −0.07 (95% CI −0.10 to −0.04) in Pakoto. For children aged <5 years, a log-linear model had a better fit to the data (Supplementary Fig. 3) which show a steep decline in VT carriage prevalence associated with a small increase in PCV coverage towards 20% followed by slower gains as coverage increases further.

Discussion

The aim of this study was to evaluate the introduction of a new, expensive vaccine programme in Nigeria using an inexpensive proxy measure of impact, vaccine-type nasopharyngeal carriage. Over five years, in a rural setting (Kumbotso) in northern Nigeria, the proportion of children aged <5 years who were vaccinated increased from 7 to 84%. During the same period, the age-standardised population prevalence of VT carriage fell from 21 to 12%, giving an adjusted prevalence ratio of 0.52 or a VT carriage reduction of 48%. Over three years, in an urban setting (Pakoto) in southern Nigeria, the proportion of children vaccinated increased from 15 to 94%. During the same period, the age-standardised population prevalence of VT carriage fell from 16 to 9%, giving an adjusted PR of 0.34 or a reduction in carriage of 66%. In both settings, we observed a decrease in VT carriage prevalence among children and older persons as vaccine coverage among children <5 years accumulated over time. For older persons (aged ≥5 years) this relationship was approximately linear representing a reduction in VT carriage prevalence of 1.4–1.5% for every 20% increase in vaccine coverage among children in the same setting.

Although carriage is only a proxy, we can use it to infer the impact of PCV10 on disease rates in these settings. A reduction in carriage prevalence will produce a proportionate reduction in the number of carriers each person contacts, reducing the incidence of carriage acquisition and the incidence of all pneumococcal diseases commensurately. A reduction in VT carriage prevalence of 66% at all ages in Pakoto is likely to translate into a reduction in the incidence of all VT pneumococcal disease of at least 66% at all ages. This estimate considers only the indirect effect of the programme, but it is, in itself, a very significant public health gain. Direct effects cannot be estimated from these surveys, but in an individually-randomised controlled trial of PCV9 in The Gambia, vaccine efficacy against VT IPD was 77%[13].

Table 2 | Crude and age-standardised[a] prevalence (and 95% CI) of overall, non-vaccine serotype (NVT) and vaccine serotype (VT) pneumococcal carriage stratified by age group and survey in the rural site

		Overall carriage		VT carriage		NVT carriage	
Survey	*N*	Crude	Age-standardised	Crude	Age-standardised	Crude	Age-standardised
Kumbotso (rural)							
All ages							
Survey 1 (2016)	872	74 (71–77)	68 (65–71)	26 (22–28)	21 (18–24)	48 (45–52)	47 (43–51)
Survey 2 (2017)	879	74 (71–77)	71 (67–74)	18 (16–21)	16 (14–19)	55 (52–59)	54 (51–58)
Survey 3 (2018)	999	77 (74–80)	77 (74–79)	16 (14–19)	16 (13–18)	60 (57–64)	61 (58–64)
Survey 4 (2019)	976	77 (74–79)	74 (71–77)	15 (13–17)	13 (11–15)	61 (59–65)	60 (57–64)
Survey 5 (2020)	953	78 (75–80)	74 (71–77)	14 (12–17)	12 (10–14)	63 (61–67)	61 (58–65)
<5 years							
Survey 1 (2016)	296	92 (88–94)	91 (88–94)	42 (37–48)	41 (35–46)	50 (44–56)	50 (45–56)
Survey 2 (2017)	264	93 (89–95)	92 (89–96)	30 (25–36)	30 (25–36)	63 (57–68)	62 (56–68)
Survey 3 (2018)	304	93 (89–95)	92 (90–95)	25 (21–30)	25 (20–30)	68 (62–73)	67 (62–72)
Survey 4 (2019)	365	91 (88–94)	91 (88–94)	21 (17–26)	22 (17–26)	70 (65–75)	69 (64–74)
Survey 5 (2020)	333	89 (85–92)	88 (84–91)	22 (18–27)	22 (18–27)	67 (61–72)	65 (60–71)
>5 years							
Survey 1 (2016)	576	65 (60–68)	62 (58–66)	17 (14–20)	16 (13–19)	48 (43–52)	46 (42–50)
Survey 2 (2017)	615	66 (62–64)	65 (61–69)	13 (11–16)	13 (10–16)	53 (49–56)	52 (48–56)
Survey 3 (2018)	695	70 (67–74)	73 (69–76)	13 (10–15)	13 (11–16)	57 (54–61)	59 (55–63)
Survey 4 (2019)	611	68 (64–71)	69 (66–73)	11 (9–14)	11 (9–14)	57 (53–61)	58 (54–62)
Survey 5 (2020)	620	72 (69–76)	70 (66–74)	10 (8–13)	9 (7–11)	62 (58–66)	61 (57–64)

[a]Standardised using the respective population structures of the two study sites taken from population models of the Nigerian census[37].

Table 3 | Crude and age-standardised[a] prevalence of overall, non-vaccine serotype (NVT) and vaccine serotype (VT) pneumococcal carriage stratified by age group and survey in the urban site

		Overall carriage		VT carriage		NVT carriage	
Survey	*N*	Crude	Age-standardised	Crude	Age-standardised	Crude	Age-standardised
Pakoto (urban)							
All ages							
Survey 1 (2017)	919	50 (47–53)	40 (36–43)	22 (19–24)	16 (13–18)	29 (25–31)	24 (21–27)
Survey 2 (2018)	941	52 (49–55)	51 (47–54)	15 (13–18)	14 (12–17)	37 (34–40)	36 (33–39)
Survey 3 (2019)	932	47 (44–50)	44 (41–48)	12 (10–14)	11 (9–14)	35 (32–38)	33 (30–36)
Survey 4 (2020)	851	40 (36–43)	39 (36–42)	9 (7–11)	9 (6–10)	31 (28–34)	31 (28–34)
<5 years							
Survey 1 (2017)	335	78 (73–82)	77 (72–81)	38 (33–43)	36 (31–42)	40 (35–45)	40 (35–45)
Survey 2 (2018)	244	70 (64–76)	70 (65–76)	23 (18–29)	23 (18–29)	47 (41–53)	47 (41–54)
Survey 3 (2019)	243	70 (64–75)	69 (63–75)	19 (15–25)	19 (14–24)	51 (44–57)	50 (43–56)
Survey 4 (2020)	185	52 (45–59)	53 (46–61)	12 (8–17)	12 (7–17)	40 (33–47)	41 (34–49)
≥5 years							
Survey 1 (2017)	584	34 (31–38)	32 (28–36)	13 (10–15)	12 (9–15)	22 (19–25)	20 (17–24)
Survey 2 (2018)	697	46 (42–50)	47 (43–50)	12 (10–15)	13 (10–15)	34 (30–37)	34 (30–38)
Survey 3 (2019)	689	39 (36–43)	40 (36–43)	9 (7–12)	10 (8–12)	30 (26–33)	29 (26–33)
Survey 4 (2020)	666	36 (33–40)	36 (33–39)	8 (6–10)	7 (5–9)	29 (25–32)	29 (25–32)

[a]Standardised using the respective population structures of the two study sites taken from population models of the Nigerian census[37].

Therefore, even among the 34% of new pneumococcal infections that have not been potentially averted by indirect effects in Pakoto, the risk of developing disease will still be attenuated (by 77%) if the infected child has been vaccinated with PCV10, as most have.

This concept of additional gains from indirect vaccine effects is substantiated by the results from other settings. In Kilifi, Kenya, for example, a 74% decline in VT carriage prevalence among children aged <5 years was associated with a 92% decline in VT IPD in this age group[14]. In Sao Paulo, Brazil, a 91% decline in VT carriage prevalence among toddlers aged 12–23 months was associated with an 83–87% decline in VT IPD in children across the whole age range <5 years[15,16].

The decline in VT carriage prevalence in Nigeria was accompanied by an increase in NVT carriage prevalence among children in Kumbotso (rural) and among older persons in both settings, with adjusted prevalence ratios of 1.26–1.34. In Kenya, the 74% decline in VT carriage prevalence was accompanied by a 1.71-fold increase in NVT carriage prevalence, though there was no significant rise in serotype replacement disease[14]. Non-vaccine serotypes with high frequency in the final surveys in children <5 years were 6A, 19A, 11A, 15B, and 16F. The first two are contained in the alternative PCV10 manufactured by Serum Institute of India, and 11A and 15B are contained in the PCV20 recently licensed for adult use[17,18]. This NVT distribution suggests that if

Table 4 | Prevalence ratios (PR), and 95% CI, showing changes in overall, non-vaccine serotype (NVT), and vaccine serotype (VT) carriage stratified by age and site

	Overall carriage		VT carriage		NVT carriage	
	Crude PR	Adjusted age-standardised PR[a]	Crude PR	Adjusted age-standardised PR[a]	Crude PR	Adjusted age-standardised PR[a]
PR for carriage in the final survey compared to the baseline survey[b]						
Kumbotso (rural)[c]						
All ages	1.06 (1.00–1.11)	1.00 (0.95–1.05)	0.55 (0.45–0.67)	0.52 (0.43–0.64)	1.32 (1.22–1.44)	1.30 (1.19–1.42)
<5 years	0.97 (0.82–1.14)	0.97 (0.92–1.02)	0.52 (0.41–0.67)	0.52 (0.41–0.67)	1.34 (1.17–1.54)	1.34 (1.17–1.54)
≥5 years	1.12 (0.97–1.28)	1.06 (0.97–1.14)	0.58 (0.43–0.78)	0.53 (0.39–0.72)	1.31 (1.18–1.46)	1.26 (1.12–1.40)
Pakoto (urban)[d]						
All ages	0.79 (0.71–0.88)	0.72 (0.65–0.80)	0.40 (0.31–0.51)	0.34 (0.26–0.45)	1.09 (0.95–1.26)	1.03 (0.89–1.20)
<5 years	0.67 (0.58–0.78)	0.68 (0.58–0.79)	0.32 (0.21–0.48)	0.31 (0.20–0.48)	1.01 (0.81–1.25)	1.02 (0.82–1.28)
≥5 years	1.05 (0.91–1.22)	1.07 (0.90–1.28)	0.61 (0.44–0.86)	0.60 (0.41–0.87)	1.30 (1.07–1.58)	1.36 (1.10–1.69)

[a]Adjusted for symptoms of upper respiratory tract infection in past 2 weeks, living with ≥2 children aged <5 years, and age-standardised to the respective age distribution of study sites.
[b]PR = prevalence ratios comparing each survey compared to the baseline (first) survey.
[c]Five surveys (2016–2020).
[d]Four surveys (2017–2020).

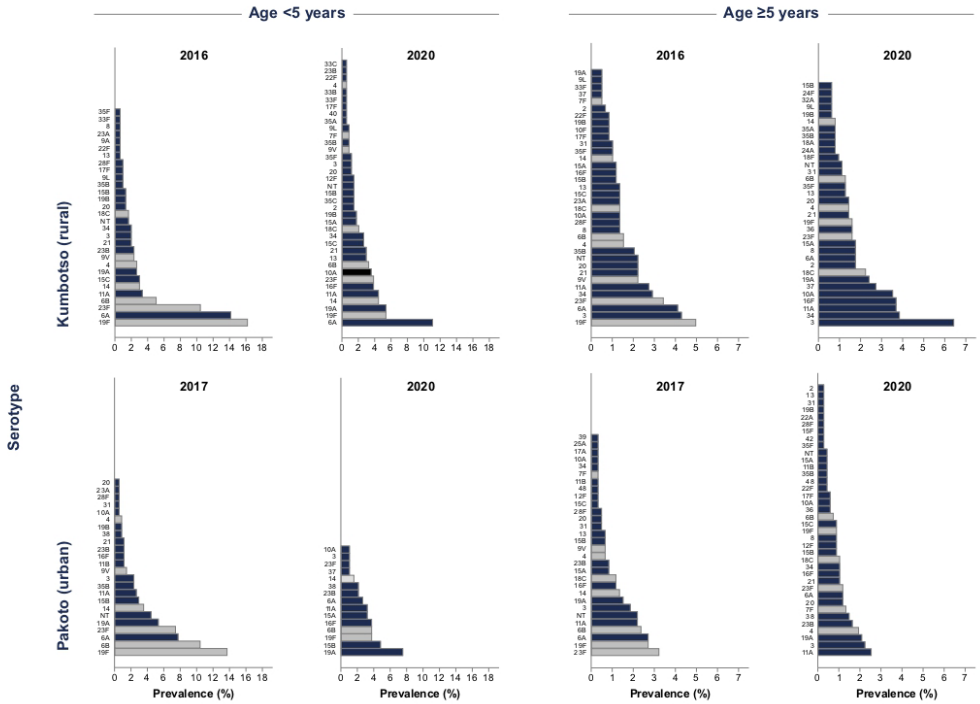

Fig. 2 | Serotype-specific carriage prevalence per survey stratified by age group. Distribution and ranking of serotypes in carriage (serotypes with >1 isolate) among children aged <5 years and persons ≥5 years by vaccine-type (greyscale bars – vaccine-serotypes, navy blue bars – non-vaccine serotypes) in the baseline and final surveys. Note the differences in scale in graphs by age.

serotype replacement disease becomes problematic, it may be controlled by wider valency vaccines. However, the relevance of serotype replacement carriage is dependent on the inherent invasiveness of the serotypes increasing in prevalence[19–21] which can only be ascertained from linked studies of carriage and IPD[14,20,22].

The study findings need to be interpreted in light of several practical constraints. The study began more than four months after PCV10 introduction, and at the baseline survey, an estimated 7–15% of children aged <5 years had already been vaccinated. Had the baseline survey pre-dated PCV10 introduction, the measured impact may have been larger. The evaluation is a 'before-after' study which is susceptible to confounding by secular trends in VT carriage prevalence. It is difficult to control for this possibility in retrospect. Nonetheless, it is unlikely that secular trends alone could account for so large an effect

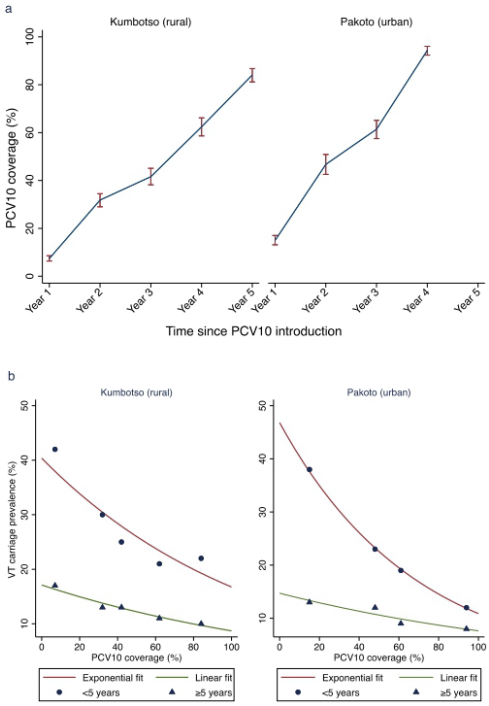

Fig. 3 | Coverage of PCV10 and its relationship to VT carriage. a (top) Annual Coverage of two doses of PCV10 among children aged < 5 years. Year 1 represents the year of PCV10 introduction. PCV10 coverage values for Year 3 to Year 5 were assessed directly among 817, 655 and 693 children in Kumbotso, and for Year 3 and 4 among 652 and 661 children in Pakoto. PCV10 coverage values for Year 1 and Year 2 were estimated using a birth-cohort analysis of children observed during Years 3–5 (among 2165 and 1140 children in Kumbotso, and 1,313 and 568 children in Pakoto). Error bar = 95% confidence interval CI). **b** (bottom). Relationship between Vaccine serotype (VT) carriage prevalence and PCV10 coverage. Scatter graph of log-linear regression among children aged <5 years and linear regression among persons ≥5 years of VT carriage prevalence against PCV10 coverage for each of the 9 surveys, stratified by age of carrier and shown separately for the Kumbotso (rural) site and Pakoto (urban) site. The lines for children (aged <5 years) are exponential fits (log-linear regression) and the lines for the older persons (age ≥5 years) are arithmetic (linear regression). Values from the log-linear regression among children are exponentiated and shown here on the non-log (arithmetic) scale.

size on VT carriage. The study design did, however, control for seasonal variation in pneumococcal carriage[23], as the surveys were done at the same time each year.

Vaccination coverage surveys were only introduced in 2018, and we inferred the coverage estimates for young children prior to 2018 from the coverage results among older children. Despite random selection and a study of adequate size, the coverage data contain internal inconsistencies; for example, in Pakoto, the rise in coverage in Year 3 (2019) was >40% and yet only ~20% of children aged <5 years were eligible to be vaccinated in that year. This may implicate poor recall of vaccination among caregivers of older children sampled in 2019. Vaccination coverage is notoriously difficult to ascertain[24]. Therefore, the ecological relationship we observe between coverage and VT carriage in older persons should be interpreted with some caution.

For practical reasons we selected two markedly different sites to represent the broad environmental and socio-demographic differences in Nigeria. However, we do not consider these sites to be wholly representative of all settings in Nigeria. Households in the rural site (Kumbotso) from northern Nigeria were larger, had more children and generally used solid cooking fuel. Households in the urban site (Pakoto) from southern Nigeria were smaller, had substantially fewer children and generally used gas and kerosene for cooking. At baseline, VT carriage prevalence was higher in the rural setting at all ages but, paradoxically, vaccine impact was greater in the urban setting, at least among children <5 years old; adjusted prevalence ratios were 0.52 in Kumbotso and 0.31 in Pakoto. This differential impact may be attributable to the steeper rise in PCV10 coverage among children aged <5 years in Pakoto. Alternatively, the lower density of children in urban households may imply a lower force of infection. A high force of infection has been proposed as an important cause of residual VT carriage in mature vaccine programmes in Africa[25], and in Kumbotso, VT carriage prevalence reaches its nadir at 22% in years 2019/2020, compared to 9% in Pakoto in 2020.

Hence, the impact of the vaccine on carriage prevalence is likely to be affected by several additional factors; the baseline serotype distribution, age-specific carriage prevalence, demography, the contact patterns of the community, the probability of transmission at each contact and the duration of carriage and of vaccine-induced immunity[26–28]. The age structure of the vaccinated population is also influential; for example, a catch-up campaign for children aged <5 years in Kenya elicited a 64–66% reduction in VT carriage prevalence at all ages within six months of PCV10 introduction[29]. The full interaction of these effects can only be understood within a formal framework, such as a dynamic transmission model. Even here, the accuracy of predicting disease depends on a clear understanding of the risk of disease per episode of carriage for both VTs and NVTs[30,31]. The full spectrum of data required to parameterise such a model is not currently available for Nigeria.

Among children, we found that VT carriage declines exponentially with a large reduction in VT carriage prevalence observed at low levels of increasing PCV10 uptake. In an ecological analysis in Australia, 73% of VT-IPD cases were estimated to have been prevented by approximately 50% vaccine uptake of PCV7 [32], which lends credence to the hypothesis that indirect effects may begin at relatively low levels of uptake. It is also possible that our data are capturing the dynamic stage of a complex polynomial effect, and the exponential fit works only within the coverage range we explored. Although both direct and indirect effects are expected in children, changes are mostly driven by the latter, which supports the non-linear effect observed. Given that the impact on adult carriage is entirely attributable to indirect effects, we would expect the same function should be observed in older people. The arithmetic decline we observed in this population is, therefore, difficult to explain.

We restricted our study to detect a single serotype in each swab despite abundant evidence supporting multiple serotype colonisation in children[32]. The dynamics and clinical importance of multiple serotypes in nasopharyngeal carriage are not fully understood[19,33]. Nonetheless, sampling a single strain per child provides a valid estimate of the distribution of serotypes colonising the population of children in these areas.

The measurable impact on VT carriage reported here should reassure immunisation policymakers and service providers in Nigeria that, in settings with similar baseline epidemiology and comparable vaccine coverage across the country, PCV10 is bringing about population protection through its indirect effect. This protection is likely to have reduced the incidence of pneumococcal disease among all ages by 48–66%, depending on the setting. Among the majority of children aged <5 years who have now received a course of PCV10, this indirect effect will have been augmented by direct effects that are likely to be

very strong. The decline in VT carriage prevalence as PCV10 coverage increases among children <5 years suggests that, in settings with suboptimal coverage, efforts to improve coverage will yield significant reductions in carriage and transmission and, therefore, disease incidence.

Methods

Study design and participants

We conducted annual cross-sectional carriage surveys in Kumbotso, Kano State and Pakoto, Ogun State (Fig. 1). The sites were purposively selected to represent a rural and urban setting, respectively. We did four surveys (2017–2020) in the rural site and three (2018–2020) in the urban site. PCV10 was introduced in Kumbotso in July 2016 and in Pakoto in October 2016 with a schedule of three primary doses (3p + 0) at ages 6, 10 and 14 weeks and no booster. There was no formal catch-up campaign for children aged ≥12 months. From 2018 onwards, we conducted annual vaccine coverage surveys in both sites simultaneously with all carriage surveys. The target population for the carriage and vaccine coverage surveys was defined as residents living within 10 km of the Kumbotso and Pakoto Comprehensive Primary Health Care Centres, respectively. Baseline carriage surveys were conducted in December 2016 (rural) and February 2017 (urban), four to five months after PCV10 was introduced, and have already been published[12]. They are included in this analysis as the reference baseline.

Carriage surveys were seasonally restricted at each site; November/December for four years (2017–2020) in the rural site and February/March for three years (2018–2020) in the urban site (Fig. 1). Carriage surveys targeted all ages, and each annual sample was independent of all other samples. PCV10 coverage surveys targeted children aged <5 years who were age-eligible to have received PCV10 at the date of the baseline carriage survey. Each annual PCV10 coverage sample was selected independently of prior samples.

Having selected representative study areas, we used a two-stage sampling design. In the first stage, we selected households using simple random sampling. To obtain a sampling frame, we conducted a census of all households in the catchment area before each survey. We selected separate samples of households for the carriage and PCV10 coverage surveys. If the household was known to be occupied, but there was no one at home, we revisited it later. If the house was non-residential, unoccupied, or empty, we chose the next household on the list.

In the second stage of sampling for the carriage surveys, we randomly selected one participant per household drawn from a specific age-stratum. We recruited participants in ten age strata (<1, 1–2, 3–4, 5–9, 10–14, 15–19, 20–39, 40–49, 50–59, and ≥60 years), starting with the lowest and moving upwards, from household to household, until we had recruited one participant per age group and then we restarted the process. If there was no participant in a particular age group in the household or if the targeted individual declined to participate, we selected the next age group in sequence and then looked for the missed age group in the next household.

The baseline surveys sampled the same defined catchment areas at all ages using a convenience sample of volunteers, recruited at the two health centres, recruited by community outreach[12]. For the baseline carriage surveys (2016/2017)[12], the sample size was set at 1000 participants to achieve a desired precision; given a VT carriage prevalence of 22–26% in this survey, we estimated a prevalence reduction of 50% could be detected with a power of 0.90 if the follow-up surveys were also 1000 in size. Therefore, we targeted to recruit 100 participants in each of the ten age groups.

In the second stage of sampling for the PCV10 coverage survey, we recruited all eligible children per selected household. A sample size of at least 639 children per site per survey was sufficient to estimate coverage of the second dose of PCV of 50% with a 5% precision (i.e., a coverage of 45–55%), assuming at least two eligible children per household, an intra-class coefficient (ICC) of 0.33 (as recommended by WHO[34]) and an 80% probability of response or participation[35]. Targeting a vaccination coverage of 50% allowed the estimation of the largest possible sample size required.

Procedure

Sociodemographic and clinical information was obtained from carriage survey participants using an interviewer-administered questionnaire. Nasopharyngeal swabbing, transport, storage and culture were done according to WHO-recommended standards[36]. We collected one swab specimen per participant from the posterior wall of the nasopharynx using nylon-tipped flexible flocked swabs (FloQSwabs®). Swabs were transported to the laboratory within 8 h of collection in skimmed milk-tryptone-glucose-glycerine (STGG) on ice packs in a cold box and were stored at −80 °C to −55 °C before shipping on dry ice to the KEMRI-Wellcome Trust Research Programme (KWTRP), Kilifi, Kenya. In Kilifi, swabs were stored at −80 °C until they were thawed and cultured on blood agar with 5 µg/ml gentamicin.

We identified pneumococci by α-haemolysis and optochin sensitivity testing. For optochin-resistant isolates (zone of inhibition <14 mm diameter), we used bile solubility testing to confirm *S. pneumoniae*. For serotyping, we selected one colony per plate from the dominant colony morphology. We identified serotypes using latex agglutination confirmed by Quellung Reaction. For isolates with inconclusive serotyping, we confirmed species and serotype by polymerase chain reaction (PCR) for autolysin (*lytA*) and capsular locus genes, respectively[36].

For the PCV10 coverage survey, we obtained the PCV10 vaccination status of each child in the household, including doses and dates received from the vaccination cards or caregiver recall, through household interviews of caregivers.

Statistical analysis

Carriage surveys. We calculated the total (all ages) and age-stratified prevalence of overall carriage (all pneumococci), VT pneumococci, and NVT pneumococci for each survey year. Vaccine serotypes (VT) were those contained in the vaccine introduced locally (PCV10 – serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F). Any other serotype, including non-typeable isolates, was classified as NVT. We recalculated VT prevalence for four other commercially licensed PCVs (Supplementary Table 8). We standardised crude prevalence estimates to the population age structure of Kumbotso (for rural) and Ifo and Ado-Ota (for urban) Local Government Areas (LGAs). These were obtained from 2019 population models of the 2016 Nigerian census data[37].

We assessed changes in carriage prevalence across the survey years using Chi-square test for trend. To derive prevalence ratios (PRs) comparing the last survey with the first, we modelled carriage prevalence using log-binomial regression or Poisson regression with robust standard errors when the models failed to converge. We adjusted PRs for exposure variables independently associated with carriage and survey year at $p < 0.1$ which included: living with children aged <5 years and a history of cough and runny nose in the preceding two weeks. We also adjusted for the stratified sampling method by (probability) weighting age-specific PRs by the local population age structure, as above, obtained from the Nigerian census data[37]. We calculated PRs for the total population (all ages), for children aged <5 years and for persons aged ≥5 years.

Vaccination coverage surveys. The purpose of the coverage survey was to infer population immunity, not to evaluate programme effectiveness. Therefore, we estimated PCV10 coverage in each survey year (2018–2020) as the proportion of children aged <5 years (regardless of age-eligibility) who received two doses of PCV10 irrespective of timing and age of receipt. In addition, because we did not conduct PCV10 coverage surveys in the early period (2016–2017), we used a birth

cohort analysis to estimate the PCV10 coverage of children aged <5 years retrospectively from the data collected in 2018–2020.

Relationship between PCV10 coverage and VT carriage. Within the range of vaccine coverage observed, we analysed a simple ecological association between population-level PCV10 coverage in children aged <5 years and VT carriage, in both children aged <5 years and persons aged ≥5 years, using linear regression. We considered a non-linear relationship between PCV10 coverage and VT carriage using a log-linear model and compared the fit of linear to the log-linear model graphically. We also examined this non-linear relationship by comparing the models using the Akaike Information Criterion (AIC). A lower value of AIC is a better fit model. To allow direct comparison of AIC values from the linear and log-transformed model, we adjusted the AIC of the log-linear model by adding the following quantity[38]:

$$2 \times \mathrm{sum}(\log(\mathrm{VT\ carriage})) \quad (1)$$

We did all the analysis separately for each site with Stata® version 15.1(College Station, TX, USA).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The authors declare that data supporting the findings of this study are available within the paper and its supplementary information files (Supplementary Data). Additional data requests can be made to the KEMRI-Wellcome Trust Research Programme Data Governance Committee (dgc@kemri-wellcome.org).

Code availability

Data were analysed using Stata® version 15.1 (College Station, Texas, USA).

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Author contributions

A.L.A., I.M.O.A., J.A.G.S. and J.O. contributed to study concept and design. A.L.A. led the fieldwork with input from D.A., A.K., M.M.B., I.A.A., C.A.N.O., V.I. and K.O.; A.K. led the laboratory work. B.A. oversaw the curation and management of data. A.L.A. performed all statistical analyses with input from J.O., I.M.O.A. and J.A.G.S.; A.L.A. wrote the first draft. A.L.A., B.K., I.M.O.A. and J.O. had direct access to and have verified the underlying data reported in the manuscript. All authors contributed to critical revision of the manuscript for intellectual content, and had final responsibility for the decision to submit for publication.

Competing interests

The authors declare no competing interests.

Ethical approval

Ethics approval for study was granted by the Research Ethics Committees of Aminu Kano Teaching Hospital (NHREC/21/08/2008/AKTH/EC/2165), Kano State Ministry of Health (MOH/OFF/797/T.I/596), Lagos University Teaching Hospital (ADM/DCST/HREC/APP/10300); the Kenya Medical Research Institute's Scientific and Ethical Review Unit (SERU 3350); and by the London School of Hygiene and Tropical Medicine Observational/Interventions Research Ethics Committee (Ref. 11670).

Informed consent

Written informed consent was obtained from participants/guardians.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-023-38277-z.

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4 Evaluation of statistical models of carriage to predict the impact of the 10-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in Nigeria (PhD Objective 2)

4.1 Preamble

In this chapter, I evaluate the applicability of three statistical models to predict the impact of PCV10 introduction on IPD using observed carriage data from Nigeria. The models are carriage-based and have been previously validated and published. I assess the output of the models, taking into consideration the validity of their underlying assumptions in Nigeria.

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Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I together with IA Adetifa JAG Scott designed the study. I participated in fieldwork for the baseline carriage survey. I led and coordinated the fieldwork and data collection for the post-PCV carriage surveys. I extracted data from secondary sources. I conducted analysis with input from J Ojal, C Mburu and analysis codes provided by authors of the models. I interpreted the findings with input from JAG Scott, K Gallagher and S Flasche. I wrote first draft of the manuscript.

SECTION E

Student Signature	[redacted]
Date	11/02/2024

Supervisor Signature	[redacted]
Date	22/02/2024

4.2 Author contributions

I, together with IA Adetifa JAG Scott designed the study. I participated in fieldwork for the baseline carriage survey. I led and coordinated the fieldwork and data collection for the post-PCV carriage surveys. D Akech led the survey preparation logistics. A Karani led the laboratory analysis and sample storage. I extracted data on IPD and case-carrier ratios from secondary sources. I conducted analysis with input from J Ojal, C Mburu and analysis codes provided by authors of the models. I interpreted the findings with input from JAG Scott, K Gallagher and S Flasche. I wrote first draft of the manuscript. All authors approved the manuscript before submission.

4.3 Title page

Evaluation of statistical models of carriage to predict the impact of the 10-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in Nigeria.

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4.4 Abstract

Background: A substantial fraction of the population-level impact of Pneumococcal Conjugate Vaccines (PCVs) on Invasive Pneumococcal Disease (IPD) is mediated through indirect effects, i.e., their capacity to protect against carriage acquisition of vaccine serotypes (VTs) among vaccinees, thereby proportionately reducing transmission and indirectly averting invasive disease in the whole population. Therefore, by relying on the consequent near elimination of VT carriage, early carriage-based models successfully captured the impact of seven-valent PCV (PCV7) in high-income settings. We sought to determine the applicability of three published statistical carriage-based models for the evaluation of PCV10 impact in Nigeria, where carriage prevalence data are available from urban and rural sites.

Methods: We applied external data, with assumptions, to empirical carriage prevalence data to predict IPD incidence rate ratios (IRRs). The models assume PCV has no effect on serotype invasiveness among carriers because VT carriage is eliminated. Model 1 uses estimates of relative proportions of pre-PCV VT-IPD to predict IRRs. Model 2 uses pre-PCV serotype IPD incidence, while Model 3 uses measures of serotype invasiveness, the case-carrier ratio (CCR).

Results: Model 1 estimates the largest PCV10 impact on overall IPD (IRR:0.38 and 0.50) in the urban and rural sites, respectively. Whereas estimates from Model 2 (IRR:0.69 and 0.78) and Model 3 (IRR:0.63 and 0.70) were more conservative.

Conclusions: VT carriage was not eliminated in our setting, so Model 1 estimates the hypothetical maximum impact. Relying entirely on indirect effects, Models 2 and 3 represent the minimum impact of PCV. Predictions would be more accurate if they accounted for

direct effects among vaccinated VT carriers. The study illustrates the importance of capturing vaccination data on individuals sampled in carriage prevalence surveys designed to estimate IPD burden at population level.

4.5 Introduction

Models have traditionally been used to simplify the complex relationships between host and agent in infectious disease dynamics to better understand disease burden and pathogen transmission and to predict the potential impact of interventions such as vaccines.[275] In pneumococcal disease epidemiology, models have been used across different settings to assess vaccine impact [116,196,247,276], predict the potential impact of vaccination [248,277], and guide decisions on vaccine schedules [218]. The pneumococcal conjugate vaccination (PCV) protects against both pneumococcal carriage acquisition and invasion among carriers. By reducing transmission, the PCV programme has the potential for substantial indirect herd effects. Ideally, PCV impact is best demonstrated via disease endpoints measured from population-linked invasive pneumococcal disease (IPD) surveillance systems. Disease surveillance systems are, however, expensive and technically challenging to establish and sustain.[205] Therefore, pneumococcal disease surveillance is rare in low- and middle-income countries (LMICs).[278]

Models that extrapolate the impact of PCV on carriage to the impact on pneumococcal disease have been developed and validated as alternatives to disease surveillance data. These include models that incorporate complex pneumococcal transmission dynamics[241,247,248,276], those that rely on the serotype distribution and changes in carriage prevalence [251,279], and those that utilise serotype-specific carriage invasiveness.[77,86,252,280] Dynamic models allow for the incorporation of direct and indirect effects, but their computational complexity makes them slow to develop and less widely applicable.

In the seven-valent PCV (PCV7) era, epidemiologists developed statistical carriage-based models that captured indirect vaccine effects to predict vaccine impact on IPD in high-income countries (HICs), where disease data could be used to evaluate the models.[86,251,252] In this paper, we compare the assumptions and outputs of three of these models and assess their applicability in evaluating the impact of PCVs on IPD in a low-income setting where IPD surveillance was absent.

4.6 Methods

4.6.1 Models

4.6.1.1 Model 1- Flasche Model

Flasche *et al.* [252] proposed a model to predict the impact of PCV on total IPD incidence. This simplified version of the more complex SIS-type dynamic transmission model uses the relative prevalence of VT and NVT serotypes among carriage and disease isolates in the pre-vaccine era.[252]

In the absence of vaccination, the incidence of IPD is expressed as a carriage rate per person-time and the average risk that a carriage episode results in invasive disease, i.e., invasive capacity (IC) or case-carrier ratio (CCR), and this can be stratified into vaccine serotypes (VT) and non-vaccine serotypes (NVTs).

$$IPD\ Pre = Carr\ Pre_{vt}\ x\ CCR_{vt}\ +\ Carr\ Pre_{nvt}\ x\ CCR_{nvt}$$

[4.1]

In the post-PCV period, IPD incidence can be estimated as follows:

$$IPD\ Post = Carr\ Post_{vt}\ x\ CCR_{vt}\ +\ Carr\ Post_{nvt}\ x\ CCR_{nvt}$$

[4.2]

The model 1 makes three assumptions (see Table 1): (i) VT are eliminated, eventually, in the post-PCV period ($Carr\ Post_{vt} = 0$), (ii) a proportion, λ, of the VT carriage will be replaced by NVT carriage ($Carr\ Post_{nvt} = \lambda Carr\ Pre_{vt} + Carr\ Pre_{nvt}$), and (iii) the invasive capacity or CCR of NVT pneumococci will remain unchanged after vaccine

introduction($CCR\ Post_{nvt} = CCR\ Pre_{nvt} = \frac{IPD\ Pre_{nvt}}{Carr\ Pre_{nvt}}$). IPD incidence post-PCV can, therefore, be reformulated as follows:

$$IPD\ Post = (\lambda Carr\ Pre_{vt} + Carr\ Pre_{nvt})\ CCR_{nvt} \quad [4.3]$$

PCV impact (Incidence rate ratio [IRR]):

$$Incidence\ Risk\ Ratio, IRR = \frac{IPD\ Post}{IPD\ Pre}$$

Which simplifies to (see Supplement: Appendix 1 for details):

$$IRR = \frac{\lambda c + 1}{d + 1} \quad [4.4]$$

Where:

c = odds of VT carriage pre-PCV d = odds of VT disease pre-PCV

The model was validated in nine settings and demonstrated a good fit. Its predictions were robust to the introduction schedule and a wide range of PCV7 uptake levels. It was timed to three years after the introduction of PCV7 and was recently applied to estimate the global effectiveness of higher-valent PCVs.[281] The assumptions for Model 1 were valid for PCV7 introduction because it was applied predominantly to HICs where the force of infection was low, vaccine uptake was high, and introduction resulted in the rapid elimination of VT carriage and near complete replacement by non-PCV7 serotypes.

4.6.1.2 Model 2 – Weinberger Model

Weinberger *et al*. [251] proposed a model to estimate the relative changes in IPD incidence as a function of the serotype-specific pre-PCV IPD incidence and changes in carriage prevalence of the serotype. The model was initially validated using IPD incidence and carriage prevalence data from different populations (the UK, the Netherlands, USA – including Native American populations) and South Africa.[116,251]

$$Expected(IPD\ Post_i) = IPD\ Pre_i \times \frac{Carriage\ Post_i}{Carriage\ Pre_i}$$

[4.5]

$$= IPD\ Pre_i \times PR_i$$

Where:

i represents individual serotypes.

The key assumptions (see Table 1) of Model 2 are: (i) vaccine effectiveness against IPD is wholly accounted for by protection against carriage; (ii) there is a constant relationship between carriage and invasion, which is not affected by the vaccination status of carriers in the post-PCV era; and (ii) the underlying population IPD risk remains constant.

$$Overall\ Expected\ (IRR) = \frac{Expected(\sum_i^n IPD\ Post_i)}{Observed(\sum_i^n IPD\ Pre_i)}$$

$$= \frac{Observed(\sum_i^n (IPD\ Pre_i \times PR_i))}{Observed(\sum_i^n IPD\ Pre_i)}$$

$$= \sum_{i}^{n} (\psi_i \times PR_i)$$

[4.6]

Where:

ψ_i = proportion of IPD in the pre-vaccine era attributable to the i^{th} serotype group.

The model considers changes in the prevalence of carriage in *i* strata. Applying the model where each serotype represents a single stratum did not produce optimal results when validated.[251] However, by grouping pneumococcal serotypes broadly into VT, high-incidence NVT, and low-incidence NVT, the model predicted (within 95% predictive interval) overall changes in IPD incidence as well as changes for the serotype groups.

As this model relies on carriage prevalence ratios, it assumes that all of the PCV impact on VT-IPD is mediated through reduction of VT carriage acquisition and that there is no additional direct effect of PCV on reducing VT invasive capacity. Therefore, it only accounts for vaccine protection against carriage and disregards any subsequent protection against invasion among VT carriers. Since the protection against carriage leads to a substantial indirect vaccine impact by reducing VT acquisition and VT exposure through reduced transmission, this assumption will be valid where VT carriage is eliminated. This is because eliminating VT transmission will nullify the benefit of any impact on invasion given carriage.

The assumption that the invasive capacity of each serotype remains constant after PCV introduction is justified by evidence that the invasiveness of serotypes is an intrinsic property independent of time and geography.[79,282] The assumption that vaccination does not affect invasiveness can be acceptable to some extent. We accept that PCV does not affect: (i)

carriage of NVTs; (ii) invasiveness of NVTs; (iii) invasiveness of VTs among NVT carriers; and (iv) invasiveness of VTs or NVTs among non-carriers. If VT carriage is almost eliminated, the impact of PCV on the invasiveness of VT among vaccinated VT carriers will be negligible, so we can reasonably accept this assumption.

The second assumption of unchanging population susceptibility to IPD is also reasonable in HICs and when considering relatively short prediction periods that are practical for vaccine assessment (5 years), although this can vary by setting. Besides, changes in population susceptibility are likely to affect the VT and NVT disease risk to the same extent.

4.6.1.3 Model 3 –Shea Model

Shea et al. [77] validated a third model which uses serotype-specific carriage prevalence and invasive capacity to estimate the incidence of IPD.

$$Incidence\ (IPD) = \sum_{i}^{n} (Carriage\ Prev_i \times IC_i)$$

[4.7]

Where carriage is the instantaneous 'prevalence of carriage', and the IC is the 'Invasive Capacity' of carriage. The incidence rate ratio can be estimated if there are data on carriage prevalence in the post- and pre-vaccine era.

$$IRR = \frac{\sum_{i}^{n} (Carriage\ Prev\ Post_i \times CCR\ Post)}{\sum_{i}^{n} (Carriage\ Prev\ Pre_i \times CCR\ Pre)}$$

[4.8]

The measure of invasive capacity here is the Case-Carrier Ratio (CCR), which can be estimated from two epidemiological observations in the same population:

$$CCR_i = \frac{Incidence\ of\ IPD_i}{Prevalence\ of\ Carriage_i}$$

[4.9]

Multiplying the carriage prevalence by the CCR would give an estimate of the serotype-specific IPD incidence. When applying this model to the Nigerian settings, we have assumed that CCRs are intrinsic serotype-specific properties, which vary little with setting. Therefore, CCR values calculated from other populations can be applied to observed Nigerian carriage prevalence to estimate IPD incidence and vaccine impact. This concept has been used to predict vaccine impact on acute otitis media in the US by applying CCRs calculated from an Israeli population to US carriage prevalence data.[77]

The model also assumes that the CCR is constant in the pre- and post-PCV eras; as in model 2, the applicability of a model requiring this assumption depends on the assumption that VT carriage will largely be eliminated by the vaccine programme, as it is otherwise likely that individual vaccinees will experience a significant reduction in the risk of invasion when they become VT carriers.

We grouped serotypes into VT, high-incidence NVT, and low-incidence NVT to allow for comparison with Model 3 output,

4.6.1.4 Relationship between Models

The *Flasche, Shea,* and *Weinberger* models share the assumption of independence of CCR from vaccine receipt but approach the subject from different perspectives. Drawing on different types of external data, the *Shea* and *Weinberger* models are mathematically equivalent (see Supplement: Appendix 1).

Assuming VT elimination in carriage will make all three models similar. What will differ will be the data needs for each. Model 3 requires pre- and post-PCV carriage to infer disease based on external CCRs (i.e., a setting without IPD surveillance but with carriage surveys). Model 1 requires pre-PCV carriage and IPD to predict potential PCV impact on ID. Model 2 requires similar data input as Model 1 (pre-PCV disease and carriage data) but also post-PCV carriage data; making it the most data-hungry formulation and likely the most accurate if, indeed, all these data are available. The challenge for Model 2 will be the likelihood of the availability of this level of pre-PCV data but no post-PCV IPD, questioning its usefulness in reality. Another difference is that Models 2 and 3 can be formulated as either serotype-specific or serotype-group-specific, while Model 1 only uses serotype groups. For the other models, grouping serotypes is more pragmatic otherwise, important disease-causing types can be missed in carriage.

Table 4.1: Summary of model assumptions

Assumption	**Model**		
	Model 1(Flasche)	**Model 2 (Weinberger)**	**Model 3 (Shea)**
PCV effect on IPD mediated entirely by protection against VT carriage	✓	✓	✓
Serotype invasive capacity unaffected by receipt of PCV		✓	✓
VT elimination in carriage	✓		
NVT replacement in carriage	✓	✓	✓
No change in underlying IPD risk	✓	✓	✓

4.6.2 Data sources

4.6.2.1 Serotype-specific carriage

To estimate serotype-specific carriage prevalence in the pre-vaccine period, we used data from baseline carriage surveys conducted 4-5 months after PCV introduction in an urban and a rural site in Nigeria.[258] As PCV10 (GSK) was introduced without a catch-up campaign and as uptake was relatively modest, we estimated only a small percentage (7-15%) of children aged <5 years were vaccinated at the time of the baseline surveys, and therefore this could represent pre-vaccine epidemiology.[283] In the post-vaccine period, we conducted four (2017-2020) annual carriage surveys in the rural site and three (2018-2020) in the urban site.[283] These annual surveys used independent age-stratified random population samples and standard WHO-recommended techniques for nasopharyngeal swabbing, transport, storage and culture. Field and laboratory techniques, including the season of swabbing, were consistent across surveys.

We categorised serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F as PCV10 vaccine serotypes (VTs) and all other serotypes as non-vaccine serotypes (NVTs). In addition, we estimated serotype prevalence and proportions of VT and NVT carriage for children aged <5 years separately for the baseline and final (post-PCV) surveys in the two sites (rural and urban).

Annual pneumococcal VT and NVT carriage prevalence among children aged <5 years and the proportion of children aged <5 years vaccinated with PCV10

vaccinated are shown in Table S1. Serotype-specific carriage prevalence is shown in Figure S1.

To assess the potential of cross-protection by PCV10 against serotype 6A as reported in other settings, we did a sensitivity analysis considering a scenario where we assume that serotype 6A was a VT when categorising the serotypes.

4.6.2.2 Serotype-specific IPD

Given that there was no direct estimate of the incidence of IPD in Nigeria in the pre-vaccine era, we obtained serotype-specific estimates of baseline IPD incidence from a systematic review of the global distribution of serotypes in IPD among children <5 years (Table S2).[84] We extracted data on serotypes from the African sub-region, which included data from 22 different studies across 13 countries spanning 1980 to 2000. Eight of the studies came from three West African countries (Burkina Faso, Mali, and The Gambia), representing ~11% of all isolates from sSA. However, 74% of the isolates from sSA were derived from South Africa (Table S3).[84]

4.6.2.3 Measures of serotype-specific invasive capacity (case-carrier ratios, CCR)

We adopted serotype-specific CCRs (Table S4) from a meta-analysis of the ratio of IPD incidence to carriage prevalence estimated from 20 systematic and paired serotype data on asymptomatic carriage prevalence and disease samples of carriage in children.[253] A majority (15/20) of the paired studies were from countries in North America and Western Europe, and only 4/20 were from LMICs (Venezuela, Papua New Guinea and Morocco). Overall, 12/20 studies had samples from children that were strictly aged <5 years, while 8/20 studies included older (<6 years, <7 years

and <18 years) children. Studies also covered the pre- (11/20) and post-PCV (9/20) periods. A summary of the number of serotypes isolated, total isolates for carriage and IPD, carriage samples and IPD surveillance population by study are shown in Table S5.

4.6.3 Estimation of Uncertainty levels of predicted IRR and IPD incidence

We calculated the uncertainty in the IRR estimates using bootstrapping and estimated the lower and upper bounds of the 95% predictive interval as 2.5% and 97.5% of 10,000 bootstrap samples for Model 1 and 1,000 for Model 2. We calculated the 95% confidence limits of the IRRs from Model 3 by adding the standard errors of the CCR and carriage prevalence using the delta method, which allows the calculation of variances of log-transformed variables.[77,81,284] Details are included in the Supplement Appendix 2.

4.7 Results

Model 1 estimated that overall IPD incidence has declined by 50% over five years in the rural site and by 62% over four years in the urban site (Tables 2 and S6).

Model 2 estimated that the incidence of VT-IPD declined significantly by 49% in the rural site and by 57% in the urban site (Table 2). The model also estimated a significant decline in overall IPD incidence by 22% and 31% in the two sites; IPD caused by low-incidence NVT was estimated to have increased by 57% and 60%, respectively.

Model 3 outputs estimated that overall IPD has declined by 30% in the rural site and 37% in the urban site (Table 2, Figure 1). The model also estimated a 48% and 68% decline in VT-IPD in the urban and rural sites, respectively. The model only estimated a significant increase for low-incidence NVT-IPD in the rural site.

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Table 4.2 Comparison of output from the three models showing estimated incidence rate ratios (IRRs) for impact of PCV10 on invasive pneumococcal disease in rural and urban sites in Nigeria.

	IRR (95% CI)							
	VT		**High-incidence NVT**		**Low-incidence NVT**		**Overall**	
Kumbotso (rural)								
Model 1	N/A	N/A	N/A	N/A	N/A	N/A	0.50	0.47-0.54
Model 2	0.51	0.35-0.72	0.96	0.65-1.42	1.57	1.23-1.97	0.78	0.65-0.95
Model 3	0.52	0.44-0.61	0.90	0.73-1.10	1.59	1.26-2.00	0.70	0.67-0.73
Pakoto (urban)								
Model 1	N/A	N/A	N/A	N/A	N/A	N/A	0.38	0.36-0.39
Model 2	0.43	0.31-0.58	1.41	0.86-2.30	1.60	1.38-1.85	0.69	0.58-0.83
Model 3	0.32	0.26-0.40	0.88	0.70-1.13	1.09	0.88-1.40	0.63	0.60-0.67

Table 4.3: Comparison of output from the three models showing estimated incidence rate ratios (IRRs) for impact of PCV10 on invasive pneumococcal disease in rural and urban sites in Nigeria.

	IRR (95% CI) with Cross-protection against 6A*							
	VT		**High-incidence NVT**		**Low- incidence NVT**		**Overall**	
Kumbotso (rural)								
Model 1	N/A	N/A	N/A	N/A	N/A	N/A	0.44	0.40-0.50
Model 2	0.59	0.43-0.73	1.33	0.69-2.71	1.55	1.22-1.96	0.84	0.67-1.06
Model 3	0.60	0.52-0.69	0.96	0.72-1.27	1.59	1.27-2.00	0.70	0.67-0.73
Pakoto (urban)								
Model 1	N/A	N/A	N/A	N/A	N/A	N/A	0.26	0.25-0.28
Model 2	0.35	0.27-0.45	1.41	1.02-1.94	1.61	1.45-1.78	0.65	0.58-0.74
Model 3	0.33	0.30-0.39	1.27	0.95-1.69	1.09	0.86-1.40	0.63	0.60-0.67

For serotype-specific analyses from Model 3, PCV10 (and PCV10-related) serotypes dominated IPD at baseline. NVT serotypes increased in dominance post-PCV, but some VTs persisted in the predictions five years after PCV introduction (Figure 1). The serotypes predicted to cause most IPD post-PCV were 14, 12F, 7F, 19A, 2, 18C and 6A in the rural site, and 19A, 14, 12F, 6B, 19F and 3 in the urban site.

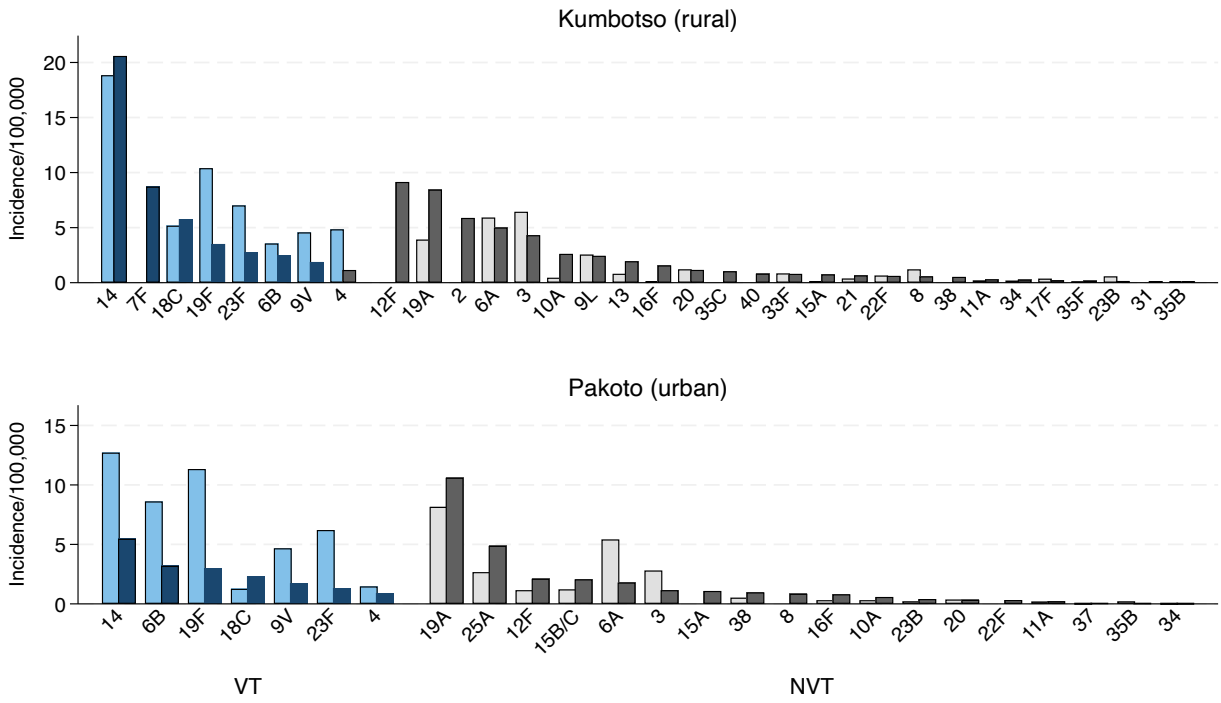

Figure 4.1: Side-by-side comparison of predicted serotype-specific incidence rates from Model 3.

Graphs show side-by-side comparison of predicted serotype-specific incidence rates for the baseline and post-PCV periods stratified by serotype groups (VT=blue and NVT=grey) in the rural (top) and urban (bottom) sites from Model 3. Lighter shades represent the baseline period and darker shades represent post-PCV period. Serotypes are arranged in descending order of incidence rates in the post-PCV period.

Assuming cross-protection against 6A led to larger estimates of impact in both sites for Model 1 and in the urban site for Model 2 (Table 3). Model 3 did not show any evidence of cross-protection in both sites.

Model 1 can only estimate overall IPD impact, and it predicted the largest relative decline in IPD incidence compared to Model 2 or Model 3. In addition to the impact on overall IPD, Models 2 and 3 also predicted the impact on VT- and NVT-IPD. The predictions from these two latter models were similar, particularly for VT and NVT-IPD in the rural site.

4.8 Discussion

In this paper, we used three previously validated statistical carriage prevalence-based models to estimate the impact of PCV introduction on IPD in Nigeria, where IPD surveillance is lacking. These models are based on the premise that carriage is a prerequisite for invasive disease and estimate vaccine effects mediated by protection against carriage, i.e., ignore any additional direct effects of PCV on invasion. Model 1 estimated a relative decline in overall IPD incidence of 50% in the rural site and 62% in the urban site. Models 2 and 3 incorporate post-PCV VT carriage prevalence, and their predictions were substantially lower, at 22-30% and 31-37% in the rural and urban sites, respectively.

For Model 1, the assumption of independence of invasiveness from vaccine receipt does not matter eventually because post-PCV, the assumption is that VT carriage is eliminated. In our setting, this key assumption was not met. VT carriage was not eliminated; indeed, VT carriage prevalence at the end of the introduction period was 22% in the rural area and 12% in urban area.[283] In HICs, VT carriage elimination was relatively rapid and complete after PCV7 introduction [73,285] supporting the use of this simple model. By contrast, PCV13 has not eliminated the extra-non-PCV7 serotypes in HICs.[286–288]. Neither PCV10 nor PCV13 has interrupted VT transmission in lower-income settings. In Mozambique, where 54% of children aged <5 years had received three doses of PCV10 three years after its introduction, VT carriage prevalence was 15-18%.[289] Even where vaccine uptake was high (>90%) or catch-up provided, VT carriage prevalence was 11% in the Gambia [290], 18% in Malawi [270] and 9% in Kenya [72] five to seven years post-PCV introduction. Thus,

by overlooking this residual VT carriage and the potential disease it causes, this model inevitably underestimates the incidence of IPD post-PCV and overestimates the impact. We could interpret the model predictions as the potential impact that would have accrued if VT carriage had been eliminated in Nigeria.

Model 2 estimated a significant reduction in overall IPD of 22% and 31% in the two sites, mostly due to a reduction in VT-IPD incidence. The model does not incorporate direct protection brought about among vaccinees against invasive disease among VT carriers. Thus, its predictions for impact on VT-IPD are probably underestimated. In South Africa, the model accurately predicted impact among unvaccinated children and adults, among whom indirect effects would drive impact.[116] In contrast, among vaccinated or vaccine-eligible children in South Africa and Kenya, the model underestimated vaccine impact, indicating the impact of the model's disregard of direct effects on invasiveness among vaccinees.[116,291]

Model 3 estimated a reduction in overall IPD of 30% and 37% in the two sites as a function of observed carriage prevalence in Nigeria and estimates of CCRs from 20 settings, none of which were in sub-Saharan Africa. This approach assumes that CCR is an intrinsic serotype characteristic [79,282], and therefore, values estimated from settings where such are available should be applicable anywhere. We have shown (Appendix 1, Supplement) how Model 3 mathematically reduces to Model 2 but uses CCRs as its input instead of prior IPD serotype distribution to interpret changes in the prevalence of carriage pre/post-vaccine. Using this approach, we predicted a significant relative decline in overall and VT-IPD incidence at nearly comparable

levels to Model 2, suggesting that the different reference data selected (CCRs versus prior IPD serotype patterns) are epidemiologically comparable.

PCV protects vaccinees against VT disease via two distinct routes, i.e., mucosal protection against VT carriage acquisition and systemic protection against VT invasion following carriage. As with model 2, model 3 also assumes that receiving PCV does not affect serotype invasiveness (CCR). Therefore, the predictions underestimate vaccine impact on VTs. For NVT carriers, the CCR does not change because PCV is assumed to have no effect on the invasive capacity of NVTs. For VTs, the prediction should take account of vaccination status. Among unvaccinated VT carriers, the CCR will remain constant in the pre- and post-vaccine era. Among vaccinated VT carriers, however, the CCR is likely to be lower because vaccine-induced systemic immunity means that were the child to become a carrier, the risk of invasion will be reduced.

For Model 3 to incorporate the additional vaccine protection against invasion among vaccinees, we suggest the following adjustments to Equation 8 (see Supplement Appendix 1 for derivation):

$$IRR = \frac{P'_{vt}\left[(VE_{inv}cov) + \left(R(1-cov)\right)\right] + P'_{nvt}}{P_{vt}R + P_{nvt}} \qquad [4.10]$$

P = prevalence in the pre-vaccine era (either VT or NVT)

P’ = prevalence in the post-vaccine era (either VT or NVT)

$VE_{inv} = \frac{CCR\prime_{vt}}{CCR_{vt}}$, the vaccine effectiveness against invasion given carriage which is estimated as the ratio of CCR_{vt} by vaccine era,

cov = vaccine coverage among VT carriers

$R = \frac{CCR_{vt}}{CCR_{nvt}}$, the ratio of CCRs by serotype group

Some evidence indicates that serotype-specific CCRs do not differ pre- and post-PCV [282], lending credence to the assumption for Models 2 and 3. However, for vaccinated VT carriers, VE against invasion is a function of VE against IPD and VE against carriage. Therefore, even if we accept that measured CCRs remain unchanged post-PCV, fewer PCV-driven VT carriage events at the population level will influence CCRs. Consequently, the average population CCR will be a function of the reduced VT carriage among vaccinees. In this scenario, the post-PCV CCR will still be lower than the pre-PCV CCR.

$$Average\ population\ post-PCV\ CCR = \frac{(CCR_u * p_u) + (CCR_v * p_v)}{N_{carr}} \quad [4.11]$$

Where:

CCR_u and CCR_v = CCR among unvaccinated and vaccinated

$CCR_v = CCR_u * VE_{inv}$,

$VE_{inv} = \frac{RR_{IPD}}{RR_{carr}}$,the ratio of relative reduction in IPD to relative reduction in carriage

$p_u \; and \; p_v$ = proportion of VT carriers among vaccinated and unvaccinated

N_{carr} = Number of carriers

Interpretation of pneumococcal carriage-based model predictions is subject to another constraint in addition to model-specific limitations discussed above. Our baseline carriage data were not strictly confined to the pre-PCV era because PCV10 had been introduced four to five months before the first survey; this may have led the models to underestimate the predicted impact on IPD. This effect is likely to be small because no formal catch-up was offered to older children when PCV10 was introduced, and we previously estimated that, at the time of the baseline survey, the coverage of two doses of PCV10 among all children aged <5 years was only 7% in the rural site and 15% in the urban site (see also Table S1). [283]

In conclusion, Model 1 makes a strong assumption about eliminating VT carriage, which has not been born out in the Nigerian setting examined. However, the intent of the model is not to predict exact PCV impact but rather to give an assessment on the plausible maximal impact that could be achieved if PCV programme is successful enough to largely eliminate VT carriage and transmission. Models 2 and 3 include an analysis incorporate post-PCV VT carriage data, but they disregard direct vaccine effects against invasion by VT, which are likely to be important in contexts like Nigeria, where there is substantial residual VT carriage. Model 2 depends critically on an accurate, observed estimate of IPD incidence in the pre-vaccine period, which was unavailable for Nigeria. The accuracy of Model 3 depends on a representative estimate of the CCR, though there is little relevant data here emanating from Africa.

Although these models are computationally simple and attractive for evaluating PCV impacts in sSA, these limitations undermine their general applicability. The fact that VT carriage persists in most African settings that have introduced PCV discounts the utility of Model 1 as a way to estimate current impact. The fact that there are no accurate data on the pre-PCV incidence of IPD discounts the utility of Model 2. Model 3 may be applicable if two modifications can be made; firstly, it requires credible estimates of the serotype-specific CCRs derived in populations that are representative of sSA; secondly, it requires adaptation to evaluate the direct effect of PCV among vaccinees in settings with persistent VT transmission. Unlike the deficiencies of Models 1 and 2, both of these deficiencies are amenable to further research, suggesting that Model 3 is the most propitious for evaluating PCV impact and guiding future policy in sSA using carriage studies as a proxy for complex and unaffordable IPD surveillance systems, but relies on selection of the most appropriate CCRs based on the setting, age group, and time period available.

4.9 Supplement to Research paper 2

Evaluation of statistical models to predict the impact of the 10-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in children aged <5 years in Nigeria.

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4.9.1 Appendix 1: Equations

Model 1

IPD incidence in the pre- and post-PCV are estimated as

$$IPD\ Pre = Carr\ Pre_{vt}\ x\ CCR_{vt}\ +\ Carr\ Pre_{nvt}\ x\ CCR_{nvt}$$

$$IPD\ Post = Carr\ Post_{vt}\ x\ CCR_{vt}\ +\ Carr\ Post_{nvt}\ x\ CCR_{nvt}$$

Assuming:

i. VT elimination, $Carr\ Post_{vt} = 0$
ii. NVT replacement λ, such that ($Carr\ Post_{nvt} = \lambda Carr\ Pre_{vt} + Carr\ Pre_{nvt}$)
iii. unchanged NVT invasiveness post-PCV

$$(CCR\ Post_{\ nvt} = CCR\ Pre_{\ nvt} = \frac{IPD\ Pre_{nvt}}{Carr\ Pre_{nvt}})$$

Then:

$$IPD\ Post = (\lambda Carr\ Pre_{vt} + Carr\ Pre_{nvt})\ CCR_{nvt}$$

PCV impact (Incidence rate ratio [IRR]):

$$Incidence\ Risk\ Ratio, IRR = \frac{IPD\ Post}{IPD\ Pre}$$

$$IRR = \frac{(\lambda Carr\ Pre_{vt} + Carr\ Pre_{nvt})\ CCR_{nvt}}{Carr\ Pre_{vt}\ x\ CCR_{vt}\ +\ Carr\ Pre_{nvt}\ x\ CCR_{nvt}}$$

IRR is then simplified to pre-PCV VT carriage and disease odds.

$$IRR = \frac{\lambda(\frac{Carr\ Pre_{vt}}{Carr\ Pre_{nvt}}) + 1}{(\frac{IPD\ Pre_{vt}}{IPD\ Pre_{nvt}}) + 1}$$

$$IRR = \frac{\lambda c + 1}{d + 1}$$

Where:

c = odds of VT carriage pre-PCV d = odds of VT disease pre-PCV

Relationship between Models 2 and 3

In both cases, this is likely to be wrong, and the effect of the vaccine in preventing invasion, conditional upon carriage, is likely to be strong, particularly in the presence of residual VT carriage. Hence, both models will underestimate the total impact of the vaccine introduction.

If we use an estimate of IC from the pre-vaccine era,

$$IC_i = \frac{IPD\ Pre_i}{Carriage\ Pre_i}$$

Then the *Shea* model resolves into the Weinberger model.

$$IRR = \frac{\sum_i^n (Carriage\ Post_i \times IC_i)}{\sum_i^n (Carriage\ Pre_i \times IC_i)}$$

$$IRR = \frac{\sum_i^n (Carriage\ Post_i \times IPD\ Pre_i / Carriage\ Pre_i)}{\sum_i^n (Carriage\ Pre_i \times IPD\ Pre_i / Carriage\ Pre_i))}$$

$$IRR = \frac{\sum_i^n (IPD\ Pre_i \times Carriage\ Post_i / Carriage\ Pre_i)}{\sum_i^n (IPD\ Pre_i))}$$

$$IRR = \frac{\sum_i^n (IPD\ Pre_i \times PR_i)}{\sum_i^n (IPD\ Pre_i)}$$

Modification of Model 3 to account for direct vaccine effects among vaccinated VT carriers

To estimate IPD, we would need to account for the reduced invasiveness among vaccinees who are VT carriers. Model 3 estimates IPD as a function of respective carriage prevalence and CCR in the pre and post-PCV periods, assuming CCR is constant across the periods.

$$IRR = \frac{Carriage\ Prev\ Post\ \times CCR}{Carriage\ Prev\ Pre\ \times CCR}$$

The equation above can be expanded to show how VT and NVT groups are incorporated, with the assumption that $CCR\ Pre = CCR\ Post$ for VTs and NVTs:

$$IRR = \frac{(Carr\ Prev\ Post_{vt} \times CCR\ Post_{vt}) + (Carr\ Prev\ Post_{nvt}\ CCR_{nvt})}{(Carr\ Prev\ Pre_{vt} \times CCR\ Pre_{vt}) +\ (Carr\ Prev\ Pre_{nvt} \times CCR\ Pre_{nvt})}$$

We adjust the equation above to incorporate different CCRs for VT carriage and vaccine uptake:

$$IRR = \frac{cov(Carr\ Prev\ Post_{vt} \times CCR\ Post_{vt(v)}) + (1 - cov)\left(Carr\ Prev\ Post_{vt} \times CCR_{vt(u)}\right) + (Carr\ Prev\ Post_{nvt}\ CCR_{nvt})}{(Carr\ Prev\ Pre_{vt}\ x\ CCR_{vt(u)}) + (Carr\ Prev\ Pre_{nvt}\ x\ CCR_{nvt}\ )}$$

Where:

vac cov = vaccine coverage in the target population (children <5 years) in the post-vaccine era (among the children in the carriage survey)

Carriage in the pre- and post-PCV periods can be broken down into VT and NVT carriage

CCR = case carrier ratio, which is different for VT and for NVT and also varies for VT, depending on whether the child has been vaccinated (v) or unvaccinated (u); all VT carriers in the pre-vaccine period experience the CCR for VT of unvaccinated individuals. Vaccination has no impact on the CCR for NVT

To simplify the equation, we divide the subparts of the equation by a common term, i.e., CCR_{nvt}

$$IRR = \frac{cov\left(\frac{Carr\ Prev\ Post_{vt} \times CCR\ Post_{vt(v)}}{CCR_{nvt}}\right) + (1 - cov)(\frac{Carr\ Prev\ Post_{vt} \times CCR_{vt(u)}}{CCR_{nvt}}) + \frac{Carr\ Prev\ Post_{nvt}\ CCR_{nvt}}{CCR_{nvt}}}{(\frac{Carr\ Prev\ Pre_{vt} \times CCR_{vt(u)}}{CCR_{nvt}}) + (\frac{Carr\ Prev\ Pre_{nvt} \times CCR_{nvt}}{CCR_{nvt}})}$$

$$IRR = \frac{cov\left(P'_{vt} \times \frac{CCR'_{vt}}{CCR_{nvt}} \right) + (1 - cov)(P'_{vt} \times \frac{CCR_{vt}}{CCR_{nvt}}) + P'_{nvt} \times \frac{CCR_{nvt}}{CCR_{nvt}}}{(P_{vt} \times \frac{CCR_{vt}}{CCR_{nvt}}) + (P_{nvt} \times \frac{CCR_{nvt}}{CCR_{nvt}})}$$

$$IRR = \frac{P'_{vt}[(VE_{inv} \times cov) + R(1 - cov)] + P'_{nvt}}{P_{vt}R + P_{nvt}}$$

Where:

P = prevalence in the pre-vaccine era (either VT or NVT)

P' = prevalence in the post-vaccine era (either VT or NVT)

VE_{inv} = the ratio of CCR_{vt} by vaccine era, hence CCR'_{vt}/CCR_{vt}

cov = vaccine coverage among VT carriers

R = the ratio of CCRs, hence CCR_{vt}/CCR_{nvt}

Note the equation can be further expanded to include further breakdown of NVTs into high-incidence and low0incidence NVTs.

Alternatively, we could also divide the equation sub-parts by $CCR_{vt(u)}$

$$IRR = \frac{cov\left(\frac{Carr\ Prev\ Post_{vt} \times\ CCR_{vt(v)}}{CCR_{vt(u)}}\right) + (1 - cov)\left(\frac{Carr\ Prev\ Post_{vt}\ \times\ CCR_{vt(u)}}{CCR_{vt(u)}}\right) + \frac{Carr\ Prev\ Post_{nvt}\ CCR_{nvt}}{CCR_{vt(u)}}}{(\frac{Carr\ Prev\ Pre_{vt}\ x\ CCR_{vt(u)}}{CCR_{vt(u)}})\ \ + (\frac{Carr\ Prev\ Pre_{nvt}\ x\ CCR_{nvt}}{CCR_{vt(u)}})}$$

$$IRR = \frac{cov\left(\ P'_{vt} \times \frac{CCR'_{vt}}{CCR_{vt}}\ \right) + (1 - cov)(\ P'_{vt} \times \frac{CCR_{vt}}{CCR_{vt}}\ ) +\ P'_{nvt} \times \frac{CCR_{nvt}}{CCR_{vt}}}{(\ P_{vt} \times \frac{CCR_{vt}}{CCR_{vt}}\ )\ \ + (P_{nvt} \times \frac{CCR_{nvt}}{CCR_{vt}}\ )}$$

$$IRR = \frac{P'_{vt}[(\ VE_{inv} \times cov) + (1 - cov)] +\ P'_{nvt}R}{P_{vt}\ \ + P_{nvt}R}$$

Where:

VE = CCR'_{vt}/CCR_{vt}

R = CCR_{nvtt}/CCR_{vt}

4.9.2 Appendix 2: Estimation of Uncertainty levels of estimated Incidence rate Ratios (IRRs)

Model 1

To calculate the predicted IRRs and their corresponding uncertainties, we assumed that the proportion of VTs among both carriers and IPD isolates were samples from binomial distributions and drew 10,000 bootstrap samples. Then, we calculated the median value of these draws as the point estimate of the IRR and the 2.5% and 97.5% of the draws as lower and upper bounds of the 95% predictive interval (PI).

Model 2

First, we calculated the prevalence ratios (post-PCV divided by the baseline carriage prevalence) of individual serotypes. The baseline carriage data used were carriage surveys for 2016 (rural site) and 2017 (urban site), while the post-PCV carriage data used were carriage surveys for 2020 in both sites. For serotypes not observed in carriage in the baseline and post-PCV surveys, we did a continuity correction (adding 0.5 to the numerator and denominator as suggested by Weinberger) prior to calculating the prevalence ratios (PR).

We conducted this analysis in three strata of serotype groups; VT, high-incidence NVT and low-incidence NVT. We classified serotypes into these groups based on a meta-analysis of serotype-specific IPD incidence for Africa[84]. The authors reported IPD incidence for 21 individual serotypes, including all ten vaccine serotypes in PCV10. We classified the 11 NVTs with incidence rates sufficiently high to be calculated

individually as ‘high incidence NVT’. For all other serotypes, the serotype-specific incidence was too low to be estimated, and we defined these as ‘low incidence NVT’.

We calculated the incidence rate ratios (IRR) using the prevalence ratios and pre-vaccination IPD proportions for each serotype. We assessed the uncertainty inherent in the IRR via probabilistic resampling, i.e., bootstrapping. For each of the 1000 bootstrap samples, we assumed a multivariate normal distribution of the log of prevalence ratios with mean and variance estimated from a weighted regression model. For the IPD incidence, we assumed a Poisson distribution with the mean equal to the pre-PCV IPD incidence of each serotype. We estimated the average predicted post-PCV IPD incidence as a product of the drawn pre-PCV IPD and weighted PR by the serotype groups (VT/high-incidence NVT/low-incidence NVT). We calculated the IRR by dividing the predicted post-PCV IPD incidence by the drawn pre-PCV IPD incidence for the three serotype groups. We calculated the median and the 2.5% and 97.5% of the predicted IRRS (for VT and NVT) from 1,000 draws as the point estimate and 95% predictive interval, respectively.

Model 3

The 95% confidence limits of the IRRs were calculated by adding the standard errors of the IC and carriage prevalence using the delta method, which allows the calculation of variances of log-transformed variables. The variance of the natural logarithms of the ICs for each serotype are normally distributed and calculated as follows:[77,81]

$$\frac{1}{No\ of\ IPD\ cases\ of\ serotype\ i} + \frac{1 - Carr\ prevalence\ of\ serotype\ i}{Carr\ prevalence\ of\ serotype\ i\ x\ No\ of\ children\ swabbed}$$

The standard error of carriage prevalence is calculated using the delta method, where the standard error of the natural logarithm of a proportion is calculated as follows:[284]

$$\frac{1}{Number\ of\ carriers} - \frac{1}{Number\ of\ children\ swabbed}$$

Where 95% confidence intervals of IPD incidence are calculated as the exponent of:

$$Log\ IPD\ incidence\ \pm 1.96\ x\ standard\ error(SE) of \log IPD\ incidence$$

Where:

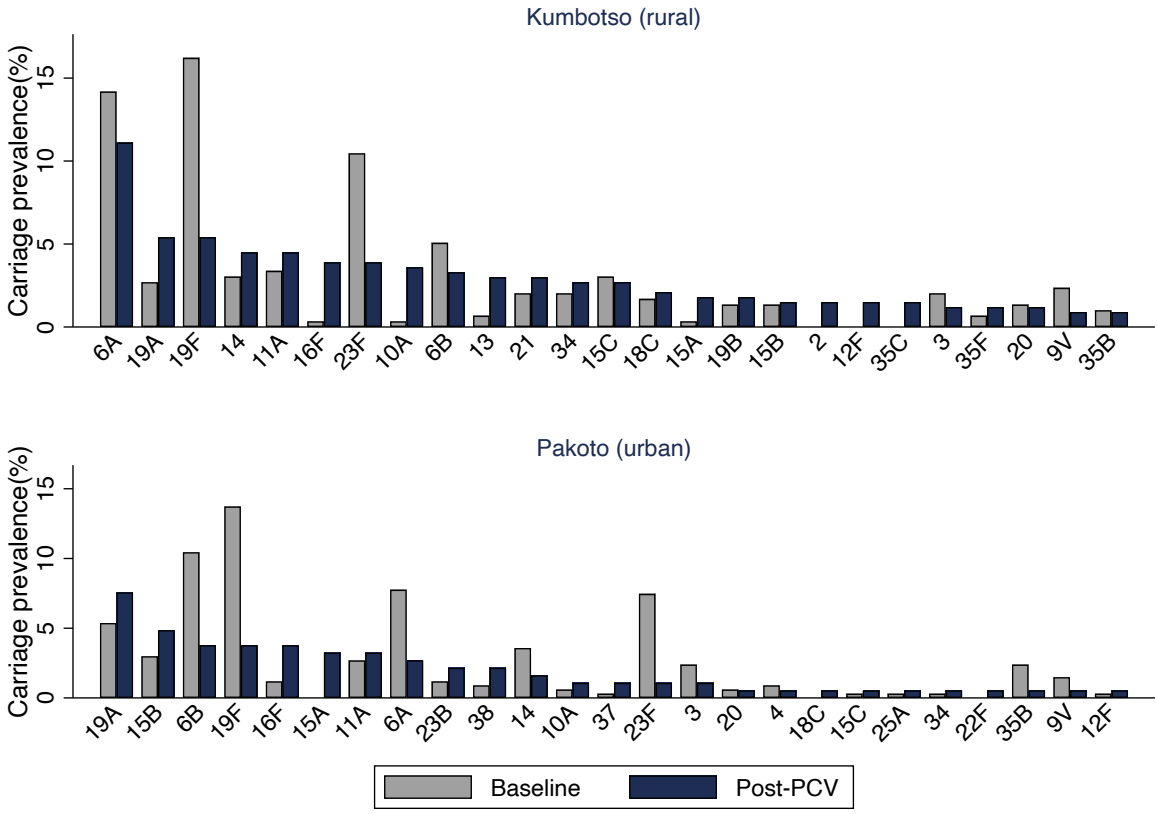
$$SE \log IPD\ incidenc = SE\ of\ IC + SE\ of\ carriage\ prevalence$$

4.9.3 Appendix 3: Supplementary Tables and Figures

Supplementary Table 4.1:Annual observed uptake of three doses of PCV10 and pneumococcal carriage (overall and vaccine type, VT) prevalence in the rural and urban sites by survey year.

	PCV10 coverage (95% CI)	Overall carriage (95% CI)	VT carriage (95% CI)
Rural			
Year 1[1]	7 (6-9)	91 (88-94)	42 (37-48)
Year 2	28 (22-34)	92 (89-96)	30 (25-36)
Year 3	57 (53-61)	92 (90-95)	25 (21-30)
Year 4	69 (64-73)	91 (88-94)	21 (17-26)
Year 5[2]	59 (51-67)	88 (84-91)	22 (18-27)
Urban			
Year 1[3]	15 (13-17)	77 (72-81)	38 (33-43)
Year 2	61 (57-65)	70 (65-76)	23 (18-29)
Year 3	75 (71-80)	69 (63-75)	19 (15-25)
Year 4[2]	81 (74-86)	53 (46-61)	12 (8-17)

[1] Baseline carriage data included in the models. Survey was conducted in 2016, five months after PCV10 was introduced.
[2] Post-PCV carriage data included in the models. Survey was conducted in 2020.
[3] Baseline carriage data included in the models. Survey was conducted in 2017, four months after PCV10 was introduced.



Supplementary Figure 4.1: Serotype-specific carriage prevalence in the baseline and post-PCV periods in the rural (top) and urban (bottom) sites. Serotypes arranged in descending of prevalence levels in the post-PCV period.

Supplementary Table 4.2: Proportions (%) and incidence rates (per 100,000) in IPD attributable to serotypes in children aged <5 years in Africa in the pre-PCV era as reported by Johnson et al. [84]

Serotype	Proportion (%)	95% CI	Incidence/100,000	LB, UB
1	11.70	9.5, 13.8	396	243, 582
2	1.90	1.0, 2.8	65	25, 119
3	1.10	0.8, 1.5	38	20, 61
4	2.30	1.7, 3.0	79	43, 125
5	10.70	7.6, 13.8	364	193, 584
6A	9.40	7.2, 11.5	317	182, 488
6B	8.50	6.3, 10.7	288	160, 451
7F	0.80	0.4, 1.3	28	10, 54
8	1.10	0.8, 1.5	38	19, 63
9A	0.40	0.2, 0.7	15	6, 28
9V	2.20	1.3, 3.1	74	34, 129
12A	0.10	0.0, 0.1	2	0, 5
12F	1.70	1.1, 2.3	57	27, 99
14	13.00	10.0, 16.0	441	254, 676
15B	0.50	0.1, 0.9	18	3, 39
18C	1.40	0.9, 2.0	48	22, 84
19A	3.90	2.5, 5.3	133	63, 226
19F	5.40	3.6, 7.1	182	92, 300
23F	6.50	4.5, 8.5	220	114, 359
45	0.50	0.0, 1.0	17	0, 44
46	1.30	0.4, 2.1	43	10, 90
All Others	15.70	12.7, 18.6	532	322, 790
TOTAL	100.00		3,395	

CI=Confidence Interval; LB=Lower bound of uncertainty estimate; UB=Upper bound of uncertainty estimate

Supplementary Table 4.3: Countries in Africa that contributed to IPD serotype data in Table S2 and numbers of isolates contributed. [84]

	Country	Study years	Total No. isolates
AFRICA (N=22 studies)			
1.	Algeria	1996-2000	45
2.	Burkina Faso	2002-2005	22
3.	Egypt	1998-2003	113
4.	Ethiopia	1993-1995	46
5.	Kenya	1994-2007	595
6.	Kenya	2004-2007	46
7.	Malawi	1996-1998	122
8.	Mali	2003-2004	54
9.	Mali	2002-2007	570
10.	Mozambique	2001-2007	259
11.	Rwanda	1984-1990	130
12.	South Africa	1989-1991	181
13.	South Africa	1993-1995	98
14.	South Africa	1998-2001	66
15.	South Africa	2000-2006	8221
16.	Tanzania	2006-2007	27
17.	The Gambia	1993-1995	105
18.	The Gambia	1989-1991	60
19.	The Gambia	1996-2003	212
20.	The Gambia	2000-2003	116
21.	The Gambia	1990-1992	46
22.	Uganda	2004-2007	47

Supplementary Table 4.4: Serotype-specific case-carrier ratios estimated for children from meta-analysis reported by Lichen et al [253] and underlying isolates for carriage and IPD.

Serotype*	CCR	Carriage isolates	IPD isolates
1	0.01736978	25	176
7F	0.00958808	51	172
5	0.00732476	7	31
12F	0.00605978	26	45
27	0.00449171	2	6
14	0.00426382	344	511
2	0.00389772	2	2
18C	0.00273942	48	91
24F	0.00223171	21	67
9V	0.00206871	50	71
3	0.00002045	201	95
8	0.00192825	33	23
4	0.00192411	62	46
25A	0.00164507	5	20
19A	0.00155419	650	402
33F	0.00134309	101	36
18B	0.00126504	2	4
22F	0.00103457	210	56
38	0.00088259	71	14
12B	0.00081015	1	2
20	0.00077023	18	5
6B	0.00075312	568	212
18F	0.00073552	1	2
10A	0.00007228	197	47
23F	0.00069569	384	139
19F	0.00064661	439	154
13	0.00064502	54	6
28F	0.00006166	1	2
9N	0.00052911	32	13
10B	0.00051616	3	3
31	0.00049194	84	7
6A	0.00043639	419	123
15A	0.00041763	223	33
16F	0.00039958	170	16
7C	0.00039639	66	5
17F	0.00038606	139	15
15B/C	0.00035059	415	70
9A	0.00033344	1	1

24A	0.00031946	1	1
23B	0.00026101	327	27
21	0.00020098	204	11
18A	0.00019777	14	2
15F	0.00001709	7	2
23A	0.00001595	256	21
35F	0.00015039	184	11
35B	0.00013092	268	11
34	0.00010173	174	3
37	0.00008861	38	1
6C	0.00008415	200	9
11A	0.00006762	391	12
29	0.00006419	27	1

*Limited to serotypes where we observed carriage in Nigeria

Supplementary Table 4.5: Summary of serotype data that contributed to CCR estimates [253] used in Model 3.

Country	Period	Number of serotypes	Number of swabs	Carriage isolates	IPD surveillance population	IPD isolates
USA -Alabama	Pre-PCV	11	827	103	19316	32
USA - Atlanta	Post-PCV	17	451	117	298831	47
USA - Atlanta	Pre-PCV	10	231	82	204680	192
USA - Massachusetts	Post-PCV	42	2969	792	820000	205
USA - Navajo	Post-PCV	39	6541	2046	65048	128
Spain	Post-PCV	23	209	186	228000	150
Colombia	Post-PCV	35	246	75	357200	83
Colombia	Pre-PCV	37	197	121	357200	339
Venezuela	Pre-PCV	12	1004	181	146125	33
Czech	Pre-PCV	27	425	153	478177	138
England and Wales	Pre-PCV	28	3752	648	3091000	461
France	Post-PCV	38	1212	160	842076	176
France	Post-PCV	47	1212	185	838866	388
Papua New Guinea	Pre-PCV	21	2844	416	96207	17
Morocco	Pre-PCV	8	200	33	212566	83
Netherlands	Post-PCV	36	659	328	222671	47
Netherlands	Post-PCV	37	660	364	232251	73
Netherlands	Pre-PCV	28	321	208	250924	100
Canada	Pre-PCV	7	1139	412	580507	69
Portugal	Pre-PCV	35	1170	730	2071223	90

Supplementary Table 4.6: Model 1 predicted Incidence Rate Ratios (IRRs) and 95% credible intervals (CIs) for PCV10 impact on overall IPD in Nigeria. Comparing observed levels of non-vaccine serotype (NVT) replacement in carriage and full model assumptions of complete NVT replacement in carriage.

Site	**NVT replacement (λ)**	**IRR (95% CI)**			
		No cross protection		**Cross protection against 6A**	
Kumbotso (rural)					
	Observed (0.4)	0.50	0.47-0.54	0.44	0.40-0.50
	Hypothetical complete (1.0)	0.69	0.62-0.79	0.71	0.60-0.84
Pakoto (urban)					
	Observed (0.0)	0.38	0.36-0.39	0.26	0.25-0.28
	Hypothetical complete (1.0)	0.73	0.65-0.83	0.69	0.59-0.82

5 The cost of illness for childhood clinical pneumonia and invasive pneumococcal disease in Nigeria (PhD objective 3)

5.1 Preamble

In this chapter, I present the results of a cost-of-illness study to assess the economic burden to the health care provider and household of IPD treatment of children aged <5 years.

I have presented some of the findings from this chapter at the **44th and 45th Annual and General Scientific Meeting of the West African College of Physicians, November 1-3, 2021**

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SECTION A – Student Details

Student ID Number	382943	**Title**	Dr
First Name(s)	Aishatu		
Surname/Family Name	Adamu		
Thesis Title	Assessing the impact of a 10-valent pneumococcal conjugate vaccine (PCV10) in the absence of pneumococcal disease surveillance data in Nigeria		
Primary Supervisor	Anthony Scott		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	BMJ Global Health		
When was the work published?	January 2022		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Yes.	Was the work subject to academic peer review?	Yes

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Where is the work intended to be published?	

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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I together with IA Adetifa and J Jemutai designed the study. I participated in obtaining study IRB approvals. I led and coordinated the fieldwork and data collection. I conducted data cleaning and analysis with input from B Karia, J Jemutai, I Adetifa and JAG Scott. I wrote first draft of the manuscript. I incorporated suggestions from peer review and responded to reviewers' comments with input from IA Adetifa, J Jemutai, J Ojal, and JAG Scott.

SECTION E

Student Signature	
Date	24/06/2022

Supervisor Signature	
Date	22/02/2024

5.2 Author contributions

I, together with IA Adetifa and J Jemutai designed the study. I participated in obtaining study IRB approvals. I led and coordinated the fieldwork and data collection. B Karia led the data entry and database management. I conducted data cleaning and analysis and interpreted the findings with input from J Jemutai, I Adetifa and JAG Scott. I wrote first draft of the manuscript. Which was commented on by all authors. I incorporated suggestions from peer review and responded to reviewers' comments with input from IA Adetifa, J Jemutai, J Ojal, and JAG Scott. All authors approved the original and reviewed versions of the manuscript before submission.

5.3 Title page

The cost of illness for childhood clinical pneumonia and invasive pneumococcal disease in Nigeria

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5.4 Abstract

Background: Pneumococcal disease contributes significantly to childhood morbidity and mortality and treatment is costly. Nigeria recently introduced the Pneumococcal Conjugate Vaccine (PCV) to prevent pneumococcal disease. The aim of this study is to estimate health provider and household costs for the treatment of pneumococcal disease in children aged <5 years (U5s), and to assess the impact of these costs on household income.

Methods: We recruited U5s with clinical pneumonia, pneumococcal meningitis, or pneumococcal septicaemia from a tertiary and a secondary level hospital in Kano, Nigeria. We obtained resource utilisation data from medical records to estimate costs of treatment to provider, and household expenses and income loss data from caregiver interviews to estimate costs of treatment to households. We defined catastrophic health expenditure (CHE) as household costs exceeding 25% of monthly household income and estimated the proportion of households that experienced it. We compared CHE across terciles of household income (from the poorest to least poor).

Results: Of 480 participants recruited, 244 had outpatient pneumonia, and 236 were hospitalised with pneumonia (117), septicaemia (66) and meningitis (53). Median (IQR) provider costs were US$17 (US$14-22) for outpatients and US$272 (US$271-360) for inpatients. Median household cost was US$51 (US$40-69). Overall, 33% of households experienced CHE, while 53% and 4% of the poorest and least poor households, experienced CHE respectively. The odds of CHE increased with admission

at the secondary hospital, a diagnosis of meningitis or septicaemia, higher provider costs, and caregiver having a non-salaried job.

Conclusion: Provider costs are substantial, and households incur treatment expenses that considerably impact on their income, and this is particularly so for the poorest households. Sustaining the PCV programme and ensuring high and equitable coverage to lower disease burden will reduce the economic burden of pneumococcal disease to the healthcare provider and households.

5.5 Introduction

Introduction of the Pneumococcal Conjugate Vaccine (PCV) has significantly reduced the global burden of pneumococcal disease.[3] Despite availability of effective vaccination, pneumococcal disease syndromes remain leading causes of preventable morbidity, mortality and economic burden, particularly among children aged <5 years (U5s) and in low- and middle-income countries (LMICs)).[3,292] In 2015, there were still ~ 9 million cases of IPD in U5 children resulting in over 300,000 deaths despite this being a significant decline of >60% from the pre-vaccination PCV era.[2,3] Slow uptake and sub-optimal coverage of PCV are partly responsible for a disproportionate pneumococcal disease burden in LMICs in the post-PCV era.[3] Unsurprisingly, pneumococcal diseases are associated with substantial annual economic health system costs of about US$13.7 billion and societal costs of US$14.3 billion globally.[281] Although associated with substantial vaccine and delivery costs, ranging between US$52 in Africa to US$599 in Europe per vaccinated child, the introduction of PCVs to infant immunisation programmes is expected to provide savings estimated as US$3.2 billion from averted hospital visits and care, and an additional US$2.6 billion from societal costs globally.[281] Economic cost studies on pneumococcal diseases report substantial costs of treatment to healthcare provider, households and families, with significant out-of-pocket (OOP) payment for health particularly in low- and middle-income countries (LMICs).[118,119,121,127,130,131,133,134] OOP payment for health care can result in catastrophic expenses capable of driving households further into poverty.

With >1 million pneumococcal disease cases resulting in nearly 50,000 deaths among U5s in 2015, Nigeria has the highest burden of pneumococcal disease in sub-Saharan Africa (sSA).[3] Approximately 40% of Nigeria's population live below the poverty line, and 15% of the population incur healthcare expenses from an illness episode that exceeds 10% of their household income annually. [293,294] In addition, 2.3% are pushed into poverty by these health expenses.[294]

Financing of healthcare in Nigeria is via multiple and largely uncoordinated channels.[122] It has one of the lowest health insurance coverage in sSA because the National Health Insurance Scheme (NHIS) currently targets persons employed in the formal sector, which represent about 5% of the population.[295,296] The huge informal sector largely finances health care through OOP payment that are over three-quarters of total expenditure on health.[123] The consequences of the huge pneumococcal disease burden and limited financial protection, especially for the poor, extend beyond the clinical as households are at high risk of impoverishment. Additionally, to avoid such unexpected financial burden, households can delay or refrain from seeking healthcare and this ultimately results in greater costs and/or poorer outcomes.[297] Existing mechanisms to provide financial protection to households range from subsidised services for vulnerable populations such as U5s and pregnant women, to the recent expansion of community-based health insurance (CBHI) to the informal sector.[298,299]

Ahead of Nigeria completing the transition to full self-financing of PCV in 2028,[216] data on the economic burden of pneumococcal diseases will help inform the policy required to assure sustainability of the PCV programme. A current description of the

costs of treating childhood pneumococcal diseases in Nigeria is lacking highlighting a significant data gap.

The objectives of this study are to: 1) to estimate the provider costs of outpatient and inpatient clinical pneumonia, and inpatient pneumococcal septicaemia and meningitis 2) to estimate the household costs of hospitalised clinical pneumonia, and pneumococcal meningitis and bacteraemia; and 3) to assess the economic impact to households of hospitalisation with clinical pneumonia, and pneumococcal septicaemia and meningitis among U5s in Kano, northern Nigeria.

5.6 Methods

5.6.1 Study design and setting

This was a cross sectional study conducted at the two largest paediatrics units in Kano, Kano State in northern Nigeria - Aminu Kano Teaching Hospital (AKTH) and Murtala Mohamed Specialist Hospital (MMSH) which serve an overlapping catchment population. AKTH is a Federal Government Teaching Hospital and MMSH is a State Government secondary hospital. Kano is the capital city of Kano state and covers approximately eight out of the forty-four local government areas (LGAs) of the state. However, catchment population of both hospitals includes other LGAs outside the city and neighbouring states. The description of the hospitals is shown in Table 5.1. Kano is the most densely populated state in the region with an estimated population of 12.2million (~1.3million U5s) occupying 20,760km^2.[261,300] About 55% of the population in Kano state reside in households below the poverty line.[293] The infant and U5 mortality per 1,000 live births in Kano (National) were 112 (70) and 203 (120) in 2018.[301]

Table 5.1: Description of study hospitals

Hospital	Hospital type	No of beds - total/paediatric	Paediatric Outpatient clinic turnover (weekly)	User charging policy	Catchment population	Source
AKTH	Tertiary – with paediatric outpatient clinic offering primary level care	750/55	~1,400	User fees charged at 50% of adult rate	Residents of Kano and neighbouring states	AKTH paediatric and hospital record units
MMSH	Secondary - with paediatric outpatient clinic offering primary level care	1,000/56	~2,100	Consultation and admission provided free to children <14 years. Patients pay for investigations and buy drugs out-of-pocket if not available	Residents of Kano and neighbouring states	MMSH paediatric and hospital record units

5.6.2 Study population

Children were recruited prospectively and were eligible if aged 1-59 months, presented to AKTH or MMSH and had at least one of three possible diagnoses of interest. These were (i) clinical pneumonia (ii) pneumococcal septicaemia (iii) pneumococcal meningitis. We excluded children that died during admission.

Eligibility criteria

1. Clinical diagnosis of non-severe or severe pneumonia as an out-patient or in-patient (see Table 5.2)
2. Microbiological diagnosis of bacterial meningitis or pneumococcal septicaemia

Table 5.2: Case definitions for the clinical syndromes

Disease syndrome	**Diagnosis**
Non-severe pneumonia (out-patient or in-patient)	Lower chest wall indrawing or fast breathing (respiratory rate ≥50 breaths/min if aged 2–11 months; ≥40 breaths/min if aged 12–59 months), and without signs of severe pneumonia
Severe pneumonia	Any one of: oxygen saturation <90%, central cyanosis, severe respiratory distress, inability to drink or breastfeed or vomiting everything, altered consciousness, and convulsions
Meningitis	Microbiological diagnosis of pneumococcal meningitis based on isolation of *Streptococcus pneumoniae* from cerebrospinal fluid (CSF) or identification of pneumococci on CSF microscopy.
Septicaemia	Microbiological diagnosis of pneumococcal septicaemia based on isolation of *Streptococcus pneumoniae* from blood

We used the formula below [302] to estimate the minimum sample sizes for (1) outpatient clinical pneumonia; (2) inpatient pneumonia; and (3) septicaemia and meningitis:

$$n = \frac{(Z\sigma)^2}{e^2}$$

[5.1][302]

Where:

n= minimum sample size

Z = the standard normal deviate for the desired confidence level (i.e., Z = 1.96 for 95% confidence)

σ = standard deviation of respective mean costs reported from previous studies[118,119]

e = precision or smallest desirable margin of error allowable for estimation of the respective costs

Sample sizes of 100, 50 and 30 were expected to provide a cost estimate for outpatient clinical pneumonia, inpatient pneumonia, and septicaemia and meningitis based on standard deviation (±precision) of US$5 (±US$1), US$21 (±US$6) and US$33 ± US$12) respectively.[118,119,260].

5.6.3 Data collection

We recruited outpatient pneumonia cases and interviewed caregivers on the day of diagnosis. For inpatient pneumonia cases, eligible children admitted 8am to 4pm were recruited on the day of admission; those admitted 4pm to 8am the next morning were enrolled on the next day. For septicaemia and meningitis cases, participants were recruited when confirmatory laboratory results were available. We collected data between January and October 2020. For each hospital, we recruited a volunteer nurse not directly involved in clinical care to collect data. We used structured

quantitative tools adapted from a similar study in The Gambia for data collection.[118]

We extracted resource use data such as length of hospital stay, type and quantity of medications and intravenous fluids used, laboratory investigations and other specialised services including blood transfusion and use of oxygen from patients' records, case folders, prescriptions, and laboratory request forms. We obtained unit costs of hospital resources e.g., medication, fluids, etc utilised from the respective hospitals (Supplementary Table 5.1).

Sociodemographic characteristics, OOP costs, non-medical expenses, productivity time loss, household income and sources of finances used to pay the treatment costs were obtained through caregiver interviews. Additional data on household income and sources of finances used to pay the treatment costs were also collected.

5.6.4 Cost components

We collected provider costs, and direct and indirect household costs.

5.6.4.1 Provider costs

Provider costs included costs of direct healthcare services i.e., costs of medications, laboratory investigations, intravenous fluids, oxygen, blood transfusion and inpatient bed-day. We used full costs for drugs and only applied dose-specific costs if the drug was re-useable and the residuals amounted to another full dose. For instance, for a re-useable drug, if a unit dose was 1,000mg and 500mg was administered, the cost

per dose would be half of the unit cost. We obtained cost of oxygen from the nursing unit, and for blood transfusion, we used previously published costs.[303]

The inpatient bed-day is the daily stay cost or the 'hotel' component and comprises costs of food, personnel, and utilities. We used the average 2020 admission charge for AKTH and assumed admission costs at MMSH to be 60% of AKTH since admission is 'free' to patients at MMSH. Studies have found up to 60-70% differences in bed-day costs between tertiary and secondary-level hospitals.[118,119]

5.6.4.2 Household costs

We collected direct healthcare costs to households which are user fees related to consultations, investigations, and medications incurred from date of admission to date of discharge. Non-healthcare costs were the costs of transportation, accommodation and feeding incurred during admission (from date of admission to date of discharge) by main and accompanying caregiver. The accompanying caregiver was defined as any household member that assisted the main caregiver with care of the patient during the admission. Preadmission costs data were collected either on the day of recruitment or on the earliest convenient day for the caregiver, while data on costs incurred over the course of admission were obtained at or close to discharge.

We collected data on caregiver's income and productivity time loss due to time away from their usual activities owing to illness.

5.6.5 Data analysis

Data were analysed using STATA 15.1 (Stata Corp LP, College Station, Texas). All costs were converted to US$ using average 2020 conversion rates 1 US$ = 360.5 NGN (Central bank of Nigeria).[304]

We summed up the components of respective cost categories for provider costs and direct household costs. We estimated indirect costs using the human-capital approach (HCA) by estimating income lost by caregiver(s) due to absence from work per day spent caring for the child. Self-employed caregivers were asked to give an estimate of daily earnings while those on monthly salary were asked to state their monthly wage from which daily income was calculated. Indirect costs were then calculated as daily income multiplied by the number of days taken off from work.

We present costs from the health provider and household's perspectives along with their components separately as means with standard deviation (SD), and medians with interquartile range (IQR). We used Kruskal-Wallis test to assess differences in costs between disease categories and Wilcoxon rank sum test to compare costs between the two hospitals.

We evaluated the impact of health expenditures on available household resources by assessing direct, indirect, and total costs as respective proportions of household income. We used household income to categorise households into terciles from the poorest (tercile 1) to least poor (tercile 3). We used Kruskal-Wallis tests to compare costs as a proportion of household income across household income terciles .[305] We also evaluated catastrophic health expenditure (CHE) as costs exceeding a

specified threshold of household available resources.[306] In this analysis, we used household income as a measure of available resources and set the base threshold as 25%.[294,307,308] We defined costs as catastrophic if they exceeded 25% of household monthly income (CHE_{25}) and also explored impact at 10% (CHE_{10}) and 40% (CHE_{40}) thresholds. We used multivariable logistic regression models to identify factors associated with CHE_{25}. Independent variables that were associated with CHE_{25} at significance level $p=0.1$ were sequentially added to the model and kept if they were significantly associated with cost ($p<0.05$) or changed effects of included variables. Excluded variables were then re-introduced to check if they further changed the effect sizes of included variables. Adjusted odds ratios and P values from the likelihood ratio test (LRT) are reported.

5.6.6 Sensitivity analysis

We conducted one-way sensitivity analyses of provider costs by varying the source of bed-day costs. We used the average cost per inpatient bed-day for tertiary and secondary facilities in Nigeria from the WHO-CHOICE after accounting for inflation and adjusting to 2020 rates.[309] We also conducted a sensitivity analysis of indirect costs by using the Willingness to pay (WTP) approach to assess productivity loss. Indirect costs using WTP approach were calculated as the product of the amount caregivers were willing to pay for main activity they would have been otherwise engaged in and the total days taken off from work due to childcare.

5.7 Results

5.7.1 Study participants

Overall, 480 out of 495 caregivers of eligible children consented to be interviewed. A total of 480 children (244 outpatient pneumonia, 117 inpatient pneumonia, 53 meningitis and 66 septicaemia) were enrolled (see Table 5.3). Of these, 387, (81%) were aged ≥1 year. Clinical pneumonia cases were younger than their counterparts with meningitis or septicaemia (mean age, 19 vs. 25 months, p=0.002). Caregivers were aged 20 to 48 years, mostly mothers, had at least secondary school level education and were employed. Caregivers of children with outpatient pneumonia were more likely to be unemployed compared to those with hospitalised children (20% vs 3%, p= <0.0001). The mean duration of hospitalisation was five days for cases with pneumonia or septicaemia but seven days for those with meningitis. Majority (362/480, 75.4%) of the children had sought care prior to index visit/hospitalisation.

Table 5.3: Description of children and caregivers

	Outpatient pneumonia N=244	**Inpatient pneumonia N=117**	**Septicaemia N=66**	**Meningitis N=53**
Hospital n (%)				
AKTH	135(57.2)	48(41.0)	32(48.5)	21(39.6)
MMSH	109(44.9)	69(59.0)	34(51.5)	32(60.4)
Child characteristics				
Age in months				
Median (IQR)	17.9 (12-27)	16.3 (12-26)	24.2 (16-36)	24.6 (18-31)
Age group(months) n (%)[1]				
<1-11	57 (23.4)	25 (21.4)	6 (9.1)	5 (9.4)
12-23	98 (39.7)	58 (49.6)	26 (39.4)	19 (35.9)
24+	90 (36.9)	34 (29.1)	34 (51.5)	29 (54.7)
Gender, Female n (%)	119 (48.8)	53 (45.3)	31 (47.0)	23 (43.4)
Prior care sought n (%)				
None	72 (29.5)	25 (21.4)	15 (22.7)	6 (11.3)
Private hospital	38 (15.6)	17 (14.5)	19 (28.8)	22 (41.5)
Chemist	106 (43.4)	60 (51.3)	28 (42.4)	18 (34.0)
Others	28 (11.5)	15 (12.8)	4 (6.1)	7 (13.2)
Missing				
Caregiver characteristics[1]				
Age in years, median (IQR)	28.0 (27-30)	29 .0 (28-30)	29.0 (28-30)	30.0 (28-31)
Relationship to child, Mother	224 (91.8)	115 (98.3)	66 (100.0)	49 (92.5)
Highest education of caregiver[1] n (%)				
None	20 (8.2)	7 (6.0)	0 (0.0)	1 (1.9)
Primary	19 (7.8)	7 (6.0)	2 (3.0)	3 (5.6)
Secondary	88 (36.1)	48 (41.0)	34 (51.5)	18 (34.0)
Tertiary	117 (47.9)	52 (44.4)	29 (43.9)	31 (58.5)
Missing	0 (0.0)	3 (2.6)	1 (1.5)	0 (0.0)
Occupation of caregiver[1] n (%)				
Self-employed	98 (40.2)	54 (46.1)	30 (45.5)	20 (37.7)
Salaried work	97 (39.7)	56 (47.9)	36 (54.5)	32 (60.4)
Unemployed	49 (20.1)	7 (6.0)	0 (0.0)	1 (1.9)

[1] Main caregiver

5.7.2 Provider costs for outpatient pneumonia

The median provider cost for outpatient pneumonia was US$17 (IQR:14-22), and was higher in AKTH (US$20, IQR:14-23) compared to MMSH (US$16; IQR:14-19, p=0.0002). Overall, costs for outpatient clinic visit, medications and investigations accounted for 43%, 37% and 20% of provider costs. The median costs for laboratory investigations were higher in AKTH US$ 7 (IQR:0-8) compared to MMSH US$0 (IQR:0-4, p<0.0001). Medications costs were similar between the two hospitals. Median expenses on seeking care elsewhere prior to index presentation were US$9 (IQR:0-13) in AKTH and US$8 (IQR:5-13) in MMSH (p=0.70).

5.7.3 Provider costs for hospitalised children

The respective median/mean provider costs, as shown in Table 5.4, were highest for meningitis in both hospitals which was mostly driven by bed-day costs. The median provider costs (all syndromes combined) were significantly higher in AKTH (US$359, IQR:308-400) compared to MMSH (US$223, IQR:196-264, p<0.0001).

Table 5.4: Provider costs for inpatient pneumonia, meningitis, and septicaemia in US$

	Cost US$					
	Inpatient pneumonia		**Septicaemia**		**Meningitis**	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
AKTH						
Length of stay (days)	5 (0.8)	5.0 (4-5)	5 (1.3)	5 (5-6)	6 (1.1)	6 (6-7)
Provider costs						
Bed day costs	272 (45)	277 (222-278)	297 (70)	277 (277-333)	351 (59)	332 (332-388)
Drugs	16 (6)	15 (13-17)	19 (6)	18 (16-20)	20 (3)	20 (18-22)
Investigations	15 (6)	14 (13-14)	14 (7)	14 (7-21)	17 (7)	20 (13-22)
Special services[1]	46 (21)	40 (30-60)	25 (36)	0 (0-54)	32 (31)	34 (0-40)
Total provider costs	348.6 (63.0)	347 (301-372)	354.0 (103.4)	325 (300-380)	420.0 (80.1)	407 (364-449)
MMSH						
Mean admission days (SD)	6 (3.3)	5 (5-6)	6 (1.5)	5 (5-7)	7 (4.8)	6 (5-7)
Provider costs						
Bed day costs	189.1 (110.3)	166 (166-200)	186.0 (50.6)	166 (166-233)	237.2 (161.3)	199 (166-233)
Drugs	17.7 (11.7)	16 (11-20)	17.8 (6.4)	17 (14-22)	21.5 (7.9)	19 (17-24)
Investigations	7.1 (2.6)	8 (7-8)	7.0 (2.5)	7 (4-8)	8.6 (1.4)	8 (7-10)
Special services[1]	27.9 (13.3)	30 (20-30)	16.5 (20.3)	14 (0-30)	29.6 (19.4)	30 (20-40)
Total provider costs	241.8 (116.9)	219 (220-247)	227.3 (67.6)	206 (179-264)	296.9 (117.5)	257 (225-280)
Combined hospitals	285.6 (111.4)	265 (215-347)	288.7 (107.2)	298 (196-335)	345.7 (158.0)	294 (253-408)

[1] Oxygen and blood transfusion

5.7.4 Household costs for hospitalised children

Median household income was similar between disease categories but was significantly higher (all syndromes combined) for those presenting to AKTH (US$250, IQR:222-277, p=0.02) compared to MMSH (US$222, IQR:194-277). Majority of caregivers (217/236, 92%) reported using a combination of current income and savings to cover expenses. Only about 3% reported using other sources such as borrowing, asking relatives, or selling assets to cover expenses.

Median direct household costs as shown in Table 5.5 were highest for meningitis and lowest for pneumonia in both hospitals. However, there was no significant difference in overall direct household costs between the two hospitals. Direct costs comprised mostly of user fees, and for each disease category in both hospitals, medication costs were the largest fraction of user fees. (Figure 5.1)

Median indirect costs were lowest for inpatient pneumonia compared to meningitis or septicaemia, as shown in Table 5.5. Comparison between the hospitals (all syndromes combined), showed indirect costs were slightly higher in AKTH compared to MMSH (US$22 [IQR:15-26] vs. US$18 [IQR:10-23], p=0.04).

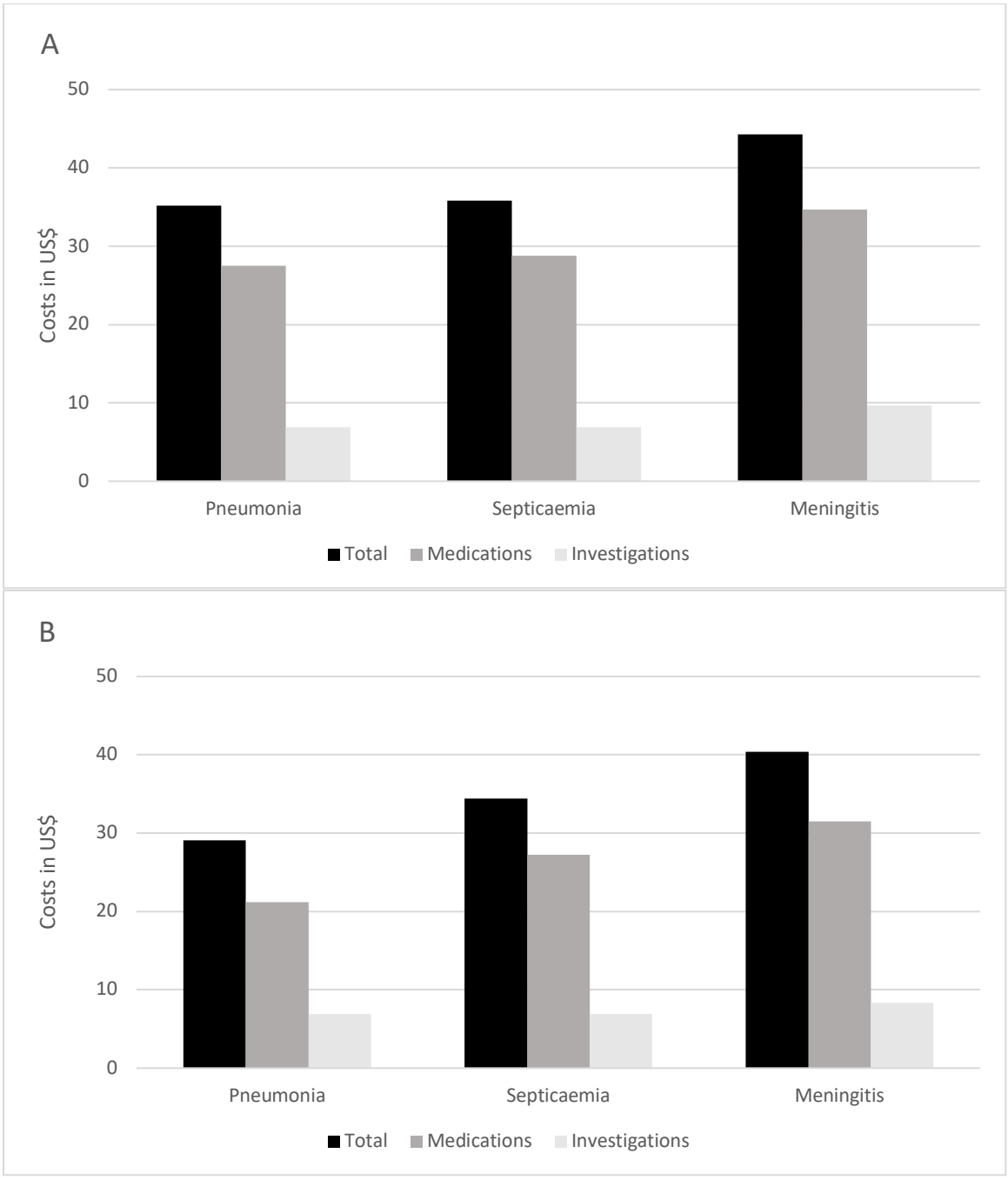

Figure 5.1: Breakdown of User fees for AKTH (A) and MMSH (B)

Table 5.5: Direct and indirect costs to households per illness episode (US$)

	Cost US$						
	Inpatient Pneumonia		**Septicaemia**		**Meningitis**		**P value**[1]
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
AKTH							
Pre-admission costs	9.4 (9.3)	8.6 (0-12)	19.8 (26.4)	13.9 (8-26)	14.9 (11.0)	13.6 (8-25)	0.01
Current admission costs							
Direct costs							
Transportation	1.1 (1.9)	0.0 (0-4)	2.1 (5.7)	0.0 (0-5)	1.1 (2.9)	0.0 (0-0)	0.84
Feeding	0.6 (2.2)	0.0 (0-0)	1.2 (4.8)	0.0 (0-0)	1.3 (6.1)	0.0 (0-0)	0.98
User fees	38.5 (29.3)	35.2 (30-38)	44.5 (25.4)	35.8 (32-47)	44.3 (6.7)	44.3 (39-50)	<0.001
Total direct household costs	50 (30.0)	43.6 (36-55)	73.5 (61.1)	60.7 (45-75)	64.3 (16.8)	68.8 (51-76)	<0.001
Indirect costs							
Working days lost	5 (0.9)	5 (4-5)	5 (1.2)	5 (5-6)	6 (1.1)	6 (6-7)	<0.001
Monthly household income	258.6	249.7 (222-277)	266.1	270.5 (222-277)	329.6	277.4 (222-361)	0.30
Daily income lost	4 (2)	4 (3-5)	4 (2)	5 (3-5)	5 (2)	5 (4-5)	0.23)
Total indirect costs	19 (7.0)	19 (14-23)	22 (12.0)	23 (15-23)	28 (14.7)	27.7 (22-28)	0.006
Total household costs	68.9 (28.2)	64.5 (55-75)	95.4 (63.8)	82.6 (63-96)	92.3 (22.1)	89.3 (79-106)	<0.001
MMSH							
Pre-admission costs	12.0 (9.8)	9.9 (7-12)	12.2 (10.4)	11.4 (0-14)	18.6 (10.4)	17.7 (11-26)	0.003
Current admission costs							
Direct costs							

	Cost US$						
	Inpatient Pneumonia		**Septicaemia**		**Meningitis**		**P value**[1]
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Transportation	2.9 (4.8)	1.9 (0-3)	1.7 (3.9)	0.0 (0-5)	2.9 (4.4)	0.0 (0-6)	0.17
Feeding	1.1 (3.4)	0.0 (0-0)	3.2 (12.8)	0.0 (0-0)	6.8 (17.8)	0.0 (0-0)	0.57
User fees	27.8 (11.3)	29.1 (22-36)	50.7 (84.3)	34.4 (29-44)	59.2 (94.3)	40.3 (36-45)	<0.001
Total direct household costs	43.7 (14.4)	42.7 (35-53)	74.3 (102.0)	53.8 (42-72)	92.2 (106.6)	71.8 (58-83)	<0.001
Indirect cost							
Working days lost	5.3 (3.3)	5.0 (4-5)	5.6 (1.5)	5.0 (5-7)	7.4 (6.5)	6.0 (5-7)	<0.001
Monthly household income	242.1	221.9 (166-277)	257.8	221.9 (194-277)	271.3	249.7 (222-277)	0.46
Daily income lost	3 (2)	3 (2-5)	4 (2)	4 (3-5)	4 (3)	4 (3-5)	
Total indirect costs	16.3 (12.4)	16.6 (7-23)	21.1 (12.0)	18.5 (114-26)	28.4 (22.5)	22.4 (19-28)	<0.001
Total household costs	60.0 (21.8)	59.1 (47-74)	95.4 (105.7)	68.4 (60-95)	120.6 (123.2)	97.6 (83-108)	<0.001
Combined hospitals							
Direct cost	46.3 (22.3)	43.6 (36-53)	73.9 (84.1)	57.3 (42.2)	81.2 (84.1)	69.6 (55-80)	<0.001
Indirect cost	17.4 (10.6)	18.5 (9-23)	21.5 (11.9)	19.4 (14-26)	28.2 (19.6)	23 (19-28)	<0.001
Total cost	63.7 (24.9)	62.2 (50-74)	95.4 (87.3)	72.2 (61-95)	109.4 (97.1)	93.8 (81-106)	<0.001

[1] P value for Kruskal-Wallis test comparing medians across disease categories

5.7.5 Economic impact to households

The poorest households spent a median of 25% of their monthly income directly on treatment costs and lost an additional 8% from loss of caregiver time, compared to 13% of income and 6% of caregiver time for the least poor households (data not shown). Treatment costs as fractions of monthly household income were inversely related to household income terciles (Table 5.6).

Table 5.6: Costs incurred by households stratified by income terciles.

	Household costs as % of monthly household income					
	Tercile 1(poorest)		Tercile 2		Tercile 3 (least poor)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Pneumonia						
Direct cost	34 (62)	21 (17-29)	18 (5)	17 (14-20)	13 (4)	13 (10-15)
Indirect cost	7 (5)	7 (5-9)	7 (3)	7 (5-8)	6 (3)	6 (4-8)
Total household cost	41 (61)	29 (23-39)	25 (5)	25 (22-28)	19 (5)	19 (15-22)
Septicaemia						
Direct cost	40 (66)	27 (20-35)	37 (56)	21 (16-33)	16 (5.40)	16 (12-20)
Indirect cost	9 (4)	8 (6-12)	9 (3)	8 (7-10)	7 (4)	6 (4-9)
Total household cost	49 (68)	35 (28-42)	46 (58)	29 (24-44)	24 (8)	21 (17-29)
Meningitis						
Direct cost	66 (120)	33 (30-42)	25 (8)	25 (21-30)	16 (5)	16 (13-20)
Indirect cost	14 (21)	9 (6-11)	10 (4)	9 (8-10)	9 (4)	8 (6-10)
Total household cost	79 (140)	42 (37-53)	34 (9)	34 (25-41)	24 (6)	24 (22-29)

Table 5.7 shows the proportion of households encountering CHE_{25} at different threshold cut-off values across household income levels. CHE was substantial, and at 10% threshold nearly all households across all income levels encountered CHE. CHE increased with decreasing household income level. This inverse relationship is further illustrated in Figure 5.2 which shows that as the threshold values increase, the proportions of households encountering catastrophic costs declines steeply for the higher income households, with slowest decline for the poorest households (tercile 1).

Table 5.7: Proportions of households with CHE at different thresholds of household income

Income tercile	CHE threshold level					
	10%		25%		40%	
	%	95% CI	%	95% CI	%	95% CI
tercile 1 (poorest)	97.2	92.2 – 99.4	53.2	43.4 - 62.8	18.3	11.6 – 26.9
tercile 2	97.2	90.3 – 99.7	25.0	15.5 - 36.6	2.8	0.3 - 9.7
tercile 3 (least poor)	81.8	69.1 – 90.9	3.6	0.4 - 12.5	0.0	0.0 - 0.0
Overall	93.6	89.7 - 96.1	33.1	27.1 - 39.4	9.3	5.9 -13.7

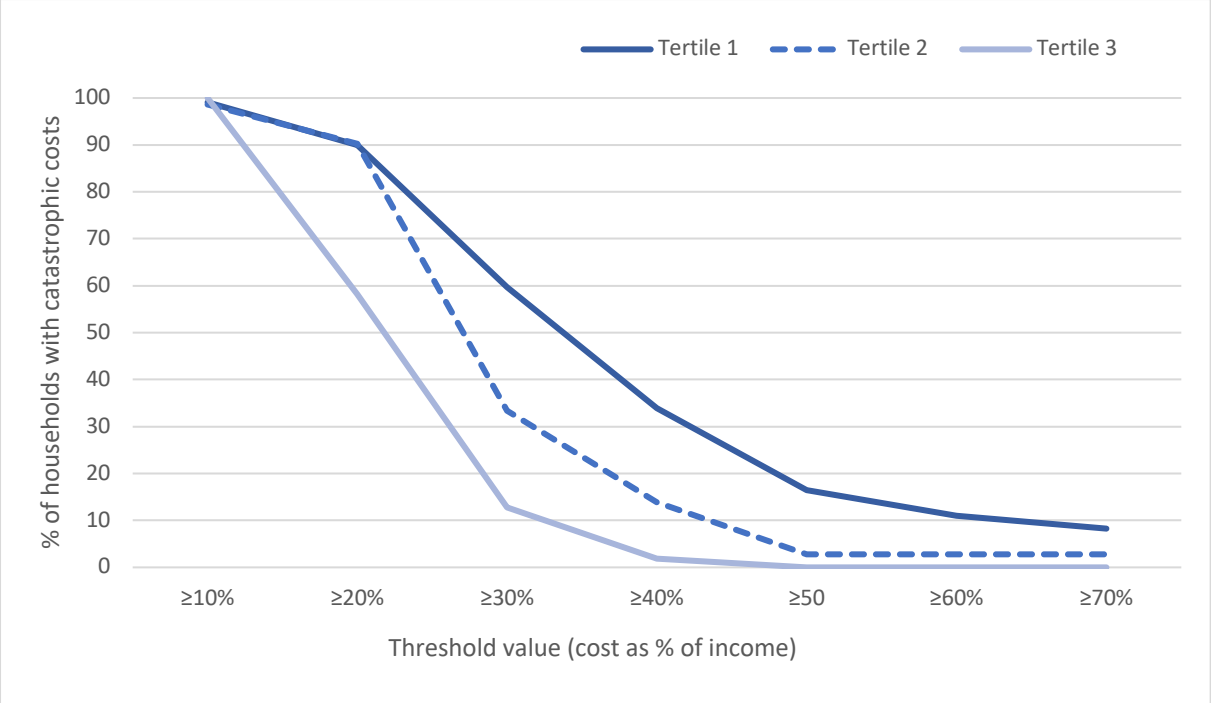

Figure 5.2: Distribution of proportions of households encountering catastrophic costs at different threshold values of cost as a fraction of household income by terciles of household income level. Terciles range from the poorest households (tercile 1) to the least poor (tercile 3).

Admitting hospital (MMSH), meningitis or septicaemia, seeking care at a private hospital prior to admission and higher provider costs were associated with increased odds of CHE_{25}, while having ≥3 U5 children and higher indirect costs lowered the odds of CHE_{25} (Table 5.8).

Table 5.8: Distribution of CHE_{25} and multivariable logistic regression of factors associated with CHE_{25}.

	Total N=236	**CHE25 N=78**	**Adjusted1 OR (95% CI)**	**P value**
Hospital, n (%)				
AKTH	101	29 (28.7)	Reference	
MMSH	135	49 (36.3)	3.6 (1.4-9.5)	0.005
IPD category, n (%)				
Pneumonia	117	26 (22.2)	Reference	
Septicaemia	66	26 (39.4)	2.5 (1.1-5.5)	
Meningitis	53	26 (49.1)	3.2 (1.3-8.3)	0.02
Pre-admission care seeking				
None	72	19 (26.4)	Reference	
Private	58	31 (53.5)	4.3 (1.8-10.5)	
Chemist	106	28 (26.4)	0.8 (0.4-1.9)	<0.001
Age of caregiver in years, n (%)				
<30	143	44 (30.8)	Reference	
≥30	93	34 (36.6)	1.1 (0.5-2.4)	0.75
Caregivers with salaried occupation, n (%)				
No	112	49 (43.8)	Reference	
Yes	124	29 (23.4)	0.5 (0.2-0.9)	0.04
Age of child in months, n (%)				
1-11	36	7 (19.4)	0.4 (0.2-1.3)	
12-23	103	32 (31.1)	Reference	
≥24	97	39 (40.2)	1.2 (0.6-2.5)	0.16
No of children <5 years, n (%)				
<3	135	53 (39.3)	Reference	
≥3	101	25 (24.8)	0.3 (0.2-0.7)	0.003
Provider cost (US$10), mean (SD)	300.0 (108.6)	330.0 (147.3)	1.09 (1.03-1.15)	<0.001
Indirect cost2 (US$10), mean (SD)	21.0 (14.1)	19.9 (15.5)	0.6 (0.4-0.8)	0.001

[1] adjusted for all variables in the table [2] using HCA

5.7.6 Sensitivity analyses

Provider costs were sensitive to source of hospital (bed-day) costs. Provider costs were between 38% and 40% lower across all disease categories and between the hospitals when the WHO-CHOICE estimates were used (Supplementary Table 5.2) compared to actual hospital admission costs (Table 5.4).

Indirect costs were also sensitive to approach used as costs were higher for all conditions in both hospitals with the WTP (Supplementary Table 5.2) compared to the HCA. However, in contrast to HCA, indirect costs were similar between the hospitals ($p=0.45$).

5.8 Discussion

In this study, we estimated the costs of treatment of clinical pneumonia, septicaemia, and meningitis in Nigerian children as well as the economic impact of these costs on households. Costs varied by hospital as they were higher in the tertiary hospital (AKTH) for all disease categories. Provider costs also varied by illness and were highest for meningitis irrespective of hospital. Costs to households were similar between the hospitals but highest for meningitis and lowest for pneumonia. The economic impact to households was considerable with total costs to households ranging between 25-37% of monthly household income for 5-7 days of hospitalisation. One third of the households incurred CHE at 25% threshold and the poorest households bore the greatest burden of CHE.

Although provider costs are likely to vary across the country and between hospitals, when applied to the global burden of disease and the proportions of the different pneumococcal disease syndromes, our cost estimates translate to annual provider costs of >US$110 million i.e., ~9% of Nigeria's 2020 health budget.[3,310] Funding of provider costs within the public sector is largely through budgetary allocations at the federal and state levels, and the overall health sector budget has been consistently below the 15% threshold of the total annual budget agreed to in the Abuja declaration. [310,311]. Treatment of pneumococcal disease exerts undue strain on the health sector, particularly at the tertiary hospitals where unit costs are higher for most components as reported elsewhere.[119,121,127] In many settings, robust pneumococcal disease surveillance has shown evidence of substantial reduction in

pneumococcal diseases attributed to PCV use.[191] The extent of savings on treatment costs will depend on the effectiveness and coverage of PCV across the country.
For each IPD category and hospital in our study, 'hospital stay' accounted for the largest proportion of provider costs. This is similar to findings in diverse settings across Africa (Kenya, Gambia), Asia (India and Vietnam) and South America.[118,119,127,128,131,133] This indicate the huge recurrent costs of hospitalisation and in-patient care to the healthcare system. Specialised services were the next largest contributor to provider costs, and they were mainly driven by oxygen costs particularly for pneumonia where oxygen administration was nearly universal indicating the severity of disease. In Gambia, these services contributed marginally to the total provider costs. This is because oxygen costs per day in our study was >10 fold the estimates in The Gambia.[118] Outside sSA, provider cost estimates tend to be considerably higher than our findings, regardless of data source for bed-day costs and whether capital costs were also included.[120,131,133,312] A multi-country study in Brazil, Chile and Uruguay estimating only recurrent costs reported hospitalisation costs >10 fold with corresponding high provider costs ranging from US$75 for pneumonia to US$5,436 for meningitis.[131] In Pakistan, when capital costs were included, provider costs ranged between US$71 for pneumonia to US$2,043 for meningitis.[312]

We found substantial household costs ranging from US$44 for pneumonia to US$72 for meningitis. These figures are higher than reported for malaria in Nigeria, which ranged from ~US$7 for outpatients to ~US$10 for hospitalised cases;[313,314] but was lower than seen for chronic conditions, such as sickle cell anaemia (US$240) and

Buruli ulcer (US$135).[315,316] These variations are attributable to differences in resource use, type of and duration of illness. User fees in our study contributed more than two-thirds of direct household costs and were largely driven by medications costs. In The Gambia, where treatment was provided at no cost to families, household OOP costs were mainly driven by non-healthcare costs including meals and visitors.[118] The main caregivers reported losing between 5-7 working days over the illness period. Although working days lost by caregivers were similar between household income levels, income loss had greater impact in the poorest households where more than half of the caregivers were also self-employed. In contrast, 80% of caregivers in the least poor households had regular salaried jobs and were likely to also receive full pay during absence for a short illness duration.

Costs incurred during treatment had considerable economic impact to households particularly for large households dependent on little income. With large numbers of economic dependents per household i.e., non-income earning household members, a one-week illness of one child, resulted in CHE_{25} in a third of households. We note the differences in CHE in ours compared to other studies in Nigeria. Although several studies analysed nationally-representative surveys, their findings differ from ours because they do not address a specific illness, target chronic conditions, and may have limited applicability to our study setting due to subnational differences in healthcare seeking behaviour.[123,124,317] At CHE_{10}, the cost of treatment costs had significant burden on households regardless of their income. At higher thresholds, our results are similar to others including those that used household income as a measure of available resources like we did.[123,124,126,315,316]

Unplanned treatment expenses are likely to affect other household expenditures. OOP payment for healthcare can provide obstacles for treatment access particularly to the poorest, skewing treatment seeking towards only those than can afford to pay.[318] The higher proportion of unemployed caregivers presenting outpatient compared to inpatient may be an indicator of reduced access to hospitalised care by poorer households. The differences in household income levels between the hospitals shows a preference for the secondary hospital by poorer households. We assume that this preference is largely due to the state policy of subsidised health services for children aged <5 years in the secondary hospital.[298] Yet these households still incurred greater burden of costs as a fraction of their income, suggesting that 'free care' to U5s provided by the state government does not translate into lower costs to households compared to the tertiary hospital. This may be the case because drugs and medical consumables are usually excluded from these subsidised care and when they are included, they are usually out-of-stock, meaning families have to get them from other providers and often at higher OOP costs.[318] CBHI is currently being implemented in many states across Nigeria including Kano state and primarily targets the formal sector with expanding cover to vulnerable groups (women and children), informal sector and rural areas. However, we show that admissions at the state facility (MMSH) where services are supposed to 'free' and U5s covered by the CBHI, increased the odds of CHE_{25} almost four-fold. This suggests the benefits of the contributory scheme are yet to reach this target population, possibly due to lack of awareness of and unwillingness to pay for pre-pay for CBHI.[299]

Having a salaried job, ≥3 children U5 in the household and higher indirect costs (HCA) reduced the odds of CHE_{25}. OOP payment from available household resources is the predominant way of financing healthcare in Nigeria. However, other non-health expenditures (rent, utilities and education) are financed with the same household resources as health care, and if substantial, can reduce resources 'available' for health expenditure.[317] We did not collect information to assess the magnitude of non-health expenses incurred by households. But having other young children or productivity losses are circumstances that can reduce resources available to households explaining their association with reduced odds of CHE. Conversely, provider costs and seeking care at a private hospital prior to hospitalisation increased odds of CHE, illustrating how burden of provider costs are pushed to households.

This study has some limitations. First, the costs here do not account for full costs to the provider because capital costs are excluded due to challenges in accessing such data. Second, we collected data on household costs on admission and close to or at discharge to limit bias because admission duration was short. However, there is still a risk of recall bias. Second, costs exclude children who died during admission and may have incurred costs from higher resource use due to more severe disease. Third, we only estimated time loss for the primary caregiver in hospital which does extend to fathers or other household members. Another limitation is the use of monthly income rather than household (or non-food) expenditure to assess CHE which may not identify the different ways of health financing. However, we believe current income reflects current resources and captures the current household capacity to pay for expenses of treatment given the short-term duration of illness. That majority of

caregivers reported using both current income and savings to cover healthcare expenses supports our decision to use current income rather than long-term household asset. Fourth, sub-national differences in household incomes may limit generalisability of our findings, particularly the costs to household cost and its economic impact. However, some components of provider costs such as bed-day costs are not likely to differ at the tertiary hospital level because these hospitals are directly funded by the Federal Government. Additionally, because many states also offer subsidised health services to children at the secondary, our findings may be generalisable to such settings. Fifth, assessing treatment costs of pneumococcal diseases after PCV may limit the interpretation of our findings. Post-PCV, it is expected a larger proportion of pneumonia will be due to non-pneumococcal pathogens, which is likely to be less severe than pneumococcal pneumonia. In such situations, costs in the post-PCV period are likely to be lower than would have been incurred pre-PCV due to less resource use.

Finally, the COVID-19 pandemic and associated restrictions may have impacted our findings. These restrictions have been associated with poor hospital attendance and low hospital utilisation and early discharge policies for non-COVID-19 illness to reduce strain on hospital resources and limit patient exposure, and this may have affected our findings in some ways.[319,320] Milder cases may be more likely to postpone or avoid hospital visits, and thus we may have captured the relatively more severe cases with more resource use and higher costs. Conversely, early discharge policy may reduce hospital stay and resource use and lead to lower costs.[321,322]

Our analyses illustrate the treatment costs of pneumococcal disease to providers and households in Nigeria. Hospitalisation particularly at tertiary level is associated with substantial costs to both the provider and households. Households incur expenses prior to diagnosis and incur substantial direct and indirect costs that has significant impact on their incomes.

Our findings have important implications for policy. First, it is evident that the PCV programme, by averting disease, can free up scarce resources for the health sector to divert to competing health problems, reduce unexpected expenditures and CHEs, and increase resources within household for savings and essential non-health expenditures. So, it is essential to achieve and maintain high PCV coverage levels to reduce this financial burden, especially for the poorer households. Second, due to higher cost of providing care at the tertiary level, strengthening lower levels of care to provide early treatment will also significantly reduce provider costs and reduce strain on the health sector resources. Finally, the current mechanisms for financing health expenditures are inadequate to protect households from catastrophic expenses. Given that OOP payments were mainly driven by medication costs, the state government when declaring 'free' health services should have a realistic plan for uninterrupted supply of drugs and other essential commodities/consumables to ensure that the families are not obliged to pay for these OOP.

5.9 Supplement to Research paper 3

Supplementary Table 5.1: Unit cost estimates and sources for parameters used in cost analysis in (US$ 2020).

Service	Unit cost US$		Source
	AKTH	MMSH	
Chest X-ray	6.9	4.2	Radiology department
CSF chemistry, microscopy, and culture	2.2	1.7	Microbiology department
Blood culture	13.9	3.3	Microbiology department
Full blood count	1.5	1.4	Haematology department
Haemoglobin	0.8	0.6	Haematology department
Urea and electrolyte	3.6	1.9	Chemical pathology department
Malaria parasite	1.1	0.6	Haematology department
Blood transfusion	13.9	13.9	Haematology department
Oxygen	20.0	10.0	Paediatric ward
Bed day AKTH (full cost)	55.5	33.3	Paediatric ward AKTH
Bed day (WHO-CHOICE)	29.8	16.7	WHO-CHOICE
OPD visit (WHO-CHOICE)	7.8	7.7	WHO-CHOICE

Supplementary Table 5.2: Sensitivity analyses for provider costs in US$ using WHO-CHOICE estimates of bed-day costs and WTP approach for indirect costs.

	Costs US$						
	Inpatient pneumonia		**Septicaemia**		**Meningitis**		**P value**
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
AKTH							
Provider costs (WHO-CHOICE)							
Bed day	146 (24)	149 (119-149)	159 (38)	149 (148-179)	189 (32)	179 (178-208)	<0.001
Total provider costs	223 (44)	219 (189-244)	217 (74)	197 (172-238)	257 (56)	253 (226-295)	0.007
Indirect costs							
WTP	25 (22)	24 (14-31)	41 (51)	28 (14-53)	56 (36)	39 (33-83)	<0.001
MMSH							
Provider costs (WHO-CHOICE)							
Bed day	95 (55)	84 (83-100)	93 (25)	84 (83-117)	119 (81)	100 (84-117)	0.004
Total provider costs	148 (63)	137 (120-153)	135 (44)	124 (108-159)	179 (98)	156 (131-174)	0.001
Indirect costs							
WTP	52 (104)	21 (13-50)	27 (25)	20 (14)	73 (134)	33 (28-74)	0.009

Original research

BMJ Global Health

The cost of illness for childhood clinical pneumonia and invasive pneumococcal disease in Nigeria

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ABSTRACT

Background Pneumococcal disease contributes significantly to childhood morbidity and mortality and treatment is costly. Nigeria recently introduced the pneumococcal conjugate vaccine (PCV) to prevent pneumococcal disease. The aim of this study is to estimate health provider and household costs for the treatment of pneumococcal disease in children aged <5 years (U5s), and to assess the impact of these costs on household income.

Methods We recruited U5s with clinical pneumonia, pneumococcal meningitis or pneumococcal septicaemia from a tertiary level hospital and a secondary level hospital in Kano, Nigeria. We obtained resource utilisation data from medical records to estimate costs of treatment to provider, and household expenses and income loss data from caregiver interviews to estimate costs of treatment to households. We defined catastrophic health expenditure (CHE) as household costs exceeding 25% of monthly household income and estimated the proportion of households that experienced it. We compared CHE across tertiles of household income (from the poorest to least poor).

Results Of 480 participants recruited, 244 had outpatient pneumonia, and 236 were hospitalised with pneumonia (117), septicaemia (66) and meningitis (53). Median (IQR) provider costs were US$17 (US$14–22) for outpatients and US$272 (US$271–360) for inpatients. Median household cost was US$51 (US$40–69). Overall, 33% of households experienced CHE, while 53% and 4% of the poorest and least poor households, experienced CHE, respectively. The odds of CHE increased with admission at the secondary hospital, a diagnosis of meningitis or septicaemia, higher provider costs and caregiver having a non-salaried job.

Conclusion Provider costs are substantial, and households incur treatment expenses that considerably impact on their income and this is particularly so for the poorest households. Sustaining the PCV programme and ensuring high and equitable coverage to lower disease burden will reduce the economic burden of pneumococcal disease to the healthcare provider and households.

Key questions

What is already known?

- Children <5 years have the highest incidence of pneumonia and invasive pneumococcal disease (IPD) and Nigeria bears the largest burden in sub-Saharan Africa.
- Pneumococcal conjugate vaccine (PCV) was introduced in Nigeria in 2016 to reduce the burden of pneumococcal disease.
- PCV is currently subsidised through Gavi (the Vaccine Alliance) financial support and Nigeria will transition to full self-financing in a few years.
- There is no contextual evidence in Nigeria on economic burden of IPD to the health system and society that can support longer term investments in PCV when Gavi co-financing terminates.

What are the new findings?

- Treatment of one hospitalised episode of pneumococcal disease cost on average, US$300 to the provider, and US$83 to the household with significant variation by clinical syndrome and level of care.
- Overall, one-third of the households encountered costs that were catastrophic (ie, >25% of household income).
- Burden of catastrophic health expenditure varied by household income tertile ranging from 4% in the least poor households (highest income tertile) to 53% in the poorest households (lowest income tertile).
- Despite the short illness duration, pneumococcal disease syndromes result in huge economic costs to providers and households.

What do the new findings imply?

- Sustaining the PCV programme and achieving high PCV coverage has the potential of saving resources at both provider and household level.
- Households are at risk of further impoverishment from catastrophic expenses associated with treatment of pneumococcal disease.
- This risk can also be significantly reduced by PCV.

INTRODUCTION

Introduction of the pneumococcal conjugate vaccine (PCV) has significantly reduced the

global burden of pneumococcal disease.[1] Despite availability of effective vaccination, pneumococcal disease syndromes remain as leading causes of preventable morbidity, mortality and economic burden, particularly among children aged <5 years (U5s) and in low-income and middle-income countries (LMICs).[1 2] In 2015, there were still ~9 million cases of invasive pneumococcal disease (IPD) in U5 children resulting in over 300 000 deaths despite this being a significant decline of >60% from the prevaccination PCV era.[1 3] Slow uptake and suboptimal coverage of PCV are partly responsible for a disproportionate pneumococcal disease burden in LMICs in the post-PCV era.[1] Unsurprisingly, pneumococcal diseases are associated with substantial annual economic health system costs of about US$13.7 billion and societal costs of US$14.3 billion globally.[4] Although associated with substantial vaccine and delivery costs, ranging between US$52 in Africa to US$599 in Europe per vaccinated child, the introduction of PCVs to infant immunisation programmes is expected to provide savings estimated as US$3.2 billion from averted hospital visits and care, and an additional US$2.6 billion from societal costs globally.[4] Economic cost studies on pneumococcal diseases report substantial costs of treatment to healthcare provider, households and families, with significant out-of-pocket (OOP) payment for health particularly in LMICs.[5–12] OOP payment for healthcare can result in catastrophic expenses capable of driving households further into poverty.

With >1 million pneumococcal disease cases resulting in nearly 50 000 deaths among U5s in 2015, Nigeria has the highest burden of pneumococcal disease in sub-Saharan Africa (sSA).[1] Approximately 40% of Nigeria's population live below the poverty line, and 15% of the population incur healthcare expenses from an illness episode that exceeds 10% of their household income annually.[13 14] In addition, 2.3% are pushed into poverty by these health expenses.[14]

Financing of healthcare in Nigeria is via multiple and largely uncoordinated channels.[15] It has one of the lowest health insurance coverage in sSA because the National Health Insurance Scheme currently targets persons employed in the formal sector, which represent about 5% of the population.[16 17] The huge informal sector largely finances healthcare through OOP payment that are over three-quarters of total expenditure on health.[18] The consequences of the huge pneumococcal disease burden and limited financial protection, especially for the poor, extend beyond the clinical as households are at high risk of impoverishment. Additionally, to avoid such unexpected financial burden, households can delay or refrain from seeking healthcare and this ultimately results in greater costs and/or poorer outcomes.[19] Existing mechanisms to provide financial protection to households range from subsidised services for vulnerable populations such as U5s and pregnant women, to the recent expansion of community-based health insurance (CBHI) to the informal sector.[20 21]

Ahead of Nigeria completing the transition to full self-financing of PCV in 2028,[22] data on the economic burden of pneumococcal diseases will help inform the policy required to assure sustainability of the PCV programme. A current description of the costs of treating childhood pneumococcal diseases in Nigeria is lacking highlighting a significant data gap.

The objectives of this study are to: (1) to estimate the provider costs of outpatient and inpatient clinical pneumonia, and inpatient pneumococcal septicaemia and meningitis; (2) to estimate the household costs of hospitalised clinical pneumonia, and pneumococcal meningitis and bacteraemia; and (3) to assess the economic impact to households of hospitalisation with clinical pneumonia, and pneumococcal septicaemia and meningitis among U5s in Kano, northern Nigeria.

METHODS

Study design and setting

This was a cross-sectional study conducted at the two largest paediatrics units in Kano, Kano State in northern Nigeria—Aminu Kano Teaching Hospital (AKTH) and Murtala Muhammed Specialist Hospital (MMSH)—which serve an overlapping catchment population. AKTH is a Federal Government Teaching Hospital and MMSH is a State Government Secondary Hospital. Kano is the capital city of Kano state and covers approximately 8 out of the 44 local government areas (LGAs) of the state. However, catchment population of both hospitals includes other LGAs outside the city and neighbouring states. The description of the hospitals is shown in table 1. Kano is the most densely populated state in the region with an estimated population of 12.2 million (~1.3million U5s) occupying 20 760 km^2.[23 24] About 55% of the population in Kano state reside in households below the poverty line.[13] The infant and U5 mortality per 1000 live births in Kano (National) were 112 (70) and 203 (120) in 2018.[25]

Study population

Children were recruited prospectively and were eligible if aged 1–59 months, presented to AKTH or MMSH and had at least one of three possible diagnoses of interest. These were (1) clinical pneumonia, (2) pneumococcal septicaemia and (3) pneumococcal meningitis. We excluded children that died during admission.

We used the formula below[26] to estimate the minimum sample sizes for (1) outpatient clinical pneumonia; (2) inpatient pneumonia; and (3) septicaemia and meningitis:

$$n = \frac{(Z\sigma)^2}{e^2}$$

Where: n=minimum sample size.

Z=the standard normal deviate for the desired confidence level (ie, Z=1.96 for 95% confidence).

σ=SD deviation of respective mean costs reported from previous studies.[8 9]

Table 1 Description of study hospitals

Hospital	Hospital type	No of beds—total/paediatric	Paediatric outpatient clinic turnover (weekly)	User charging policy	Catchment population	Source
AKTH	Tertiary—with paediatric outpatient clinic offering primary level care	750/55	~1400	User fees charged at 50% of adult rate	Residents of Kano and neighbouring states	AKTH paediatric and hospital record units
MMSH	Secondary—with paediatric outpatient clinic offering primary level care	1000/56	~2100	Consultation and admission provided free to children <14 years. Patients pay for investigations and buy drugs out-of-pocket if not available	Residents of Kano and neighbouring states	MMSH paediatric and hospital record units

AKTH, Aminu Kano Teaching Hospital; MMSH, Murtala Muhammed Specialist Hospital.

e=precision or smallest desirable margin of error allowable for estimation of the respective costs.

Sample sizes of 100, 50 and 30 were expected to provide a cost estimate for outpatient clinical pneumonia, inpatient pneumonia and septicaemia and meningitis based on SD (±precision) of US$5 (±US$1), US$21 (±US$6) and US$33 (±US$12), respectively.[8 9 27]

Data collection

We recruited outpatient pneumonia cases and interviewed caregivers on the day of diagnosis. For inpatient pneumonia cases, eligible children admitted from 08:00 to 16:00 were recruited on the day of admission; those admitted from 16:00 to 08:00 the next morning were enrolled on the next day. For septicaemia and meningitis cases, participants were recruited when confirmatory laboratory results were available. We collected data between January and October 2020. For each hospital, we recruited a volunteer nurse not directly involved in clinical care to collect data. We used structured quantitative tools adapted from a similar study in The Gambia for data collection.[9]

We extracted resource use data such as length of hospital stay, type and quantity of medications and intravenous fluids used, laboratory investigations and other specialised services including blood transfusion and use of oxygen from patients' records, case folders, prescriptions and laboratory request forms. We obtained unit costs of hospital resources, for example, medication, fluids used from the respective hospitals (see online supplemental table S1).

Sociodemographic characteristics, OOP costs, non-medical expenses, productivity time loss, household income and sources of finances used to pay the treatment costs were obtained through caregiver interviews. Additional data on household income and sources of finances used to pay the treatment costs were also collected.

Cost components

We collected provider costs, and direct and indirect household costs.

Provider costs

Provider costs included costs of direct healthcare services, that is, costs of medications, laboratory investigations, intravenous fluids, oxygen, blood transfusion and inpatient bed-day. We used full costs for drugs and only applied dose-specific costs if the drug was re-useable and the residuals amounted to another full dose. For instance, for a re-useable drug, if a unit dose was 1000 mg and 500 mg was administered, the cost per dose would be half of the unit cost. We obtained cost of oxygen from the nursing unit, and for blood transfusion, we used previously published costs.[28]

The inpatient bed-day is the daily stay cost or the 'hotel' component and comprises costs of food, personnel and utilities. We used the average 2020 admission charge for AKTH and assumed admission costs at MMSH to be 60% of AKTH since admission is 'free' to patients at MMSH. Studies have found up to 60%–70% differences in bed-day costs between tertiary-level and secondary-level hospitals.[8 9]

Household costs

We collected direct healthcare costs to households which are user fees related to consultations, investigations and medications incurred from date of admission to date of discharge. Non-healthcare costs were the costs of transportation, accommodation and feeding incurred during admission (from date of admission to date of discharge) by main and accompanying caregiver. The accompanying caregiver was defined as any household member that assisted the main caregiver with care of the patient during the admission. Preadmission costs data were collected either on the day of recruitment or

on the earliest convenient day for the caregiver, while data on costs incurred over the course of admission were obtained at or close to discharge.

We collected data on caregiver's income and productivity time loss due to time away from their usual activities owing to illness.

Data analysis

Data were analysed using Stata V.15.1 (Stata Corp LP). All costs were converted to US$ using average 2020 conversion rates 1 US$=360.5 NGN (Central bank of Nigeria).[29]

We summed up the components of respective cost categories for provider costs and direct household costs. We estimated indirect costs using the human-capital approach (HCA) by estimating income lost by caregiver(s) due to absence from work per day spent caring for the child. Self-employed caregivers were asked to give an estimate of daily earnings while those on monthly salary were asked to state their monthly wage from which daily income was calculated. Indirect costs were then calculated as daily income multiplied by the number of days taken off from work.

We present costs from the health provider and household's perspectives along with their components separately as means with SD, and medians with IQR. We used Kruskal-Wallis test to assess differences in costs between disease categories and Wilcoxon rank-sum test to compare costs between the two hospitals.

We evaluated the impact of health expenditures on available household resources by assessing direct, indirect and total costs as respective proportions of household income. We used household income to categorise households into tertiles from the poorest (tertile 1) to least poor (tertile 3). We used Kruskal-Wallis tests to compare costs as a proportion of household income across household income tertiles.[30] We also evaluated catastrophic health expenditure (CHE) as costs exceeding a specified threshold of household available resources.[31] In this analysis, we used household income as a measure of available resources and set the base threshold as 25%.[14 32 33] We defined costs as catastrophic if they exceeded 25% of household monthly income (CHE_{25}) and also explored impact at 10% (CHE_{10}) and 40% (CHE_{40}) thresholds. We used multivariable logistic regression models to identify factors associated with CHE_{25}. Independent variables that were associated with CHE_{25} at significance level p=0.1 were sequentially added to the model and kept if they were significantly associated with cost (p<0.05) or changed effects of included variables. Excluded variables were then re-introduced to check if they further changed the effect sizes of included variables. Adjusted ORs and p values from the likelihood ratio test (LRT) are reported.

Sensitivity analysis

We conducted one-way sensitivity analyses of provider costs by varying the source of bed-day costs. We used the average cost per inpatient bed-day for tertiary and secondary facilities in Nigeria from the WHO-CHOICE after accounting for inflation and adjusting to 2020 rates.[34] We also conducted a sensitivity analysis of indirect costs by using the willingness to pay (WTP) approach to assess productivity loss. Indirect costs using WTP approach were calculated as the product of the amount caregivers were willing to pay for main activity they would have been otherwise engaged in and the total days taken off from work due to childcare.

Patient involvement

Patients were not directly involved in the design, conduct, reporting or dissemination plans of this research.

RESULTS

Study participants

Overall, 480 out of 495 caregivers of eligible children consented to be interviewed. A total of 480 children (244 outpatient pneumonia, 117 inpatient pneumonia, 53 meningitis and 66 septicaemia) were enrolled (see online supplemental table S2). Of these, 387 (81%) children were aged ≥1 year. Clinical pneumonia cases were younger than their counterparts with meningitis or septicaemia (mean age, 19 vs 25 months, p=0.002). Caregivers were aged 20–48 years, mostly mothers, had at least secondary school level education and were employed. Caregivers of children with outpatient pneumonia were more likely to be unemployed compared with those with hospitalised children (20% vs 3%, p=<0.0001). The mean duration of hospitalisation was 5 days for cases with pneumonia or septicaemia but 7 days for those with meningitis. Majority (362/480, 75.4%) of the children had sought care prior to index visit/hospitalisation.

Provider costs for outpatient pneumonia

The median provider cost for outpatient pneumonia was US$17 (IQR: 14–22), and was higher in AKTH (US$20, IQR: 14–23) compared with MMSH (US$16; IQR: 14–19, p=0.0002). Overall, costs for outpatient clinic visit, medications and investigations accounted for 43%, 37% and 20% of provider costs. The median costs for laboratory investigations were higher in AKTH US$7 (IQR: 0–8) compared with MMSH US$0 (IQR: 0–4, p<0.0001). Medications costs were similar between the two hospitals. Median expenses on seeking care elsewhere prior to index presentation were US$9 (IQR: 0–13) in AKTH and US$8 (IQR: 5–13) in MMSH (p=0.70).

Provider costs for hospitalised children

The respective median/mean provider costs, as shown in table 2, were highest for meningitis in both hospitals which was mostly driven by bed-day costs. The median provider costs (all syndromes combined) were significantly higher in AKTH (US$359, IQR: 308–400) compared with MMSH (US$223, IQR: 196–264, p<0.0001).

Household costs for hospitalised children

Median household income was similar between disease categories but was significantly higher (all syndromes

Table 2 Provider costs for inpatient pneumonia, meningitis and septicaemia in US$

	Cost US$						
	Inpatient pneumonia		Septicaemia		Meningitis		
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	P value
AKTH							
Length of stay (days)	5 (0.8)	5.0 (4–5)	5 (1.3)	5 (5–6)	6 (1.1)	6 (6–7)	<0.001
Provider costs							
Bed-day costs	272 (45)	277 (222–278)	297 (70)	277 (277–333)	351 (59)	332 (332–388)	<0.001
Drugs	16 (6)	15 (13–17)	19 (6)	18 (16–20)	20 (3)	20 (18–22)	<0.001
Investigations	15 (6)	14 (13–14)	14 (7)	14 (7–21)	17 (7)	20 (13–22)	0.23
Special services*	46 (21)	40 (30–60)	25 (36)	0 (0–54)	32 (31)	34 (0–40)	<0.001
Total provider costs	348.6 (63.0)	347 (301–372)	354.0 (103.4)	325 (300–380)	420.0 (80.1)	407 (364–449)	0.001
MMSH							
Mean admission days (SD)	6 (3.3)	5 (5–6)	6 (1.5)	5 (5–7)	7 (4.8)	6 (5–7)	0.004
Provider costs							
Bed-day costs	189.1 (110.3)	166 (166–200)	186.0 (50.6)	166 (166–233)	237.2 (161.3)	199 (166–233)	0.004
Drugs	17.7 (11.7)	16 (11–20)	17.8 (6.4)	17 (14–22)	21.5 (7.9)	19 (17–24)	0.01
Investigations	7.1 (2.6)	8 (7–8)	7.0 (2.5)	7 (4–8)	8.6 (1.4)	8 (7–10)	<0.001
Special services*	27.9 (13.3)	30 (20–30)	16.5 (20.3)	14 (0–30)	29.6 (19.4)	30 (20–40)	0.001
Total provider costs	241.8 (116.9)	219 (220–247)	227.3 (67.6)	206 (179–264)	296.9 (117.5)	257 (225–280)	0.002
Combined hospitals	285.6 (111.4)	265 (215–347)	288.7 (107.2)	298 (196–335)	345.7 (158.0)	294 (253–408)	0.01

*Oxygen and blood transfusion.
AKTH, Aminu Kano Teaching Hospital; MMSH, Murtala Muhammed Specialist Hospital.

combined) for those presenting to AKTH (US$250, IQR: 222–277, p=0.02) compared with MMSH (US$222, IQR: 194–277). Majority of caregivers (217/236, 92%) reported using a combination of current income and savings to cover expenses. Only about 3% reported using other sources such as borrowing, asking relatives or selling assets to cover expenses.

Median direct household costs as shown in table 3 were highest for meningitis and lowest for pneumonia in both hospitals. However, there was no significant difference in overall direct household costs between the two hospitals. Direct costs comprised mostly of user fees, and for each disease category in both hospitals, medication costs were the largest fraction of user fees (online supplemental figure S1A, B).

Median indirect costs were lowest for inpatient pneumonia compared with meningitis or septicaemia, as shown in table 3. Comparison between the hospitals (all syndromes combined), showed indirect costs were slightly higher in AKTH compared with MMSH (US$22 (IQR: 15–26) vs US$18 (IQR: 10–23), p=0.04).

Economic impact to households

The poorest households spent a median of 25% of their monthly income directly on treatment costs and lost an additional 8% from loss of caregiver time, compared with 13% of income and 6% of caregiver time for the least poor households (data not shown). Treatment costs as fractions of monthly household income were inversely related to household income tertiles (see online supplemental table S3).

Table 4 shows the proportion of households encountering CHE_{25} at different threshold cut-off values across household income levels. CHE was substantial, and at 10% threshold nearly all households across all income levels encountered CHE. CHE increased with decreasing household income level. This inverse relationship is further illustrated in figure 1 which shows that as the threshold values increase, the proportions of households encountering catastrophic costs declines steeply for the higher income households, with slowest decline for the poorest households (tertile 1).

Admitting hospital (MMSH), meningitis or septicaemia, seeking care at a private hospital prior to admission and higher provider costs were associated with increased odds of CHE_{25}, while having ≥3 U5 children and higher indirect costs lowered the odds of CHE_{25} (see table 5).

Sensitivity analyses

Provider costs were sensitive to source of hospital (bed-day) costs. Provider costs were between 38% and 40% lower across all disease categories and between the hospitals when the WHO-CHOICE estimates were used (online supplemental table S4) compared with actual hospital admission costs (online supplemental table S4).

Table 3 Direct and indirect costs to households per illness episode (US$)

	Cost US$						
	Inpatient pneumonia		Septicaemia		Meningitis		
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	P value*
AKTH							
Pre-admission costs	9.4 (9.3)	8.6 (0–12)	19.8 (26.4)	13.9 (8–26)	14.9 (11.0)	13.6 (8–25)	0.01
Current admission costs							
1. Direct costs							
Transportation	1.1 (1.9)	0.0 (0–4)	2.1 (5.7)	0.0 (0–5)	1.1 (2.9)	0.0 (0–0)	0.84
Feeding	0.6 (2.2)	0.0 (0–0)	1.2 (4.8)	0.0 (0–0)	1.3 (6.1)	0.0 (0–0)	0.98
User fees	38.5 (29.3)	35.2 (30–38)	44.5 (25.4)	35.8 (32–47)	44.3 (6.7)	44.3 (39–50)	<0.001
Total direct household costs	50 (30.0)	43.6 (36–55)	73.5 (61.1)	60.7 (45–75)	64.3 (16.8)	68.8 (51–76)	<0.001
2. Indirect costs							
Working days lost	5 (0.9)	5 (4–5)	5 (1.2)	5 (5–6)	6 (1.1)	6 (6–7)	<0.001
Monthly household income	258.6	249.7 (222–277)	266.1	270.5 (222–277)	329.6	277.4 (222–361)	0.30
Daily income lost	4 (2)	4 (3–5)	4 (2)	5 (3–5)	5 (2)	5 (4–5)	0.23)
Total indirect costs	19 (7.0)	19 (14–23)	22 (12.0)	23 (15–23)	28 (14.7)	27.7 (22–28)	0.006
Total household costs	68.9 (28.2)	64.5 (55–75)	95.4 (63.8)	82.6 (63–96)	92.3 (22.1)	89.3 (79–106)	<0.001
MMSH							
Pre-admission costs	12.0 (9.8)	9.9 (7–12)	12.2 (10.4)	11.4 (0–14)	18.6 (10.4)	17.7 (11–26)	0.003
Current admission costs							
1. Direct costs							
Transportation	2.9 (4.8)	1.9 (0–3)	1.7 (3.9)	0.0 (0–5)	2.9 (4.4)	0.0 (0–6)	0.17
Feeding	1.1 (3.4)	0.0 (0–0)	3.2 (12.8)	0.0 (0–0)	6.8 (17.8)	0.0 (0–0)	0.57
User fees	27.8 (11.3)	29.1 (22–36)	50.7 (84.3)	34.4 (29–44)	59.2 (94.3)	40.3 (36–45)	<0.001
Total direct household costs	43.7 (14.4)	42.7 (35–53)	74.3 (102.0)	53.8 (42–72)	92.2 (106.6)	71.8 (58–83)	<0.001
2. Indirect cost							
Working days lost	5.3 (3.3)	5.0 (4–5)	5.6 (1.5)	5.0 (5–7)	7.4 (6.5)	6.0 (5–7)	<0.001
Monthly household income	242.1	221.9 (166–277)	257.8	221.9 (194–277)	271.3	249.7 (222–277)	0.46
Daily income lost	3 (2)	3 (2–5)	4 (2)	4 (3–5)	4 (3)	4 (3–5)	
Total indirect costs	16.3 (12.4)	16.6 (7–23)	21.1 (12.0)	18.5 (114–26)	28.4 (22.5)	22.4 (19–28)	<0.001
Total household costs	60.0 (21.8)	59.1 (47–74)	95.4 (105.7)	68.4 (60–95)	120.6 (123.2)	97.6 (83–108)	<0.001
Combined hospitals							
Direct cost	46.3 (22.3)	43.6 (36–53)	73.9 (84.1)	57.3 (42–73)	81.2 (84.1)	69.6 (55–80)	<0.001
Indirect cost	17.4 (10.6)	18.5 (9–23)	21.5 (11.9)	19.4 (14–26)	28.2 (19.6)	23 (19–28)	<0.001
Total cost	63.7 (24.9)	62.2 (50–74)	95.4 (87.3)	72.2 (61–95)	109.4 (97.1)	93.8 (81–106)	<0.001

*P value for Kruskal-Wallis test comparing medians across disease categories.
AKTH, Aminu Kano Teaching Hospital; MMSH, Murtala Muhammed Specialist Hospital.

Table 4 Proportions of households with CHE at different thresholds of household income

	CHE threshold level					
	10%		25%		40%	
Income tertile	%	95% CI	%	95% CI	%	95% CI
Tertile 1 (poorest)	97.2	92.2 to 99.4	53.2	43.4 to 62.8	18.3	11.6 to 26.9
Tertile 2	97.2	90.3 to 99.7	25.0	15.5 to 36.6	2.8	0.3 to 9.7
Tertile 3 (least poor)	81.8	69.1 to 90.9	3.6	0.4 to 12.5	0.0	0.0 to 0.0
Overall	93.6	89.7 to 96.1	33.1	27.1 to 39.4	9.3	5.9 to 13.7

CHE, catastrophic health expenditure.

Indirect costs were also sensitive to approach used as costs were higher for all conditions in both hospitals with the WTP (online supplemental table S4) compared with the HCA. However, in contrast to HCA, indirect costs were similar between the hospitals (p=0.45)

DISCUSSION

In this study, we estimated the costs of treatment of clinical pneumonia, septicaemia and meningitis in Nigerian children as well as the economic impact of these costs on households. Costs varied by hospital as they were higher in the tertiary hospital (AKTH) for all disease categories. Provider costs also varied by illness and were highest for meningitis irrespective of hospital. Costs to households were similar between the hospitals but highest for meningitis and lowest for pneumonia. The economic impact to households was considerable with total costs to households ranging between 25% and 37% of monthly household income for 5–7 days of hospitalisation. One-third of the households incurred CHE at 25% threshold and the poorest households bore the greatest burden of CHE.

Although provider costs are likely to vary across the country and between hospitals, when applied to the global burden of disease and the proportions of the different pneumococcal disease syndromes, our cost estimates translate to annual provider costs of >US$110 million, that is, ~9% of Nigeria's 2020 health budget.[1 35] Funding of provider costs within the public sector is largely through budgetary allocations at the federal and state levels, and the overall health sector budget has been consistently below the 15% threshold of the total annual budget agreed to in the Abuja declaration.[35 36] Treatment of pneumococcal disease exerts undue strain on the health sector, particularly at the tertiary hospitals where unit costs are higher for most components as reported elsewhere.[5 7 8] In many settings, robust pneumococcal disease surveillance has shown evidence of substantial reduction in pneumococcal diseases attributed to PCV use.[37] The extent of savings on treatment costs will depend on the effectiveness and coverage of PCV across the country.

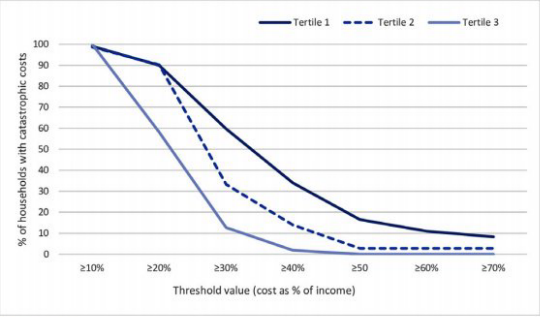

Figure 1 Distribution of proportions of households encountering catastrophic costs at different threshold values of cost as a fraction of household income by tertiles of household income level. Tertiles range from the poorest households (tertile 1) to the least poor (tertile 3).

For each IPD category and hospital in our study, 'hospital stay' accounted for the largest proportion of provider costs. This is similar to findings in diverse settings across Africa (Kenya and The Gambia), Asia (India and Vietnam) and South America.[6–10 38] This indicate the huge recurrent costs of hospitalisation and inpatient care to the healthcare system. Specialised services were the next largest contributor to provider costs, and they were mainly driven by oxygen costs particularly for pneumonia where oxygen administration was nearly universal indicating the severity of disease. In The Gambia, these services contributed marginally to the total provider costs. This is because oxygen costs per day in our study was >10-fold the estimates in The Gambia.[9] Outside sSA, provider cost estimates tend to be considerably higher than our findings regardless of data source for bed-day costs and whether capital costs were also included.[6 10 39 40] A multicountry study in Brazil, Chile and Uruguay estimating only recurrent costs reported hospitalisation costs >10-fold with corresponding high provider costs ranging from US$75 for pneumonia to US$5436 for meningitis.[6] In Pakistan, when capital costs were included, provider costs ranged between US$71 for pneumonia and US$2043 for meningitis.[39]

We found substantial household costs ranging from US$44 for pneumonia to US$72 for meningitis. These figures are higher than reported for malaria in Nigeria, which ranged from ~US$7 for outpatients to ~US$10 for hospitalised cases[41 42]; but was lower than seen for chronic conditions, such as sickle cell anaemia (US$240) and Buruli ulcer (US$135).[43 44] These variations are attributable to differences in resource use, type of

Table 5 Distribution of CHE_{25} and multivariable logistic regression of factors associated with CHE_{25}

	Total N=236	CHE_{25} N=78	Adjusted* OR (95% CI)	P value
Hospital, n (%)				
AKTH	101	29 (28.7)	Reference	
MMSH	135	49 (36.3)	3.6 (1.4 to 9.5)	0.005
IPD category, n (%)				
Pneumonia	117	26 (22.2)	Reference	
Septicaemia	66	26 (39.4)	2.5 (1.1 to 5.5)	
Meningitis	53	26 (49.1)	3.2 (1.3 to 8.3)	0.02
Pre-admission care seeking				
None	72	19 (26.4)	Reference	
Private	58	31 (53.5)	4.3 (1.8 to 10.5)	
Chemist	106	28 (26.4)	0.8 (0.4 to 1.9)	<0.001
Age of caregiver in years, n (%)				
<30	143	44 (30.8)	Reference	
≥30	93	34 (36.6)	1.1 (0.5 to 2.4)	0.75
Caregivers with salaried occupation, n (%)				
No	112	49 (43.8)	Reference	
Yes	124	29 (23.4)	0.5 (0.2 to 0.9)	0.04
Age of child in months, n (%)				
1–11	36	7 (19.4)	0.4 (0.2 to 1.3)	
12–23	103	32 (31.1)	Reference	
≥24	97	39 (40.2)	1.2 (0.6 to 2.5)	0.16
No of children <5 years, n (%)				
<3	135	53 (39.3)	Reference	
≥3	101	25 (24.8)	0.3 (0.2 to 0.7)	0.003
Provider cost (US$10), mean (SD)	300.0 (108.6)	330.0 (147.3)	1.09 (1.03 to 1.15)	<0.001
Indirect cost† (US$10), mean (SD)	21.0 (14.1)	19.9 (15.5)	0.6 (0.4 to 0.8)	0.001

*Adjusted for all variables in the table.
†Using human-capital approach.
AKTH, Aminu Kano Teaching Hospital; CHE, catastrophic health expenditure; IPD, invasive pneumococcal disease; MMSH, Murtala Muhammed Specialist Hospital.

and duration of illness. User fees in our study contributed to more than two-thirds of direct household costs and were largely driven by medications costs. In The Gambia, where treatment was provided at no cost to families, household OOP costs were mainly driven by non-healthcare costs including meals and visitors.[9] The main caregivers reported losing between 5 and 7 working days over the illness period. Although working days lost by caregivers were similar between household income levels, income loss had greater impact in the poorest households where more than half of the caregivers were also self-employed. In contrast, 80% of caregivers in the least poor households had regular salaried jobs and were likely to also receive full pay during absence for a short illness duration.

Costs incurred during treatment had considerable economic impact to households particularly for large households dependent on little income. With large numbers of economic dependents per household, that is, non-income earning household members, a 1-week illness of one child, resulted in CHE_{25} in one-third of households. We note the differences in CHE in ours compared with other studies in Nigeria. Although several studies analysed nationally-representative surveys, their findings differ from ours because they do not address a specific illness, target chronic conditions and may have limited applicability to our study setting due to subnational differences in healthcare seeking behaviour.[18 45 46] At CHE_{10}, the cost of treatment costs had significant burden on households regardless of their income. At higher thresholds, our results are similar to others including those that used household income as a measure of available resources like we did.[18 43 44 46 47]

Unplanned treatment expenses are likely to affect other household expenditures. OOP payment for healthcare can provide obstacles for treatment access particularly

to the poorest, skewing treatment seeking towards only those that can afford to pay.[48] The higher proportion of unemployed caregivers presenting outpatient compared with inpatient may be an indicator of reduced access to hospitalised care by poorer households. The differences in household income levels between the hospitals show a preference for the secondary hospital by poorer households. We assume that this preference is largely due to the state policy of subsidised health services for children aged <5 years in the secondary hospital.[20] Yet these households still incurred greater burden of costs as a fraction of their income, suggesting that 'free care' to U5s provided by the state government does not translate into lower costs to households compared with the tertiary hospital. This may be the case because drugs and medical consumables are usually excluded from these subsidised care and when they are included, they are usually out-of-stock, meaning families have to get them from other providers and often at higher OOP costs.[48] CBHI is currently being implemented in many states across Nigeria including Kano state and primarily targets the formal sector with expanding cover to vulnerable groups (women and children), informal sector and rural areas. However, we show that admissions at the state facility (MMSH) where services are supposed to 'free' and U5s covered by the CBHI, increased the odds of CHE_{25} almost fourfold. This suggests that the benefits of the contributory scheme are yet to reach this target population, possibly due to lack of awareness and unwillingness to pre-pay for CBHI.[21]

Having a salaried job, ≥3 children U5 in the household and higher indirect costs (HCA) reduced the odds of CHE_{25}. OOP payment from available household resources is the predominant way of financing healthcare in Nigeria. However, other non-health expenditures (rent, utilities and education) are financed with the same household resources as healthcare, and if substantial, can reduce resources 'available' for health expenditure.[45] We did not collect information to assess the magnitude of non-health expenses incurred by households. But having other young children or productivity losses are circumstances that can reduce resources available to households explaining their association with reduced odds of CHE. Conversely, provider costs and seeking care at a private hospital prior to hospitalisation increased odds of CHE, illustrating how burden of provider costs are pushed to households.

This study has some limitations. First, the costs here do not account for full costs to the provider because capital costs are excluded due to challenges in accessing such data. Second, we collected data on household costs on admission and close to or at discharge to limit bias because admission duration was short. However, there is still a risk of recall bias. Second, costs exclude children who died during admission and may have incurred costs from higher resource use due to more severe disease. Third, we only estimated time loss for the primary caregiver in hospital which does extend to fathers or other household members. Another limitation is the use of monthly income rather than household (or non-food) expenditure to assess CHE which may not identify the different ways of health financing. However, we believe current income reflects current resources and captures the current household capacity to pay for expenses of treatment given the short-term duration of illness. That majority of caregivers reported using both current income and savings to cover healthcare expenses supports our decision to use current income rather than long-term household asset. Lastly, subnational differences in household incomes may limit generalisability of our findings, particularly the costs to household cost and its economic impact. However, some components of provider costs such as bed-day costs are not likely to differ at the tertiary hospital level because these hospitals are directly funded by the Federal Government. Additionally, because many states also offer subsidised health services to children at the secondary, our findings may be generalisable to such settings.

CONCLUSIONS

Our analyses illustrate the treatment costs of pneumococcal disease to providers and households in Nigeria. Hospitalisation particularly at tertiary level is associated with substantial costs to both the provider and households. Households incur expenses prior to diagnosis and incur substantial direct and indirect costs that has significant impact on their incomes.

Our findings have important implications for policy. First, it is evident that the PCV programme, by averting disease, can free up scarce resources for the health sector to divert to competing health problems, reduce unexpected expenditures and CHEs and increase resources within household for savings and essential non-health expenditures. So, it is essential to achieve and maintain high PCV coverage levels to reduce this financial burden, especially for the poorer households. Second, due to higher cost of providing care at the tertiary level, strengthening lower levels of care to provide early treatment will also significantly reduce provider costs and reduce strain on the health sector resources. Finally, the current mechanisms for financing health expenditures are inadequate to protect households from catastrophic expenses. Given that OOP payments were mainly driven by medication costs, the state government when declaring 'free' health services should have a realistic plan for uninterrupted supply of drugs and other essential commodities/consumables to ensure that the families are not obliged to pay for these OOP.

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6 Discussion

6.1 Background

Introduction

This chapter provides an integrated discussion of the findings from the three research papers presented in this thesis. First, I summarise the aim, objectives, and key findings of each research paper. Then, I discuss the methodological limitations of the thesis as a single research body and the implications of the findings for policy and future research.

Summary of the overall purpose of the dissertation

The overall goal of this PhD thesis was to use vaccine-induced changes in the pneumococcal carriage prevalence to assess the impact of PCV10 introduction in Nigeria. To achieve this, I had the following objectives:

1. To estimate the impact of PCV10 introduction against nasopharyngeal carriage of vaccine-serotype (VT) and non-vaccine-serotype (NVT) pneumococci in vaccine-target and non-target populations in rural and urban Nigerian settings.
2. To evaluate the applicability of statistical models of carriage prevalence in estimating the impact of the 10-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in Nigeria.
3. To assess the economic cost of treatment of IPD among children aged < 5 years in Nigeria.

To meet the aim and these objectives, I used a combination of secondary data extraction, primary data collection from research surveys, and statistical models to assess PCV10 impact in light of Nigeria's lack of pneumococcal disease surveillance. The three articles of this PhD combine the following approaches to evaluate PCV impact:

1. Surveys –
    a. Annual carriage surveys 2017 to 2020 – seven surveys
    b. Annual PCV coverage surveys 2018-2020 – five surveys
    c. Cost-of-illness study 2020
2. Statistical models
    a. To assess the population impact of PCV on pneumococcal carriage prevalence and serotype distribution (Obj #1)
    b. To explore the relationship between changes in VT carriage prevalence and PCV coverage using annual carriage and PCV coverage surveys (Obj # 1)
    c. To predict the impact of PCV on IPD using baseline carriage and changes in carriage prevalence (Obj #2)
3. Economic cost analysis to assess average treatment costs of pneumonia and IPD and the impact of treatment expenses on household income (Obj #3)

6.2 Summary of main findings from each of the included manuscripts

6.2.1 Introduction of PCV10 was associated with significant population-level reduction in VT carriage prevalence and a variable increase in NVT carriage prevalence. PCV10 coverage in children <5 years was negatively correlated with population-level VT carriage prevalence over time (Objective 1).

This study assessed the population-level impact of introducing PCV10 into routine infant immunisation programme in diverse Nigerian settings. Within five years of PCV10 introduction using three primary doses without a booster or catch-up, VT carriage prevalence significantly declined at a population level, even with a slow but steady PCV10 uptake. At a population level, the age-standardised VT carriage prevalence fell from 21% to 12%, giving a relative VT carriage reduction of 48% (PR 0.52, 95% CI 0.43-0.64) among rural participants. Among urban participants, the age-standardised VT carriage prevalence fell from 16% to 9%, giving a relative VT carriage reduction of 66% (PR 0.34, 95% CI 0.26-0.45). Among the total population sample, there was a significant trend for an increase in NVT carriage over the survey years in the rural site (PR 1.30, 95% CI 1.19-1.42) but not in the urban site (PR 1.03, 95% CI 10.89-1.20). I also found changes in the ranking of serotypes at a population level, and some of the prominent non-PCV10 serotypes in carriage post-PCV10 introduction were 3, 6A, 10A, 11A, 16F, 19A, and 34. Notably, prominence in carriage of non-PCV10 PCV13 serotypes 6A and 19A may indicate that these serotypes are causing SRD in Nigeria. In countries using PCV10 or where PCV13 was replaced with PCV10, the incidence of serotype 19A increased in IPD, but this

increase did not offset the net PCV10 benefits.[323–327] Moreover, increase in SRD due to serotypes included in higher-valent PCVs provides an opportunity for prevention via a switch in PCV type.

Using an ecological analysis, I found a decline in VT carriage prevalence with increasing PCV10 uptake among children aged <5 years, at least within the ranges of value of 'observed' uptake. Among children aged <5 years, there was a log-linear (exponential) relationship between declining VT carriage prevalence and PCV10 uptake in children aged <5 years. This relationship is characterised by a steep decline in VT carriage prevalence associated with a modest increase in PCV10 uptake, followed by a slower decline as uptake further increased. This finding supports arguments suggesting indirect PCV effects begin at relatively low uptake levels.[198,199,328] In Malawi, transmission dynamic modelling projected that reduction in force of infection and VT carriage prevalence among younger children aged 0-5 years was faster in the three years immediately following PCV13 introduction, and this was followed by a slower reduction in VT carriage, thereafter.[269]

Among persons aged ≥5 years, by contrast, there was a linear relationship between the decline in VT carriage prevalence and the increase in childhood PCV10 uptake; the gradient on this line suggested a reduction of 1.4-1.5% in VT carriage prevalence among adults/older children for every 20% increase in PCV10 uptake in young children. In Malawi, the fit of the dynamic model was optimised by a non-linear decline in VT carriage among older children (6-9 years) in the same manner as with Malawian children. Among the older children, a slower decline in VT carriage

prevalence three years post-PCV13 introduction preceded a faster decline 3-5 years post-PCV13, suggesting that indirect effects take time to percolate through the whole population.[269] Evidence for indirect effects for non-PCV target or unvaccinated populations is mixed. Some studies point towards little or no indirect effect among such groups in settings with high carriage burden.[329–332] However, others indicate substantial indirect effects among non-PCV target groups starting at moderate levels of PCV uptake. The indirect effect may result from a combination of vaccine-induced reduction in VT transmission and age-related development of naturally-acquired capsule-specific and non-specific immunity.[180,333]

Despite this considerable impact, residual carriage of vaccine serotypes was still substantial, with VT carriage prevalence of 22% among children aged <5 years in the rural site and 12% in the urban site. In contrast to countries in Europe and North America that observed a decline that reached an equilibrium at close to zero VT in carriage [334–340], particularly following PCV7 use, many low and middle-income countries report an equilibrium at ≥10% residual VT carriage with longer duration of PCV use. [72,270,289,290,341–343] The relatively lower impact in such settings may be related to a higher force of infection due to factors that increase the probability of contact and transmissibility. For instance, in Mongolia, the PCV-related decline in VT carriage was greater in formal (less crowded) settlements compared to informal (crowded) settlements, particularly at lower levels of PCV coverage.[331]

In a rural setting in Malawi, three years post-PCV13 with 3p+0 schedule and 3-dose catch-up to all infants at introduction, VT carriage prevalence declined significantly among infants aged 18 weeks, vaccinated children aged 1-4 years and children aged

5-15 years.[342] Decrease in VT carriage prevalence was not significant for infants aged six weeks and too young to be vaccinated and unvaccinated children aged 1-4 years. This heterogeneity in vaccine impact suggests a combination of factors. Firstly, waning of direct vaccine-induced immunity is indicated by differences in prevalence ratio for VT carriage of 0.24 (95% CI: 0.08–0.75) among vaccinated infants 18 weeks of age) and 0.54 (95% CI: 0.33–0.88) among vaccinated children 1-4 years. Secondly, absence of substantial indirect effects with short duration of vaccine use (3 years) is demonstrated by the lack of effect on VT carriage prevalence for unvaccinated infants aged six weeks and children aged 1-4 years. Thirdly, the significant reduction in VT carriage prevalence observed for unvaccinated children aged 5-15 years and HIV-negative mothers is likely attributable to differences in contact patterns between age groups.

The 3p+0 schedule may not be optimised to eliminate VT carriage as direct immunity wanes rapidly.[344] In urban Malawi, seven years post-PCV13 with a 3p+0 schedule, VT carriage prevalence was similar (18%) for vaccinated (3-7 years old) and unvaccinated children (3-10 years old), indicating a lack of added advantage of direct protection after some period.[270] A 3p+0 PCV schedule, particularly in the presence of high VT carriage prevalence (and transmission) among older PCV-ineligible children and adults, presents an additional dilemma. In such settings, very high PCV coverage with three primary doses will provide infants with the most needed timely direct protection. However, rapid waning of direct immunity, continuous VT carriage among older persons, and contact patterns that favour transmission will allow VT carriage to persist.[269]

Hypo-responsiveness to PCV from early carriage acquisition and vaccination in the presence of carriage has been suggested as an alternative explanation for suboptimal vaccine responses that could contribute to residual VT carriage.[345,346] Analysis of clinical trials immunogenicity data in Kenya showed that infants who were carriers (of PCV7 serotypes) at the time of vaccination had a lower rise in GMC of the homologous serotypes one week post-booster compared to non-carriers.[345] The consequences of this hypo-responsiveness may be important, particularly where conditions favour transmission and carriage acquisition before vaccination.

The findings that the introduction of PCV10 into the routine infant immunisation programme in Nigeria was associated with a significant decline in VT carriage at a population level suggests that there are direct and indirect vaccine effects that would translate, at a minimum, to a comparable reduction in VT-IPD. The findings also suggest that a further increase in PCV uptake will likely reduce transmission further. However, host or environmental factors may contribute to waning immunity and lead to the persistence of VT transmission. Thus, alternate strategies to improve population immunity, such as schedules with a booster dose beyond infancy or catch-up campaigns to older children, could be considered to eliminate VT carriage and achieve (indirect) control of VT-IPD through vaccination.

6.2.2 Statistical models of carriage will not accurately predict PCV10 impact on IPD because they account only for vaccine effects mediated via reduction in VT carriage, and VT carriage has not been eliminated in Nigeria, indicating a residual dependency on direct effects against invasion (Objective 2).

I predicted the impact of PCV10 introduction on IPD among children aged <5 years by applying the carriage data obtained from the baseline carriage survey and the post-PCV carriage surveys (Objective #2) [258,283] to three separate statistical models.[77,251,252]

The first model (Model 1) assumes that VT carriage is eliminated post-PCV and thus predicts the maximum potential impact of the vaccine.[252] To extrapolate carriage to IPD from Model 1, I used pre-PCV carriage data from Nigeria [258] and the pre-PCV ratio of VT/NVT IPD from a systematic review using data extracted from sub-Saharan Africa.[84] Model 1 predicted a decline in overall IPD of 50% in the rural and 62% in the urban site. The other two models (Models 2 and 3) are mathematically comparable and have similar assumptions but use different data sources. Models 2 and 3 assume that PCV does not affect serotype invasiveness and that its effects on IPD are entirely indirect. For Model 2, I used pre-PCV IPD serotype distribution from sub-Saharan Africa [84]to translate changes in observed post-PCV carriage prevalence in Nigeria[283] to disease. Model 2 predicted a 22% decline in the incidence of overall IPD and a 49% decline in the incidence of VT-IPD in the rural site; and a decline of 31% and 57%, respectively, in the urban site. For Model 3, I used external measures of serotype-specific CCRs [253] to translate pre- and post-

PCV carriage prevalence [283]to IPD incidence. Model 3 predicted a 30% decline in overall IPD incidence, a 48% decline in VT-IPD incidence in the rural site, and a decline of 37% and 68%, respectively, in the urban site. Model 3 also made predictions for the level of individual serotypes, and these suggested that serotype 19A (vaccine-related type), serotype 14 (vaccine type), and serotype 12F (non-vaccine type) dominate in IPD in the post-PCV10 period. The model predictions also suggest that four to five years after PCV10 introduction, many VTs still rank among the top ten causes of IPD.

PCVs prevent disease via two pathways – directly among the vaccinated by protecting against VT carriage acquisition and against invasion when VT carriage occurs, and indirectly among the entire population (vaccinated and unvaccinated) by reducing VT transmission via reduced carriage acquisition of the vaccinated. These carriage-based models were developed and validated in the PCV7 era when VT carriage was rapidly eliminated and, thus, PCV7 impact on IPD was primarily driven by indirect effects. Given the substantial residual VT carriage we observed (22% and 12%) after introduction of PCV10 in Nigeria, Model 1 cannot provide an accurate prediction for our setting. Rather, Model 1 provides a measure for the potentially preventable IPD when VT carriage is eliminated.

Models 2 and 3, as they are, have a common flaw in that they only measure indirect effects and ignore direct PCV effects altogether. In the Nigerian setting, this will always underestimate the predicted vaccine impact. First, residual VT carriage means that the direct effect against invasion is still an important component of the protection against IPD. Second, model 3 uses CCRs to predict IPD from carriage but

assumes that these CCRs are unaffected by vaccination status. Yet vaccination, in theory, provides substantial efficacy against IPD among carriers. This incorrect assumption will overestimate IPD incidence in vaccinated VT carriers and underestimate vaccine impact. Third, external data on IPD or CCR are required for these models, and they may not accurately represent the epidemiological setting of Nigeria. The serotype IPD data extracted from the systematic review included data from only 13 sSA countries, however, 74% of the isolates were from South Africa alone, which is a very different setting from Nigeria. Differences in the population age structure and contact pattern; the distribution of underlying risk factors such as antibiotic use and HIV; and the geographical risk of outbreaks can also influence serotype distribution.[44,101,109,347] For instance, countries within the meningitis belt contributed only 11% of the isolates, meaning our data source may underestimate the relative contribution of epidemic-prone serotypes. Furthermore, the serotype CCR data did not include data from any sSA country, strengthening the argument of a probable non-representativeness of these data sources.

The attraction of these models is their simplicity and potential ease of use to guide policymaking in the absence of IPD surveillance. However, a critical evaluation of the respective models' assumptions and the reliance on external data sources indicate that they have significant limitations when applied to Nigerian carriage data. Adjustments to the models to account for these limitations may not be tenable for all models. Model 1 cannot be adjusted to accommodate residual VT carriage, which is still substantial for Nigeria. For model 2, although it is theoretically possible to improve its accuracy by using more representative pre-PCV IPD data sources, the

model is inherently structured to only measure indirect effects. Model 3 is the only one that can be improved with some simple modifications. First, using CCR estimates from settings that are more representative of sSA could provide a better measure of the likelihood of invasion given carriage. Second, the serotype-specific CCRs can be adjusted for vaccination and VT carriage status. Accounting for a lower CCR among vaccinated individuals who are VT carriers will capture direct PCV effects against invasion and improve model accuracy.

The findings from this research paper indicate that IPD incidence has declined by at least 22% to 30% five years after PCV10 introduction in the rural site and by at least 31% to 37% four years after PCV10 introduction in the urban site. However, unless VT carriage is eliminated or adjustments are made to additionally capture direct effects, these estimates will be inaccurate. Close evaluation suggests that only Model 3 is amenable to further adjustments to capture direct effects and also improve data source accuracy.

6.2.3 Treatment costs of pneumococcal diseases in children aged <5 years are substantial to the health provider and to households

In this research paper, I conducted a cost-of-illness study to estimate the health provider and household costs of treating pneumococcal disease (pneumonia, pneumococcal septicaemia, and meningitis) in children aged <5 years and to assess the impact of these costs on household income. This study delineated the direct and indirect costs to households and estimated the proportion of households that experienced catastrophic health expenditures from direct treatment costs.

For an average 7-day hospitalisation from pneumococcal disease, this study found that the median (IQR) health provider costs were higher for tertiary hospital care than for secondary hospital care. In the tertiary hospital, provider costs were US$347 (IQR: 301-372) for pneumonia, US$325 (IQR: 300-380) for septicaemia, and US$407 (IQR: 364-449) for meningitis. In the secondary hospital, provider costs were US$219 (IQR: 220-247) for pneumonia, US$206 (IQR: 179-264) for septicaemia, and US$294 (IQR: 253-408) for meningitis.

Direct costs to households differed by pneumococcal syndrome diagnosis but were similar between children hospitalised in the tertiary and secondary hospitals. The median (IQR) of the total (direct + indirect) costs was US$62 (IQR: 50-74) for pneumonia, US$72 (IQR: 61-96) for septicaemia, and US$94 (IQR: 81-106) for meningitis. Households financed these costs via income and savings. Overall, a third of the households experienced catastrophic health expenditure at ≥25% of their total monthly income (CHE_{25}). However, the proportion of households encountering CHE_{25} varied widely by income level, ranging between 4% of the least poor and 53% of the poorest households.

Health provider costs translate to >US$110 million annually, representing nearly a tenth of the annual health budget in 2020 and nearly half of Gavi disbursements to Nigeria between 2000-2019 for PCV.[213,310] The findings from this paper show that in addition to reducing disease burden, PCV use would also reduce healthcare provider and household costs related to treatment and would protect poorer households from further impoverishment due to catastrophic expenditures. The findings from the CCR-based model (Model 3) predicted a decline in IPD incidence of

30-37%, which is the minimum impact expected from vaccine protection mediated via reduced VT carriage prevalence. This translates to a minimum savings of US$33-40 million annually in health provider recurrent costs, which is likely more if direct protection against invasion among vaccinees is included. Presuming the PCV programme can potentially reduce IPD incidence (Model 1) by 50-62% if VT carriage is eliminated or by 54-74% if there is additional cross-protection against serotype 6A, potential savings in healthcare provider recurrent costs will amount to US$55-US$81million annually. Given the relatively high levels of residual VT carriage in Nigeria and sub-optimal PCV10 uptake, there is ample room for considerable improvement of the PCV programme to get more value.

6.3 Methodological considerations and limitations

The limitations related to the approach have been discussed in detail in the respective results chapters. Here, I discuss the overarching limitations that affect the interpretation of the key PhD findings.

6.3.1 Carriage surveys

- The cross-sectional nature of surveys has a limitation, which is based on stochastic events, such that serotypes with low prevalence are less likely to be identified, and when identified, their prevalence will be overestimated. This limitation can be overcome by increasing the sample size or through multiple surveys, as was done in this thesis. In addition, cross-sectional studies could underestimate transient changes in carriage prevalence, such as during outbreaks, and could also be sensitive to missing transient temporal changes. The surveys were conducted at

the same time each year to control for seasonal variations and maintain the assumption of steady-state or equilibrium of prevalence underlying the relationship between CCR and IPD prediction.

- The vaccination (PCV10) status of children enrolled in carriage surveys could not be assessed due to missing cards. Stratifying vaccine impact in children by their vaccination status would have allowed some extrapolation of direct vaccine effects in the models.
- The impact of the PCV10 programme may have been underestimated because the baseline survey occurred 4-5 months after the introduction of the PCV10 programme. Therefore, a fraction of the infants may have received PCV at this baseline. However, this fraction is likely negligible due to low PCV coverage and the absence of catch-up.
- Colony selection based on morphology could lead to bias toward identifying serotypes with distinct morphologies, underestimating subdominant serotypes.
- The selection of only a single colony per plate neglects the possibility of co-carriage.[348,349] The high carriage prevalence, particularly in the rural site, implies a higher than average occurrence of co-carriage. All of the models considered assume that the carriage surveys provide an accurate picture of the carriage prevalence in the population; if sub-dominant populations are also at risk of causing invasive disease, this appears to be a gap in the theory. However, in most cases, the estimation of the CCRs is drawn from similar carriage surveys. If both the surveys defining the CCR and the surveys in the test population are random samples of the human population followed by random samples of the pneumococcal population (in selecting colonies on a plate), then in each case,

they will give an accurate representation of the serotype distribution of invasive disease risk due to carriage (whether dominant or non-dominant)

6.3.2 Models: measures of serotype invasiveness

- The key assumption for the statistical models I used in this thesis is that the capsule/serotype is the main determinant of invasiveness. As reviewed in the introduction, this assumption is reasonable from prior evidence.[75,350] Most importantly, vaccination can affect the invasiveness of VTs due to direct protection against invasion given carriage. Theoretically, vaccinated VT carriers will have lower CCR compared to their unvaccinated counterparts. Strain characteristics may independently influence invasiveness.[351,352] Strain characteristics can sometimes be shared by more than one serotype. Accounting for strain background as well as serotype characteristics may give a more accurate measure of invasiveness than either alone. [253] However, serotype characteristics are likely to influence invasiveness more than other factors, particularly for highly invasive serotypes.
- Host and environmental factors can modify the relationship between carriage and invasion, although they may not be significant confounders in children. For example, carriage prevalence and serotype distribution among HIV-infected individuals did not differ from HIV-uninfected individuals.[353–355] In theory, the presence of factors that undermine other immunological mechanisms, such as concurrent viral respiratory tract infections and undernutrition, can alter the likelihood of a serotype carried to cause invasive disease irrespective of how

intrinsically invasive the serotype is. This emphasises the need for CCR data from representative populations or settings.

- Another major assumption is that the data for IPD estimates I used in the models are representative of Nigeria. For compatibility, I restricted extracted data to sSA, although this is dominated by South Africa, where the HIV prevalence is much higher, and levels of wealth are much higher. Serogroups commonly carried contributed to a larger proportion of IPD in HIV-infected compared to HIV-uninfected children in South Africa, so this may have introduced a bias in the 'background' serotype distribution assumed.[204,356]

6.4 Implications for policy and future research

6.4.1 What is known?

The Global Burden of Disease models estimate that Nigeria has the largest pneumococcal disease burden in sSA and is among the top ten globally.[2,3] This is not surprising, given a total population of approximately 210 million. However, local data on incidence and serotype distribution in pneumococcal disease is almost non-existent. Few studies in Nigeria have reported pneumococcal serotypes in disease and these are very old; were conducted when many serotypes/groups were yet to be identified [357,358]; have poor yield with very few isolates identified and serotyped [244,245,359–362]; were sampled only from specific IPD syndromes (meningitis)[244,362] or; lacked linked denominators.[246] Additionally, they are all hospital-based studies and not population-linked.

Pneumococcal carriage prevalence among healthy populations was high before PCV introduction in Nigeria.[258,363] Carriage prevalence, age distribution of carriage prevalence and risk factors for carriage varied from site to site. PCV impact on carriage has been demonstrated in studies from a number of sub-Saharan African countries that have introduced either PCV10 or PCV13. These studies have shown consistent, substantial reductions in PCV-serotypes in vaccinated children or children within the target age of PCV and variable reductions among adults or age groups ineligible for vaccination.[72,272,289,290,342,364–367] However, only a few countries in sub-Saharan Africa have been able to demonstrate vaccine impact on pneumococcal disease, highlighting the surveillance data gap.[72,202,242,368–370]

Changes in serotype burden and distribution in carriage were accompanied by contemporaneous changes in IPD in other African settings.[72,116] Serotype replacement in carriage is significant, while serotype replacement in IPD has been more modest. Serotype replacement in carriage is rapid, resulting in largely unchanged levels of pneumococcal carriage. Because the non-vaccine (PCV10 or PCV13) serotypes that take up the empty nasopharyngeal niche are not as invasive as the PCV serotypes that have left, there is largely a net benefit with a reduction in overall IPD. However, this net reduction in overall IPD incidence is not uniform in all age groups and settings. For example, in England and Wales, a significant increase in NVT-IPD incidence in older adults was observed.[113]

6.4.2 Key messages

1. Introduction of PCV10 was associated with a significant reduction in carriage prevalence of VT in children aged <5 years and persons aged ≥5 years and a variable increase in carriage prevalence of NVT.
2. There was an inverse relationship between coverage of ≥2 doses of PCV 10 in children aged <5 years and VT carriage prevalence among children aged <5 years and persons ≥5 years.
3. There is residual VT carriage four to five years after PCV10 was introduced, and there is a need to optimise the PCV programme to build up indirect protection.
4. Modelling suggests that the introduction of PCV10 has reduced the burden of IPD among children aged <5 years.
5. Statistical carriage models cannot accurately predict PCV impact in Nigeria because they either ignore persistent VT carriage post-PCV or direct vaccine protection against invasion among VT carriers that can provide additional protection if VT carriage occurs.
6. Health providers and households incur significant costs related to the treatment of IPD, which substantially impact household income and result in catastrophic household expenses that disproportionately affect the poorest households.

<u>Sustaining the PCV10 programme in Nigeria will be beneficial.</u>

Overall, the findings from this PhD show that PCV introduction reduced the burden of IPD by at least 22-39%, which would translate to at least 22-39% lower incidence from pneumococcal diseases and savings from the costs of treatment, but also

demonstrates a considerable opportunity for improving and optimising the PCV programme in Nigeria.

Increasing coverage and optimising schedules to boost herd immunity.

The evidence of the direct and indirect impact of PCV10 on pneumococcal carriage observed in this population is expected to translate to protection against vaccine-type pneumococcal disease at a population level.[72,74,368,371] Residual VT carriage and NVT replacement may be potential threats to vaccine impact, especially if significant NVT pneumococcal disease occurs.

Efforts to increase vaccination coverage should be prioritised to ensure maximum benefit. However, modelling indicates that this may not be sufficient on its own to eliminate VT carriage. A number of factors may be contributing to this residual VT disease. First, sub-optimal PCV10 coverage will directly influence herd immunity and VT elimination in carriage and disease. Second, direct vaccine-induced protection, which the 3p+0 schedule is targeted to build up, wanes rapidly (within 6-12 months).[344] Thus, incomplete vaccination in the absence of strategies to boost indirect protection (post-infancy booster dose or catch-up vaccination to older children) may explain sustained VT carriage. Finally, high VT carriage prevalence in older PCV-ineligible children suggests that they could serve as continuous sources of VT transmission depending on contact patterns.[256,271]

Improve accuracy of statistical models to predict IPD.

The underlying assumptions of the statistical models undermine the reliability and accuracy of their output. I previously demonstrated how to incorporate vaccination

coverage and different CCRs for vaccinated (post-PCV) VT carriers while retaining pre-PCV CCR for vaccinated NVT carriers and unvaccinated VT and NVT carriers. These adjustments could not be made in this study because vaccination status was not recorded for carriage survey participants. Therefore, in future, vaccination status should be measured among carriage survey participants so adjustments can be made to incorporate direct vaccine protection.

Advanced models to incorporate more context-specific parameters.

The statistical models in this thesis are not able to account for real-life complexities that undermine predictions. Such complexities include vaccine efficacy and coverage, alternate schedules or alternative PCVs, vaccine campaigns, variable contact patterns and waning immunity. Transmission dynamic models would be able to incorporate these parameters to provide more nuanced options to support policymaking.

Cost-effectiveness analysis

A full cost-effectiveness analysis (CEA) would be more helpful to policymakers. CEA would compare costs and health outcomes – disability-adjusted life years (DALYs) with and without the PCV10 programme. Such an analysis would incorporate PCV10 costs (vaccine and delivery), treatment costs, overall IPD and VT-IPD burden, and PCV10 impact on IPD.

PCV options to reduce costs.

The similar vaccine serotype coverage of SII-PCV and PCV10 in predicted IPD cases has implications for policymaking regarding PCV options. At $2 per dose, the SII-PCV

is 43% cheaper than the Gavi agreed price of PCV10 ($3.05).[372] The similar vaccine serotype coverage of both vaccines could be used to argue for an equivalent impact on IPD. Therefore, SII-PCV may be a more cost-effective and, hence, more attractive option for countries like Nigeria, planning to transition to self-financing.

6.5 Conclusions

The main focus of this thesis was to assess the impact of PCV10 introduction in the absence of pneumococcal disease surveillance data in Nigeria. Roll-out of the PCV10 programme in Nigeria has been accompanied by significant reduction in carriage prevalence of vaccine serotypes among vaccine-target and non-target populations. Following which it is expected the overall incidence of VT-IPD in the population will be reduced by a similar proportion, at minimum. Carriage-based statistical models using externally derived IPD and CCR data predict a decline in overall IPD, which is relatively lower than anticipated from the reduction in population-level VT carriage prevalence. However, as presently formulated, these models do not capture the protection PCV provides against invasion, which undoubtedly will be substantial given the persistent VT carriage in Nigeria. A major implication is the considerable potential to optimise the programme to enhance its impact. The primary focus would be to improve the vaccination coverage of target children. Given the considerable VT carriage, including among infants within the routine immunisation target, completing the three primary doses in the schedule will enhance direct vaccine protection. Another potential option to improve herd protection is the inclusion of a booster dose beyond infancy with reduced primary series.[220] However, for Nigeria, options that reduce the number of primary doses have to be carefully considered. Persistent VT

transmission in the population means that reducing primary doses comes with a risk of leaving infants most at risk of IPD unprotected. Extending vaccination to older children through vaccination campaigns may be another reasonable option to reduce VT transmission and improve herd protection.[226] But vaccination campaigns will come with cost implications, therefore, the cost-effectiveness has to be assessed.

PCV is one of the most expensive vaccines in Nigeria's routine childhood immunisation programme. Currently heavily subsidised by Gavi, Nigeria will commence transition to self-financing of PCV in 2028. And when this happens, the country's National Immunisation Technical Advisory Group (NITAG) will have to recommend or not, sustaining the PCV programme through self-financing and possibly consider options for reducing PCV costs. Efforts are ongoing elsewhere to reduce cost of PCV and improve its cost-effectiveness. Kenya switched to SII-PCV in 2022, which costs about a third less than the GSK-PCV.[373] The non-inferiority of fractionated PCV dosing at 20% and 40% is another promising strategy to reduce overall PCV programme costs.[225,226]

This work provides evidence to the Nigeria NITAG on the impact of the PCV programme and the potential to enhance the value of the programme. Mathematical modelling to predict the impact of different strategies under different scenarios can provide a clearer picture to guide future policy in Nigeria.

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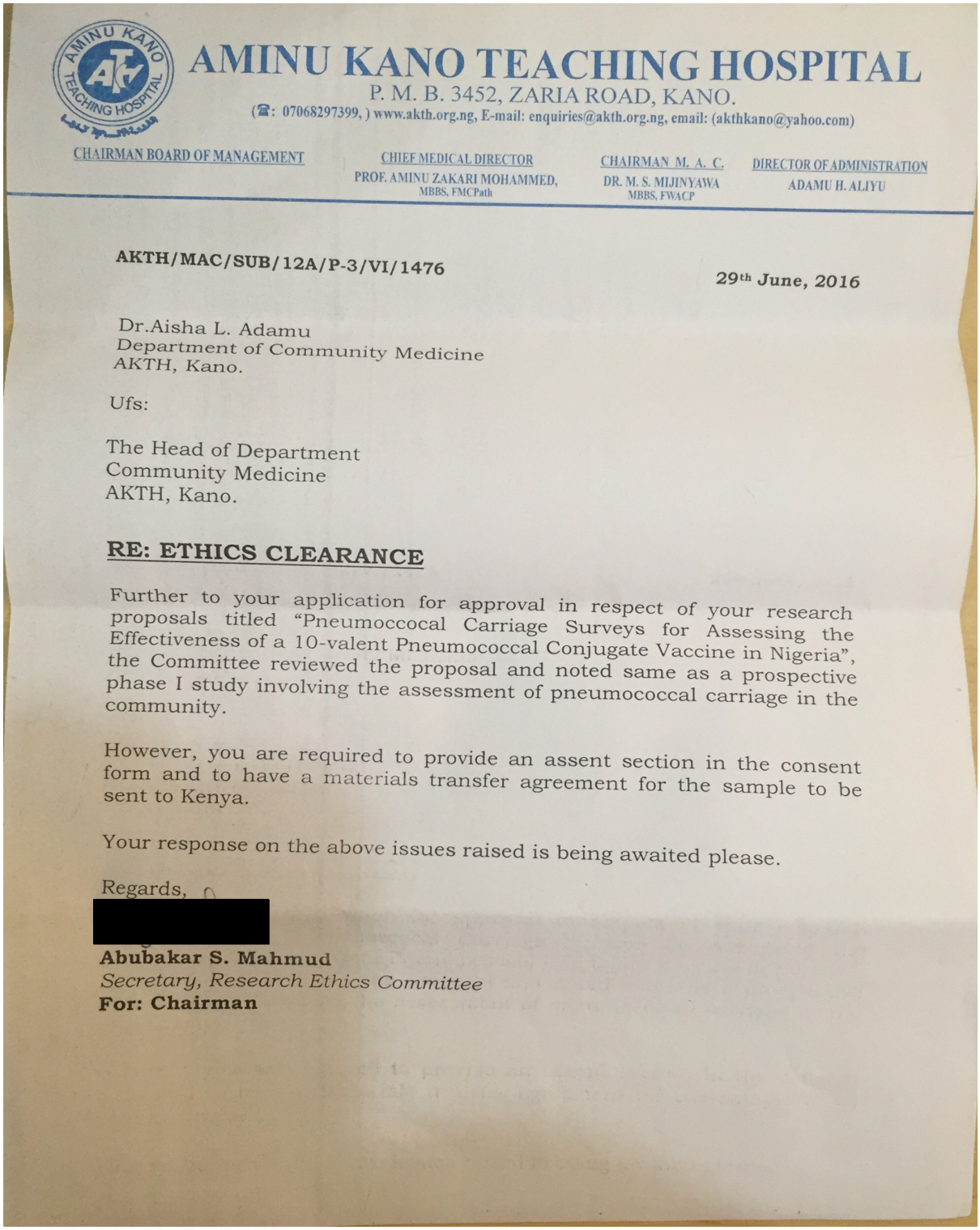
Annexes

Annex 1: Ethical approvals from Kano and Lagos, Nigeria



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AKTH/MAC/SUB/12A/P-3/VI/1476 — **29th June, 2016**

Dr.Aisha L. Adamu
Department of Community Medicine
AKTH, Kano.

Ufs:

The Head of Department
Community Medicine
AKTH, Kano.

RE: ETHICS CLEARANCE

Further to your application for approval in respect of your research proposals titled "Pneumoccocal Carriage Surveys for Assessing the Effectiveness of a 10-valent Pneumococcal Conjugate Vaccine in Nigeria", the Committee reviewed the proposal and noted same as a prospective phase I study involving the assessment of pneumococcal carriage in the community.

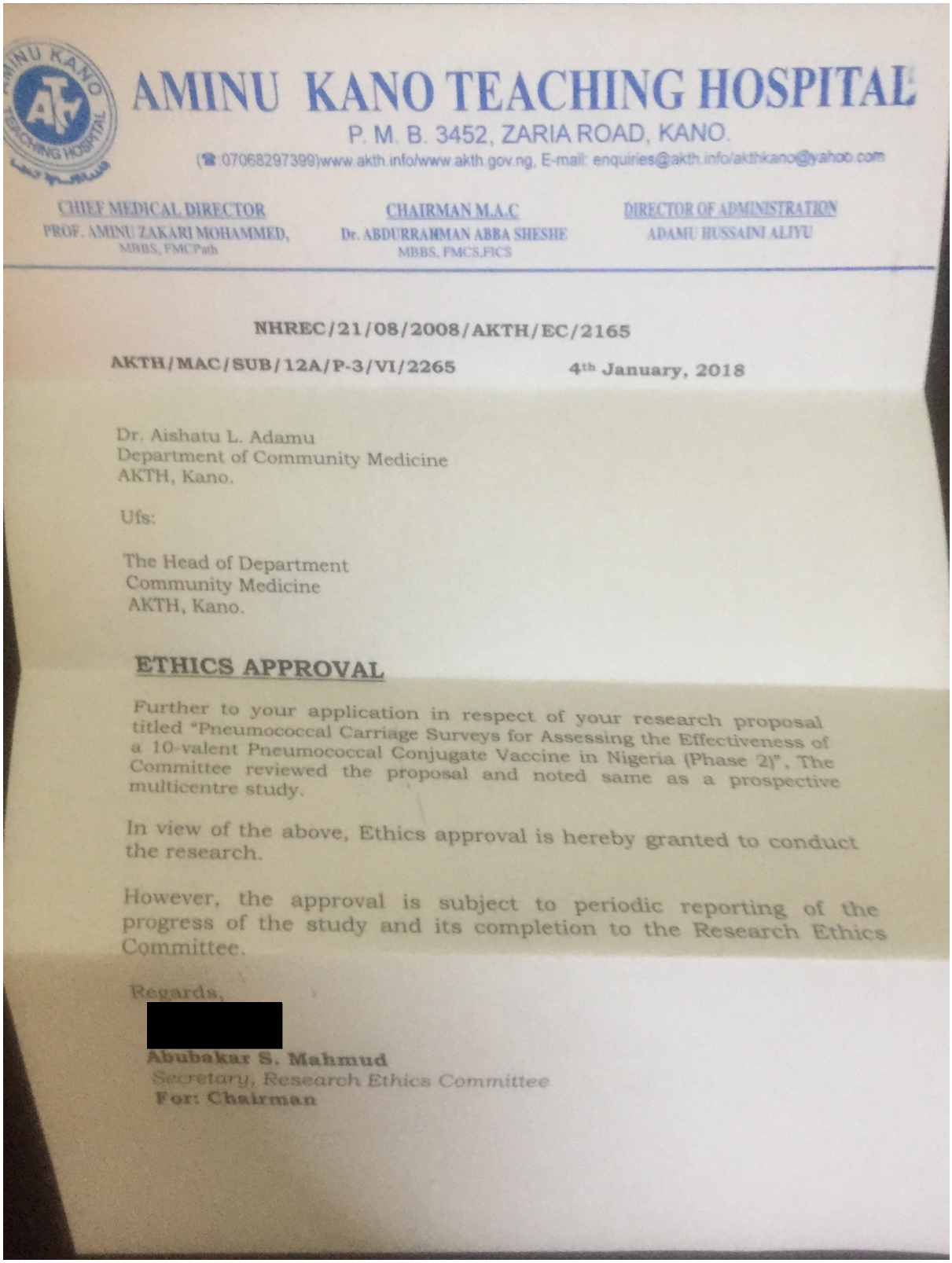
However, you are required to provide an assent section in the consent form and to have a materials transfer agreement for the sample to be sent to Kenya.

Your response on the above issues raised is being awaited please.

Regards,

[redacted]

Abubakar S. Mahmud
Secretary, Research Ethics Committee
For: Chairman



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NHREC/21/08/2008/AKTH/EC/2165

AKTH/MAC/SUB/12A/P-3/VI/2265 **4th January, 2018**

Dr. Aishatu L. Adamu
Department of Community Medicine
AKTH, Kano.

Ufs:

The Head of Department
Community Medicine
AKTH, Kano.

ETHICS APPROVAL

Further to your application in respect of your research proposal titled "Pneumococcal Carriage Surveys for Assessing the Effectiveness of a 10-valent Pneumococcal Conjugate Vaccine in Nigeria (Phase 2)", The Committee reviewed the proposal and noted same as a prospective multicentre study.

In view of the above, Ethics approval is hereby granted to conduct the research.

However, the approval is subject to periodic reporting of the progress of the study and its completion to the Research Ethics Committee.

Regards,

[redacted]

Abubakar S. Mahmud
Secretary, Research Ethics Committee
For: Chairman

KANO STATE OF NIGERIA
MINISTRY OF HEALTH
2nd & 3rd Floor, Post Office Road,
P.M.B. 3066, Kano.

Commissioner: 08023337417
Permanent Secretary: 09096619985
website: www.kanostateministryofhealth.gov.ng

Ref: MOH/OFF/797/T.I/596

Date: 3rd November, 2017

Dr Aisha Adamu
Department of Community Medicine,
Aminu Kano Teaching Hospital,
Kano.

RE: APPLICATION FOR ETHICAL APPROVAL TO CONDUCT A RESEARCH

Reference to your letter dated 3rd November, 2017 on the above request addressed to the Chairman Health Research Ethics Committee of the Ministry requesting for ethical approval to conduct research at Kumbotso in kano state.

2. The research entitled *"Pneumococcal carriage surveys for assessing the effectiveness of a 10-valent pneumococcal conjugate vaccine in Nigeria"* is for the second phase study to conduct a survey of pneumococcal carriage to assess impact of vaccine introduction.

3. In view of the foregoing, I wish to convey the Ministry's approval for you to conduct the research at the above mentioned LGA in Kano.

4. You are also requested to share your findings with the Ministry of Health, Kano.

[redacted]
Liti Gwarzo, Abdullahi
Ag. DPRS
Secretary (HREC)
For: Honourable Commissioner

[redacted]

LAGOS UNIVERSITY TEACHING HOSPITAL
HEALTH RESEARCH ETHICS COMMITTEE

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8th July, 2016

NOTICE OF EXPEDITED REVIEW AND APPROVAL

PROJECT TITLE: "PNEUMOCOCCAL CARRIAGE SURVEYS FOR ASSESSING THE EFFECTIVENESS OF A 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN NIGERIA".
HEALTH RESEARCH COMMITTEE ASSIGNED NO.: ADM/DCST/HREC/APP/1030
NAME OF PRINCIPAL INVESTIGATOR: DR. IFEDAYO ADETIFA
ADDRESS OF PRINCIPAL INVESTIGATOR: INFECTIOUS DISEASE EPIDEMIOLOGY, FACULTY OF EPIDEMIOLOGY AND POPULATION HEALTH, LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE, KEPPEL STREET, LONDON, WC1E 7HT.
DATE OF RECEIPT OF VALID APPLICATON: 10-06-16

This is to inform you that the research described in the submitted protocol, the consent forms, and all other related materials where relevant have been reviewed and given full approval by the Lagos University Teaching Hospital Health Research Ethics Committee (LUTHHREC).

This approval dates from 08-07-16 to 08-07-17. If there is delay in starting the research, please inform the HREC so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of this dates. All informed consent forms used in this study must carry the HREC assigned number and duration of HREC approval of the study. In multiyear research, endeavor to submit your annual report to the HREC early in order to obtain renewal of your approval and avoid disruption of your research.

The National code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the code including ensuring that all adverse events are reported promptly to the HREC. No changes are permitted in the research without prior approval by the HREC except in circumstances outlined in the code. The HREC reserves the right to conduct compliance visits to your research site without previous notification.

[redacted]

PROF. N. U. OKUBADEJO
CHAIRMAN, LUTH HEALTH RESEARCH ETHICS COMMITTEE

LAGOS UNIVERSITY TEACHING HOSPITAL
HEALTH RESEARCH ETHICS COMMITTEE

PRIVATE MAIL BAG 12003, LAGOS, NIGERIA
e-mail address: luthethics@yahoo.com

Chairman
PROF. N.U. OKUBADEJO
MB. ChB, FMCP

Administrative Secretary
D.J. AKPAN
B.Sc. (Hons) BUS. ADMIN,
MIHSAN

LUTH

Chief Medical Director:
PROF. CHRIS BODE
FMCS (NIG) FWACS

Chairman, Medical Advisory Committee
PROF. O.A. FASANMADE
MBBS, FWACP, FACE, FNSEM

LUTH HREC REGISTRATION NUMBER: NHREC: 19/12/2008a
Office Address: Room 107, 1st Floor, LUTH Administrative Block
Telephone: 234-1-5850737, 5852187, 5852209, 5852158, 5852111

5th February, 2018

NOTICE OF EXTENSION OF RESEARCH APPROVAL DATE

PROJECT TITLE: "PNEUMOCOCCAL CARRIAGE SURVEYS FOR ASSESSING THE EFFECTIVENESS OF A 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN NIGERIA".
HEALTH RESEARCH COMMITTEE ASSIGNED NO.: ADM/DCST/HREC/APP/1030
NAME OF PRINCIPAL INVESTIGATOR: DR. IFEDAYO ADETIFA
ADDRESS OF PRINCIPAL INVESTIGATOR: INFECTIOUS DISEASE EPIDEMIOLOGY, FACULTY OF EPIDEMIOLOGY AND POPULATION HEALTH, LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE, KEPPEL STREET, LONDON, WC1E 7HT.
DATE OF RECEIPT OF VALID APPLICATION: 10-06-16
DATE OF RE-APPLICATION FOR EXTENSION OF RESEARCH APPROVAL DATE: 05-02-18

This is to inform you that the research described in the submitted protocol, the consent forms, and all other related materials where relevant have been reviewed and given full approval by the Lagos University Teaching Hospital Health Research Ethics Committee (LUTHHREC).

This approval dates from 05-02-2018 to 05-02-2019. If there is delay in starting the research, please inform the HREC so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of this dates. All informed consent forms used in this study must carry the HREC assigned number and duration of HREC approval of the study. In multiyear research, endeavor to submit your annual report to the HREC early in order to obtain renewal of your approval and avoid disruption of your research.

The National code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the code including ensuring that all adverse events are reported promptly to the HREC. No changes are permitted in the research without prior approval by the HREC except in circumstances outlined in the code. The HREC reserves the right to conduct compliance visits to your research site without previous notification.

[redacted]

PROF. N. U. OKUBADEJO
CHAIRMAN, LUTH HEALTH RESEARCH ETHICS COMMITTEE

LAGOS UNIVERSITY TEACHING HOSPITAL
HEALTH RESEARCH ETHICS COMMITTEE

PRIVATE MAIL BAG 12003, LAGOS, NIGERIA
e-mail address: luthethics@yahoo.com

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Chief Medical Director:
PROF. CHRIS BODE
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Chairman, Medical Advisory Committee
PROF. O.A. FASANMADE
MBBS, FWACP, FACE, FNSEM

LUTH HREC REGISTRATION NUMBER: NHREC: 19/12/2008a
Office Address: Room 107, 1st Floor, LUTH Administrative Block
Telephone: 234-1-5850737, 5852187, 5852209, 5852158, 5852111

18th January, 2019

NOTICE OF EXTENSION OF RESEARCH APPROVAL DATE

PROJECT TITLE: "PNEUMOCOCCAL CARRIAGE SURVEYS FOR ASSESSING THE EFFECTIVENESS OF A 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN NIGERIA".
HEALTH RESEARCH COMMITTEE ASSIGNED NO.: ADM/DCST/HREC/APP/1030
NAME OF PRINCIPAL INVESTIGATOR: DR. IFEDAYO ADETIFA
ADDRESS OF PRINCIPAL INVESTIGATOR: INFECTIOUS DISEASE EPIDEMIOLOGY, FACULTY OF EPIDEMIOLOGY AND POPULATION HEALTH, LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE, KEPPEL STREET, LONDON, WC1E 7HT.
DATE OF RECEIPT OF VALID APPLICATION: 10-06-16
DATE OF RE-APPLICATION FOR EXTENSION OF RESEARCH APPROVAL DATE: 17-01-19

This is to inform you that the research described in the submitted protocol, the consent forms, and all other related materials where relevant have been reviewed and given full approval by the Lagos University Teaching Hospital Health Research Ethics Committee (LUTHHREC).

This approval dates from 18-01-2019 to 18-01-2020. If there is delay in starting the research, please inform the HREC so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of this dates. All informed consent forms used in this study must carry the HREC assigned number and duration of HREC approval of the study. In multiyear research, endeavor to submit your annual report to the HREC early in order to obtain renewal of your approval and avoid disruption of your research.

The National code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the code including ensuring that all adverse events are reported promptly to the HREC. No changes are permitted in the research without prior approval by the HREC except in circumstances outlined in the code. The HREC reserves the right to conduct compliance visits to your research site without previous notification.

[redacted]

PROF. N. U. OKUBADEJO
CHAIRMAN, LUTH HEALTH RESEARCH ETHICS COMMITTEE

LAGOS UNIVERSITY TEACHING HOSPITAL
HEALTH RESEARCH ETHICS COMMITTEE

PRIVATE MAIL BAG 12003, LAGOS, NIGERIA
e-mail address: luthethics@yahoo.com

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MIHSAN

LUTH

Chief Medical Director:
PROF. CHRIS BODE
FMCS (NIG) FWACS

Chairman, Medical Advisory Committee
PROF. O.A. FASANMADE
MBBS, FWACP, FACE, FNSEM

LUTH HREC REGISTRATION NUMBER: NHREC: 19/12/2008a
Office Address: Room 107, 1st Floor, LUTH Administrative Block
Telephone: 234-1-5850737, 5852187, 5852209, 5852158, 5852111

21st February, 2020

NOTICE OF EXTENSION OF RESEARCH APPROVAL DATE

PROJECT TITLE: "PNEUMOCOCCAL CARRIAGE SURVEYS FOR ASSESSING THE EFFECTIVENESS OF A 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN NIGERIA".
HEALTH RESEARCH COMMITTEE ASSIGNED NO.: ADM/DCST/HREC/APP/1030
NAME OF PRINCIPAL INVESTIGATOR: DR. IFEDAYO ADETIFA
ADDRESS OF PRINCIPAL INVESTIGATOR: INFECTIOUS DISEASE EPIDEMIOLOGY, FACULTY OF EPIDEMIOLOGY AND POPULATION HEALTH, LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE, KEPPEL STREET, LONDON, WC1E 7HT.
DATE OF RECEIPT OF VALID APPLICATION: 10-06-16
DATE OF RE-APPLICATION FOR EXTENSION OF RESEARCH APPROVAL DATE: 21-02-2020

This is to inform you that the research described in the submitted protocol, the consent forms, and all other related materials where relevant have been reviewed and given full approval by the Lagos University Teaching Hospital Health Research Ethics Committee (LUTHHREC).

This approval dates from 21-02-2020 to 21-02-2021. If there is delay in starting the research, please inform the HREC so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of this dates. All informed consent forms used in this study must carry the HREC assigned number and duration of HREC approval of the study. In multiyear research, endeavor to submit your annual report to the HREC early in order to obtain renewal of your approval and avoid disruption of your research.

The National code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the code including ensuring that all adverse events are reported promptly to the HREC. No changes are permitted in the research without prior approval by the HREC except in circumstances outlined in the code. The HREC reserves the right to conduct compliance visits to your research site without previous notification.

CHAIRMAN

[redacted]

PROF. N. U. OKUBADEJO
CHAIRMAN, LUTH HEALTH RESEARCH ETHICS COMMITTEE

Annex 2: Ethical approvals from KEMRI

KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200, NAIROBI, Kenya
Tel: (254) (020) 2722541, 2713349, 0722-205901, 0733-400003, Fax: (254) (020) 2720030
E-mail: director@kemri.org, info@kemri.org, Website. www.kemri.org

KEMRI/RES/7/3/1

May 8, 2018

TO: **DR. IFEDAYO ADETIFA,**
PRINCIPAL INVESTIGATOR

THROUGH: **THE DIRECTOR, CGMR-C,**
KILIFI

Forwarded
DIRECTOR
CENTRE FOR GEOGRAPHIC MEDICINE RESEARCH, COAST

Dear Sir,

RE: **SERU PROTOCOL NO. 3350(*REQUEST FOR ANNUAL RENEWAL AND PROTOCOL DEVIATION*): PNEUMOCOCCAL CARRIAGE SURVEYS FOR ASSESSING THE EFFECTIVENESS OF A 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN NIGERIA**

Thank you for the continuing review report for the period October 2016 to October 2017 and November 2017 to March 2018.

The Expedited Review Team noted that a protocol deviation form has been submitted as the request for annual renewal was done after the expiration date of the last approval. Measures taken to address deviation are adequate.

This is to inform you that the Expedited Review Team of the KEMRI Scientific and Ethics Review Unit (SERU) was of the informed opinion that the progress made during the reported period is satisfactory. The study has therefore been granted **approval** for continuation.

This approval is valid from **May 8, 2018** through to **May 7, 2019**. Please note that authorization to conduct this study will automatically expire on **May 7, 2019**. If you plan to continue with data collection or analysis beyond this date please submit an application for continuing approval to the SERU by **March 26, 2019.**

You are required to submit any amendments to this protocol and any other information pertinent to human participation in this study to the SERU for review prior to initiation.

Yours faithfully,

[redacted]

FOR: **THE HEAD,**
KEMRI SCIENTIFIC AND ETHICS REVIEW UNIT

KEMRI WELCOME TRUST RESEARCH PROGRAMME
P.O. Box 230
17 MAY 2018
DIRECTOR'S OFFICE
KILIFI

KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200, NAIROBI, Kenya
Tel: (254) 2722541, 2713349, 0722-205901,0733-400003, Fax: (254) (020) 2720030
Email: director@kemri.org, info@kemri.org, Website. www.kemri.org

KEMRI/RES/7/3/1 **April 27, 2020**

TO: **DR. IFEDAYO ADETIFA**
PRINCIPAL INVESTIGATOR

THROUGH: **THE DIRECTOR, CGMR-C**
KILIFI

Dear Sir,

RE: **KEMRI/SERU/CGMR-C/060/3350 (*REQUEST FOR EXPEDITED ANNUAL RENEWAL*): PNEUMOCOCCAL CARRIAGE SURVEYS FOR ASSESSING THE EFFECTIVENESS OF A 10-VALENT PNEUMOCCCAL CONJUGATE VACCINE IN NIGERIA**

Thank you for the continuing review report for the period **May 04, 2019** to **March 24, 2020.**

This is to inform you that the Expedited Review Team of the KEMRI Scientific and Ethics Review Unit (SERU) was of the informed opinion that the progress made during the reported period is satisfactory. The study has therefore been granted **approval** for continuation.

This approval is valid from **May 8, 2020** through to **May 7, 2021**. Please note that authorization to conduct this study will automatically expire on **May 7, 2021**. If you plan to continue with data collection or analysis beyond this date please submit an application for continuing approval to the SERU by **March 26, 2021.**

You are required to submit any amendments to this protocol and any other information pertinent to human participation in this study to the SERU for review prior to initiation.

Yours faithfully

[redacted]

ENOCK KEBENEI,
THE ACTING HEAD,
KEMRI SCIENTIFIC AND ETHICS REVIEW UNIT.

KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200, NAIROBI, Kenya
Tel: (254) 2722541, 2713349, 0722-205901,0733-400003, Fax: (254) (020) 2720030
Email: director@kemri.org, info@kemri.org, Website. www.kemri.org

KEMRI/RES/7/3/1 **April 27, 2021**

TO: **PROF. IFEDAYO ADETIFA,**
PRINCIPAL INVESTIGATOR.

THROUGH: **THE DEPUTY DIRECTOR, CGMR-C**
KILIFI.

Dear Sir,

RE: **KEMRI/SERU/CGMR-C/060/3350 *(REQUEST FOR EXPEDITED ANNUAL RENEWAL)*: PNEUMOCOCCAL CARRIAGE SURVEYS FOR ASSESSING THE EFFECTIVENESS OF A 10-VALENT PNEUMOCCCAL CONJUGATE VACCINE IN NIGERIA**

Thank you for the continuing review report for the period **March 25, 2020** to **March 22, 2021.**

This is to inform you that the Expedited Review Team of the KEMRI Scientific and Ethics Review Unit (SERU) was of the informed opinion that the progress made during the reported period is satisfactory. The study has therefore been granted **approval** for continuation.

This approval is valid from **May 08, 2021** through to **May 07, 2022**. Please note that authorization to conduct this study will automatically expire on **May 07, 2022**. If you plan to continue with data collection or analysis beyond this date please submit an application for continuing approval to the SERU by **March 26, 2022.**

You are required to submit any amendments to this protocol and any other information pertinent to human participation in this study to the SERU for review prior to initiation.

Yours faithfully,

[redacted]

ENOCK KEBENEI,
THE ACTING HEAD,
KEMRI SCIENTIFIC AND ETHICS REVIEW UNIT.

KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200, NAIROBI, Kenya
Tel: (254) 2722541, 2713349, 0722-205901,0733-400003, Fax: (254) (020) 2720030
Email: director@kemri.org, info@kemri.org, Website. www.kemri.org

KEMRI/RES/7/3/1 **April 27, 2021**

TO: **PROF. IFEDAYO ADETIFA,**
PRINCIPAL INVESTIGATOR.

THROUGH: **THE DEPUTY DIRECTOR, CGMR-C**
KILIFI.

Dear Sir,

RE: **KEMRI/SERU/CGMR-C/060/3350 *(REQUEST FOR EXPEDITED ANNUAL RENEWAL)*: PNEUMOCOCCAL CARRIAGE SURVEYS FOR ASSESSING THE EFFECTIVENESS OF A 10-VALENT PNEUMOCCCAL CONJUGATE VACCINE IN NIGERIA**

Thank you for the continuing review report for the period **March 25, 2020** to **March 22, 2021.**

This is to inform you that the Expedited Review Team of the KEMRI Scientific and Ethics Review Unit (SERU) was of the informed opinion that the progress made during the reported period is satisfactory. The study has therefore been granted **approval** for continuation.

This approval is valid from **May 08, 2021** through to **May 07, 2022**. Please note that authorization to conduct this study will automatically expire on **May 07, 2022**. If you plan to continue with data collection or analysis beyond this date please submit an application for continuing approval to the SERU by **March 26, 2022.**

You are required to submit any amendments to this protocol and any other information pertinent to human participation in this study to the SERU for review prior to initiation.

Yours faithfully,

[redacted]

ENOCK KEBENEI,
THE ACTING HEAD,
KEMRI SCIENTIFIC AND ETHICS REVIEW UNIT.

In Search of Better Health

KENYA MEDICAL RESEARCH INSTITUTE

OFFICE OF THE DIRECTOR RESEARCH & DEVELOPMENT

Tell: +254 020 2722541, 2713349,
0722 205 901, 0733 400 003

P.O. Box 54840-00200, Nairobi
Email: ddrt@kemri.go.ke
Website: www.kemri.go.ke

KEMRI/RD/22 **July 24, 2023**

TO: **PROF. IFEDAYO ADETIFA**
PRINCIPAL INVESTIGATOR

THROUGH: **THE DEPUTY DIRECTOR, CGMR-C**
KILIFI.

Dear Sir,

RE: **KEMRI/SERU/CGMR-C/060/3350 (*REQUEST FOR EXPEDITED ANNUAL RENEWAL WITH PROTOCOL DEVIATION*): PNEUMOCOCCAL CARRIAGE SURVEYS FOR ASSESSING THE EFFECTIVENESS OF A 10-VALENT PNEUMOCCCAL CONJUGATE VACCINE IN NIGERIA**

Thank you for the continuing review report for the period **23rd March 2022 to 22nd March 2023 & 23rd March 2023 to 30th June 2023.**

The Expedited Review Team noted that a protocol deviation was submitted due to the late submission of request for continuation. The measures taken to preclude future occurrence was deemed satisfactory.

This is to inform you that the Expedited Review Team of the KEMRI Scientific and Ethics Review Unit (SERU) was of the informed opinion that the progress made during the reported period is satisfactory. The study has therefore been granted **approval** for continuation.

This approval is valid from **July 24, 2023** through to **July 23, 2024**. Please note that authorization to conduct this study will automatically expire on **July 23, 2024**. If you plan to continue with data collection or analysis beyond this date, please submit an application for continuing approval to the SERU by **June 11, 2024.**

You are required to submit any amendments to this protocol and any other information pertinent to human participation in this study to the SERU for review prior to initiation.

Yours faithfully,

[redacted]

ENOCK KEBENEI,
THE ACTING HEAD,
KEMRI SCIENTIFIC AND ETHICS REVIEW UNIT

Annex 3: Material Transfer Agreements

Pneumococcal Carriage Surveys for assessing the effectiveness of a 10-valent Pneumococcal Conjugate Vaccine in Nigeria

Pneumococcal conjugate vaccines (PCV) have been introduced in high burden settings like Nigeria at an unprecedented rate that are predominantly driven by support from Gavi, The Vaccine Alliance

Gavi subsidized vaccine introductions in Nigeria that has the highest burden of pneumococcal diseases in children < 5 years in Africa have not been accompanied by proportional investments in development of local capacity for vaccine evaluation and policy. This situation is exacerbated by the absence of mature invasive bacterial diseases surveillance systems in the country. Yet, data on vaccine impact and cost effectiveness will be required to justify continuation of the PCV immunization programme especially when the country graduates from Gavi support and current financial support comes to an end.

We propose to fill this evidence gap by deriving the effectiveness of the PCV immunisation programme from disease impact models. Specifically, we intend to utilise changes in nasopharyngeal carriage of *Streptococcus pneumoniae* in several mathematical models to predict vaccine impact on invasive pneumococcal disease (IPD).

Pneumococcus carriage data is a more an attractive alternative because it is a prerequisite for IPD, is more common in populations and the data is cheaper and easier to obtain than IPD data. We previously confirmed this by conducting a carriage survey in Pakoto, Ifo LGA, Ogun, Nigeria and this was the first detailed pneumococcal carriage survey in Nigeria. Estimates of cost effectiveness will also be obtained using the predicted impact on IPD.

[redacted]

ALA

Material Transfer Agreement Form

This Material Transfer Agreement (the "Agreement") is by and between Aminu Kano University Teaching Hospital Kano ("Provider") represented by Dr. Aishatu Adamu, Consultant Community Health Physician to the hospital/Investigator, and Dr. Ifedayo MO Adetifa of College of Medicine, University of Lagos, Nigeria and Kenya Medical Research Institute/Wellcome Trust Research Programme, Kilifi, Kenya ("Recipient") regarding the transfer of human nasopharyngeal swabs and associated demographic and clinical data, from the provider to the recipient for research purposes as further defined below.

Throughout this Agreement,
Provider and Recipient are collectively referred to as the "Parties." This Agreement will become effective upon the date of the last signature affixed below.

The Provider and Recipient agree as follows:

1. **DEFINITIONS**. Within this Agreement, the following terms will have the same meaning and effect as defined below:

(a) "De-identified" information is information that formerly contained individually identifiable health information but which has had all unique identifying information, numbers, characteristics, and codes removed such that the information a record contains cannot be used alone or in combination with other information to identify the individual who is the subject of the information.

(b) "Protected Health Information" or "PHI" means any information, whether oral or recorded in any form or medium: (i) that relates to the past, present, or future physical or mental condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual, and (ii) that identifies the individual or with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

[redacted]

ALA

2. **DESCRIPTION OF MATERIAL AND DATA**. The Provider will transfer to the Recipient the following bio-specimens and/or derivatives ("MATERIAL") nasopharyngeal swabs obtained from healthy populations across all age groups with personal demographic and clinical data ("DATA").

3. **COLLECTION OF MATERIAL AND DATA**. The MATERIAL and DATA will be collected and/or processed from healthy consenting populations in Kumbotso, Kumbotso LGA, Kano State, Nigeria in accordance with approval of the Research Ethics Committee of Aminu Kano University Teaching Hospital Kano.

4. **TRANSFER OF MATERIAL AND DATA**. The MATERIAL and DATA provided by Provider will be de-identified and all Protected Health Information (PHI) where applicable removed.

5. **RESPONSIBILITIES AND AUTHORIZATIONS OF RECIPIENT**

(a) Recipient agrees to use the MATERIAL and DATA for the approved research project only (see Appendix 1 "Research Project") and will not use the MATERIAL and DATA for any unapproved commercial purposes, including selling or transferring to a third party for commercial purposes.

(b) Recipient is responsible for obtaining any necessary Human research Ethics approvals or exemptions required to use the MATERIAL and DATA at the KEMRI-Wellcome Research Programme, Kilifi, Kenya. The Recipient will use MATERIAL and DATA in compliance with all applicable National, federal, state, and local statutes and regulations.

(c) Recipient will allow the use of MATERIAL and DATA only by Dr. Ifedayo Adetifa ("Recipient /Principal Investigator") and Recipient's research team that are under the direct supervision of the Recipient, and only after they have been informed of and agreed to the provisions and restrictions stated herein. Any transfer of MATERIAL and DATA to other than Recipient Investigator's research team requires the advanced written approval of the Provider.

[redacted]

ALA

(d) It is acknowledged that the Recipient may already have in his possession or will obtain from another source, PHI related to the MATERIAL and DATA, and to which the Recipient may be subject to additional restrictions or obligations under separate agreements. Recipient shall notify Provider in writing within five (5) working days of its discovery of any unauthorized use or disclosure of PHI related to the MATERIAL and DATA of which Recipient becomes aware. Recipient shall take (i) prompt corrective action to cure any deficiencies or (ii) any action pertaining to such unauthorized disclosure.

(e) Recipient agrees to not identify or contact any donor, or living relative of a donor, who may have provided the MATERIAL or any DATA received by Recipient under this Agreement from Provider.

(f) Recipient agrees to report data, inventions, and publications resulting from the use of the MATERIAL and/or DATA to Provider.

6. THE MATERIAL AND DATA ARE NOT FOR USE IN HUMAN SUBJECTS OR FOR THE TREATMENT OR DIAGNOSIS OF HUMAN SUBJECTS.

1. **DISCLAIMER**. Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. THE PROVIDER MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE HUMAN MATERIAL WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS.
2. **TERMINATION AND DISPOSAL.** Either Party may terminate this Agreement with sixty (60) days written notice to the other Party before the research project commences.
3. **ACKNOWLEDGEMENT**. In all oral presentations or written publications resulting from the use of the MATERIAL and DATA, the Recipient will

[redacted]

ALA

acknowledge the provider as the source of the MATERIAL and DATA, unless requested otherwise by Provider.

4. **COST AND SHIPPING.** The MATERIAL and DATA are provided at no cost to Recipient. Recipient will be responsible for shipping costs of the MATERIAL and DATA.

The Parties have executed this Agreement by their respective duly authorized officers on the day and year hereinafter written. Any communication or notice to be given shall be forwarded in writing to the respective addresses listed below.

Signed: Date:
Dr Aishatu Adamu
Department of Community Health
Aminu Kano University Teaching Hospital
Kano

[redacted] 24/11/2016

[redacted] Date: 24/11/16

Signed Recipient
Dr. Ifedayo Adetif
KEMRI-Wellcome Trust Research Programme,
Kilifi, Kenya

Pneumococcal Carriage Surveys for assessing the effectiveness of a 10-valent Pneumococcal Conjugate Vaccine in Nigeria

Pneumococcal conjugate vaccines (PCV) have been introduced in high burden settings like Nigeria at an unprecedented rate that are predominantly driven by support from Gavi, The Vaccine Alliance

Gavi subsidized vaccine introductions in Nigeria that has the highest burden of pneumococcal diseases in children < 5 years in Africa have not been accompanied by proportional investments in development of local capacity for vaccine evaluation and policy. This situation is exacerbated by the absence of mature invasive bacterial diseases surveillance systems in the country. Yet, data on vaccine impact and cost effectiveness will be required to justify continuation of the PCV immunization programme especially when the country graduates from Gavi support and current financial support comes to an end.

We propose to fill this evidence gap by deriving the effectiveness of the PCV immunisation programme from disease impact models. Specifically, we intend to utilise changes in nasopharyngeal carriage of *Streptococcus pneumoniae* in several mathematical models to predict vaccine impact on invasive pneumococcal disease (IPD).

Pneumococcus carriage data is a more an attractive alternative because it is a prerequisite for IPD, is more common in populations and the data is cheaper and easier to obtain than IPD data. We previously confirmed this by conducting a carriage survey in Pakoto, Ifo LGA, Ogun, Nigeria and this was the first detailed pneumococcal carriage survey in Nigeria. Estimates of cost effectiveness will also be obtained using the predicted impact on IPD.

Material Transfer Agreement Form

This Material Transfer Agreement (the "Agreement") is by and between Lagos University Teaching Hospital, Lagos, Nigeria ("Provider") represented by Dr. Kofo Odeyemi, Department of Community Health and Primary Care, College of Medicine University of Lagos and Lagos University Teaching Hospital/Co-Investigator, and Dr. Ifedayo MO Adetifa of Kenya Medical Research Institute/Wellcome Trust Research Programme, Kilifi, Kenya and College of Medicine, University of Lagos, Nigeria and ("Recipient") regarding the transfer of human nasopharyngeal swabs and associated demographic and clinical data, from the provider to the recipient for research purposes as further defined below.

Throughout this Agreement,
Provider and Recipient are collectively referred to as the "Parties." This Agreement will become effective upon the date of the last signature affixed below.

The Provider and Recipient agree as follows:
1. **DEFINITIONS**. Within this Agreement, the following terms will have the same meaning and effect as defined below:
(a) "De-identified" information is information that formerly contained individually identifiable health information but which has had all unique identifying information, numbers, characteristics, and codes removed such that the information a record contains cannot be used alone or in combination with other information to identify the individual who is the subject of the information.

(b) "Protected Health Information" or "PHI" means any information, whether oral or recorded in any form or medium: (i) that relates to the past, present, or future physical or mental condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual, and (ii) that identifies the individual or with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

2. **DESCRIPTION OF MATERIAL AND DATA.** The Provider will transfer to the Recipient the following bio-specimens and/or derivatives ("MATERIAL") nasopharyngeal swabs obtained from healthy populations across all age groups with personal demographic and clinical data ("DATA").

3. **COLLECTION OF MATERIAL AND DATA.** The MATERIAL and DATA will be collected and/or processed from healthy consenting populations in Pakoto and environs, Ifo LGA, Ogun State, Nigeria in accordance with approval of the Research Ethics Committee of Lagos University Teaching Hospital, Lagos.

4. **TRANSFER OF MATERIAL AND DATA.** The MATERIAL and DATA provided by Provider will be de-identified and all Protected Health Information (PHI) where applicable removed.

5. **RESPONSIBILITIES AND AUTHORIZATIONS OF RECIPIENT**

(a) Recipient agrees to use the MATERIAL and DATA for the approved research project only (see Appendix 1 "Research Project") and will not use the MATERIAL and DATA for any unapproved commercial purposes, including selling or transferring to a third party for commercial purposes.

(b) Recipient is responsible for obtaining any necessary Human research Ethics approvals or exemptions required to use the MATERIAL and DATA at the KEMRI-Wellcome Research Programme, Kilifi, Kenya. The Recipient will use MATERIAL and DATA in compliance with all applicable National, federal, state, and local statutes and regulations.

(c) Recipient will allow the use of MATERIAL and DATA only by Dr. Ifedayo Adetifa ("Recipient/Principal Investigator") and Recipient's research team that are under the direct supervision of the Recipient, and only after they have been informed of and agreed to the provisions and restrictions stated herein. Any transfer of MATERIAL and DATA to other than Recipient Investigator's research team requires the advanced written approval of the Provider.

(d) It is acknowledged that the Recipient may already have in his possession or will obtain from another source, PHI related to the MATERIAL and DATA, and to which the Recipient may be subject to additional restrictions or obligations under separate agreements. Recipient shall notify Provider in writing within five (5) working days of its discovery of any unauthorized use or disclosure of PHI related to the MATERIAL and DATA of which Recipient becomes aware. Recipient shall take (i) prompt corrective action to cure any deficiencies or (ii) any action pertaining to such unauthorized disclosure.

(e) Recipient agrees to not identify or contact any donor, or living relative of a donor, who may have provided the MATERIAL or any DATA received by Recipient under this Agreement from Provider.

(f) Recipient agrees to report data, inventions, and publications resulting from the use of the MATERIAL and/or DATA to Provider.

6. THE MATERIAL AND DATA ARE NOT FOR USE IN HUMAN SUBJECTS OR FOR THE TREATMENT OR DIAGNOSIS OF HUMAN SUBJECTS.

1. **DISCLAIMER**. Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. THE PROVIDER MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE HUMAN MATERIAL WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS.
2. **TERMINATION AND DISPOSAL**. Either Party may terminate this Agreement with sixty (60) days written notice to the other Party before the research project commences.
3. **ACKNOWLEDGEMENT**. In all oral presentations or written publications resulting from the use of the MATERIAL and DATA, the Recipient will

acknowledge the provider as the source of the MATERIAL and DATA, unless requested otherwise by Provider.

4. **COST AND SHIPPING**. The MATERIAL and DATA are provided at no cost to Recipient. Recipient will be responsible for shipping costs of the MATERIAL and DATA.

The Parties have executed this Agreement by their respective duly authorized officers on the day and year hereinafter written. Any communication or notice to be given shall be forwarded in writing to the respective addresses listed below.

Signed: [redacted] Date: 19/1/17
Dr. Kofo Odeyemi
Department of Community Health and Primary Care
College of Medicine, University of Lagos,
Lagos and Lagos University Teaching Hospital

Signed Recipient [redacted] Date: 19/5/17
Dr. Ifedayo Adetifa
Clinical Epidemiologist
KEMRI-Wellcome Trust Research Programme,
Kilifi, Kenya