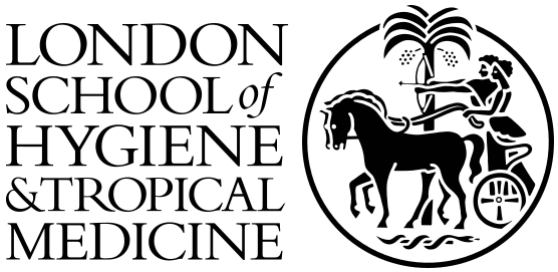

Preventing pneumococcal disease among vulnerable adults in low- and middle-income settings in the era of routine infant pneumococcal vaccination.

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I, Deus Thindwa, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Despite indirect protection against vaccine serotype (VT) pneumococcal disease from widespread use of infant pneumococcal conjugate vaccines (PCV) in low/middle-income settings, a substantial disease burden remains among vulnerable adults, those living with human immunodeficiency virus (HIV+) or aged ≥55 years-old (y), composed of serotypes not targeted by childhood PCV and substantial residual VT circulation. In this thesis, I aimed to address this gap by reviewing the burden and risk factors for pneumococcal carriage and transmission, and assessing vaccination strategies against pneumococcal disease in vulnerable adults in the mature infant PCV era.

I first assessed the contribution of HIV+ adults to household carriage transmission by developing a hidden Markov model fitted to intensively sampled longitudinal carriage study with 115,595 samples. I estimated that HIV+ adults transmit pneumococci similarly to healthy adults implying no greater herd immunity if directly vaccinated, in addition to their direct protection from pneumococcal disease. I further investigated the role of HIV infection status in social contacts relevant to pneumococcal spread, by designing and conducting a social contacts survey yielding 12,540 contact events, and showed that mixing patterns are also similar between HIV+ and healthy adults. I extended my study for pneumococcal carriage risk by using existing rolling cross-sectional carriage data, and identified male sex and living without a <5y child as key factors for persistent VT carriage in HIV+ adults in the infant PCV era. Finally, I showed that healthy adults ≥55y who are similarly at high-risk of pneumococcal disease should be vaccinated at 55y and 65y in considered low/middle- and high-income countries, respectively, to maximise prevented invasive pneumococcal disease burden at population-level.

Overall, my work demonstrates persistent adult carriage risk and transmission, and provides crucial evidence of the likely impact, and particularly indirect effects, of vaccination strategies targeting pneumococcal disease burden in vulnerable adults in low/middle-income.

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Preface

This PhD thesis has adopted a paper style format. The first chapter is a general introduction to the pneumococcus, pneumococcal disease risk and burden, pneumococcal carriage, and transmission, as well as pneumococcal vaccination against disease in vulnerable adults. The introduction highlights the knowledge gaps and sets the scenery for the six manuscripts, each as a chapter, that provide solutions to underlined gaps. Five of the manuscripts have already been published in peer reviewed journals, and the last one is undergoing revision in order to submit to a journal for peer review. The last discussion chapter combines the results of the six studies to respond to gaps highlighted in the introductory chapter.

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Table of abbreviations

ALWHIV	Adults living with human immunodeficiency virus
ART	Antiretroviral therapy
CAP	Community acquired pneumonia
COVID-19	Disease caused by SARS-CoV-2 infection
CD4	Cluster of differentiation 4
EPI	Extended program on immunisation
GAM	Generalised additive model
HIC	High-income country
HIV	Human immunodeficiency virus
HMM	Hidden Markov model
IgA	Immunoglobulin A
IPD	Invasive pneumococcal disease
LIC	Low-income country
LMIC	Low- and middle-income country
LRI	Lower respiratory tract infection
MIC	Middle-income country
NP	Nasopharyngeal
NVT	Non-vaccine serotype
PCV	Pneumococcal conjugate vaccine
PPV	Pneumococcal polysaccharide vaccine
qPCR	Quantitative polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SIS	Susceptible infected susceptible
VT	Vaccine serotype

Chapter 1: General introduction

1.1 Context

By 2020, more than 80% of eligible low- and middle-income countries (LMICs) rolled out pneumococcal conjugate vaccines (PCV) for use in infants in their extended program on immunisation (EPI) with financial support from Gavi, the Vaccine Alliance [1]. However, some countries have experienced less herd protection, compared to high income-countries (HIC), against pneumococcal carriage and disease from their infant PCV programs [2–4], and more so in the presence of persistent generalised human immune deficiency virus (HIV) epidemic [5]. Thus, vulnerable adults, defined here as HIV-infected adults and adults aged ≥55 years, remain at persistent high risk of pneumococcal carriage and disease [6–9]. Also, pneumococcal vaccination programs that could directly protect vulnerable adults against pneumococcal carriage and disease do not exist in such countries [10]. This PhD research focussed on vulnerable adults by assessing their risk for pneumococcal carriage and transmission, and exploring their direct vaccination potential against pneumococcal disease in the era of mature infant PCV.

1.2 *Streptococcus pneumoniae*

Streptococcus pneumoniae (pneumococcus) is a bacterium in the family Streptococcaceae [11,12]. Pneumococcus is microbiologically characterised as a gram-positive coccus, extracellular and nonmotile pathogen, about 0.5-1.25 micrometres in diameter, often found in a diplococcus configuration and surrounded by a capsular carbohydrate called polysaccharide [11,13]. Pneumococci are categorised into serotypes based on the seroreactivity of rabbit antisera against the bacterial capsule composed of polysaccharide molecules [13,14]. Variation in the constituent monosaccharides and their sequence and position of linkage

creates variety. Each of the more than 100 serotypes identified to date, vary in their ability to resist human phagocytosis, due to variation in the physico-electrical properties [14]. Most capsules are negatively charged to help prevent clearance by mucus while also repelling phagocytes electrostatically [13]. Thus, the capsule plays a major role in the virulence and susceptibility of the bacterium to host killing and clearance. By targeting antibodies against the capsular polysaccharides which can opsonise and facilitate clearance, this is the basis on which all current pneumococcal vaccines are based, incorporating multiple serotypes to target the most important capsular serotypes [13].

Pneumococci normally reside in mucosal surfaces of the nasal and oro-pharynx in healthy asymptomatic individuals [7]. The bacteria typically cause disease in persons with immature or weakened immune system such as infants and vulnerable adults [7]. Pneumococcal colonisation can result in (1) non-invasive infection which develops outside of body organs and the bloodstream such as sinusitis and otitis media, or (2) invasive infection which develops in normally sterile sites most commonly including bacteraemia (blood infection), pneumonia, meningitis and less often other focal infections such as osteomyelitis (bone infection), arthritis and endocarditis [12].

1.3 Burden of and risk factors for pneumococcal disease in vulnerable adults

Pneumococcal disease in vulnerable adults is usually related to pneumonia, most of which is community-acquired pneumonia (CAP). In the United States, 25-30% of CAP is attributed to pneumococcus [15,16], and these estimates are higher in Europe and developing countries [17–20], with mortality rates of 5-20% [21]. Pneumococcal pneumonia is accompanied by bacteraemia in 10-30% of cases [22], and together with meningitis cause a substantial burden of invasive pneumococcal disease (IPD). Immune suppression is a major risk factor for

pneumonia, with HIV-infected adults presenting 25-fold increase in the risk for bacterial pneumonia compared to the general community [23]. IPD risk in HIV-infected adults was previously reported up to 300 times higher than those without HIV, but this risk and subsequent mortality have declined greatly in the era of widespread antiretroviral therapy (ART) [24,25], even more so due to indirect impact of infant PCV [26–28], although the relative risk remains sevenfold higher in healthy HIV-infected adults on ART compared to adults without HIV [29]. While seasonal changes in temperature and humidity alter nasal mucosal conditions and increase susceptibility to IPD mediated by respiratory virus activity, low CD4-cell count, uncontrolled HIV replication, smoking, alcoholism, diabetes mellitus, cirrhosis, drug use, and chronic obstructive pulmonary disease are largely host factors that increase IPD risk [30–33]. Moreover, pneumococcal virulence factors such as capsular type, cell wall, pneumolysin, surface proteins, autolysis, and IgA protease as well as coinfection with other viruses such as influenza are also reported to increase invasiveness and/or severity [32,34].

Global pneumococcal deaths due to lower respiratory infections (LRI) in older adults aged ≥50 years in LMICs in 2017 was estimated at 501 deaths per 100,000 population, 49.4% (325,320) of total global deaths due to LRI [35]. Also, of the 9,601 global meningitis deaths, 78% occurred in LMICs [35]. While the fraction of pneumococcal CAP pooled from 6 pre-PCV and 11 post-PCV studies declined from 22% to 18%, pneumococcal CAP remained 67% due to PPV23 serotypes and 49% due to PCV13 serotypes of which 49% were caused by serotype 3 [35]. Moreover, the proportion of pneumococcal CAP caused by vaccine serotype (VT) were higher in adults with bacteraemic than non-bacteraemic pneumonia [36,37]. There are limited data in LMICs, with only one study in Malawi showing 21.4% of pneumococcal CAP in hospitalised adults, with mean age of 34 years, of whom 78% are

HIV-infected, and 68% on ART [38]. The risk of pneumococcal disease in older adults increases due to immunosenescence and comorbidities including cardiovascular and renal diseases, diabetes, and malignancy [8,39].

1.4 Pneumococcal carriage and transmission in vulnerable adults

HIV-infected adults usually have slightly higher pneumococcal carriage prevalence than their HIV-uninfected counterparts [40], and with those on ART having faster carriage clearance than those not on ART [41]. The mechanism for elevated carriage in HIV-infected adults is partly linked to impaired humoral responses to extracellular pathogens and control of pneumococcus at the mucosal level due to detrimental effects of HIV on T and B cell functions [7,42]. While the risk factors for pneumococcal carriage in vulnerable adults in the pre-PCV era included exposure to infants exposed to HIV, low social economic status, high density household size with inadequate ventilation, intense physical contacts and seasonality [6,40,43,44], factors that shape pneumococcal carriage in post-PCV era are less well known in the presence of indirect carriage protection from childhood PCV and improved adult ART uptake partly due to innovative “test and treat” strategies [45].

Pneumococcal transmission between vulnerable adults and younger children has been characterised in the pre-PCV era [6,40,46], revealing higher transmission rates from HIV-infected than HIV-uninfected adults. For instance, a South African study found that HIV-infected mothers transmitted pneumococci more frequent to their infants compared to their HIV-uninfected counterparts [40], in contrast to what has been shown in Malawi [47]. However, these studies were only limited to mothers and their infants and not all HIV-infected adults in the household, masking a clear contribution of vulnerable adults to pneumococcal transmission. In the PCV era, where younger children are better protected

from VT, it is unclear if carriage transmission interruption with their mothers and other household adults has substantially occurred, and more specifically, if HIV-infected adults within the household contribute disproportionately higher to pneumococcal transmission than their HIV-uninfected counterparts due to presumption that they usually carry pneumococcus for longer and at higher density which individually or in combination may increase their risk for transmission. More importantly, as close social contacts are a major route for pneumococcal transmission [48], there have been no studies to investigate the role of HIV infection status in social mixing patterns, particularly for potential differential contact patterns compared to healthy adults.

1.5 Vaccination against pneumococci

Two infant PCV formulations are currently licensed and in use globally [49]; PCV10 which targets serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F, and PCV13 which targets additional serotypes, 3, 6A, and 19A. On the other hand, four pneumococcal vaccines are currently licensed and offered to vulnerable adults; PCV13, PCV15 (PCV13 serotypes, 22F and 33F), PCV20 (PCV15 serotypes, 8, 10A, 11A, 12F, and 15B) and 23-valent pneumococcal polysaccharide vaccine (PPV23) (PCV20 minus 6A, plus 2, 9N, 17F, and 20). Both PCV10 and PCV13 have comparable effectiveness and have been licensed based on their noninferior immunogenicity to a previous 7-valent formulation (PCV7) which targets PCV10 serotypes except 1, 5, and 7F [49]. The use of infant PCV has substantially reduced VT pneumococcal disease burden in vulnerable adults globally due to indirect effects [4]. However, considerable pneumococcal disease burden remains in vulnerable adults, composed of serotypes not targeted by childhood PCV programs and high residual circulation of VT [3,35,50].

Among HIV-infected healthy adults, PPV23 has been recommended for use since 1980s by the United States Centres for Disease Control for direct protection against targeted serotypes despite conflicting evidence about efficacy and hyporesponsiveness in those with advanced immunosuppression, with potential risk for all-cause pneumonia [51–59]. On the other hand, PCVs are more immunogenic than PPV23 [57,59] in HIV-infected adults, and are shown to be efficacious against VT-IPD especially within first year of receipt, and even among those with low CD4+ count and unsuppressed viral load at vaccination [59]. Unlike LMICs who do not have pneumococcal immunisation programs for HIV-infected adults and rely on carriage reduction strategies [10], some HICs recommend sequential dosing of PCV followed by PPV23 against VT-IPD [51,60,61], including a recently recommendation to use PCV15 followed by PPV23 or PCV20 alone in HIV-infected adults in the United States [62–65].

Among older adults in HICs, PCV13 and PPV23 are used for the prevention of pneumococcal disease, usually offered at 60 or 65 years old [51]. Efficacy of PCV against VT-IPD (75%) in the Netherlands and VT-CAP (73%) in the United States have been reported to be higher than 42-54% for PPV23 against VT-IPD [66–68]. However, there are mixed regulations in Europe on what should be the primary vaccine, age at which to offer vaccination and number of doses [51]. Nonetheless, most European countries still recommend the use of PPV23 in older adults because of the substantial indirect protection from infant PCV immunisation [51,69], which may be different in LICs where herd protection has been less pronounced [2]. While IPD incidence increases with age, the population size benefitting from pneumococcal vaccines and immune response to vaccine declines, posing a conundrum for identifying the optimal age at which to offer pneumococcal vaccination to inform implementation policy especially in LMICs. Furthermore, given the previous evidence of substantial pneumococcal-influenza coinfections during the 1920

influenza pandemic and 2009 H1N1 pandemic [70,71], the use of pneumococcal vaccines may potentially prevent the worst outcomes of influenza by reducing pneumococcal coinfection disease. Thus, assessing the benefits of using pneumococcal vaccines or expanding their coverage in older adults during disease pandemic caused by SARS-CoV-2 infection (COVID-19) would potentially prevent the worst outcomes of COVID-19 by reducing pneumococcal coinfection disease.

While LMICs have the highest pneumococcal disease burden [72], barriers to implement pneumococcal vaccine programs that directly target vulnerable adults exist and include high cost of PCVs [73], and limited evidence on effective or cost-effective vaccine strategies.

1.6 Research aim and objectives

This PhD research was aimed at reviewing the burden and risk factors for pneumococcal carriage and transmission, and assessing vaccination strategies against pneumococcal disease in vulnerable adults in the era of mature infant PCV.

The objectives of the PhD research presented in this thesis were to:

1. Review potential vaccine strategies to reduce the burden of pneumococcal disease in HIV-infected adults.
2. Estimate the contribution of HIV-infected adults to household pneumococcal transmission in the era of infant PCV.
3. Assess social contacts relevant to infectious disease spread by close contacts in LICs and the role of adult HIV infection status in social contact frequency.
4. Assess risk factors for pneumococcal carriage in HIV-infected adults on ART.

5. Identify optimal age-targeting for pneumococcal vaccination in immunocompetent older adults in the era of infant PCV.
6. Assess potential benefit of using pneumococcal vaccines to prevent the worst consequences of SARS-CoV-2 and pneumococcal coinfections in older adults.

1.7 Overview of methods for addressing the research objectives

To address the gap of preventing persistent pneumococcal disease burden in HIV-infected adults in LMICs in infant PCV era, I undertook a non-systematic review, through literature search, of pneumococcal disease burden and evidence on vaccination programs among HIV-infected adults in HICs. Based on the magnitude of disease burden and risk-benefits of current vaccination programs in HICs, I then proposed new vaccine strategies against pneumococcal disease in LMICs either through direct protection or indirect protection through infant immunisation under high vaccine coverage and/or changed vaccine schedules.

To estimate household pneumococcal transmission from HIV-infected adults, and therefore evaluate potential indirect effects of their vaccination, I have constructed a continuous-time, time-homogeneous hidden Markov model (HMM) which assumes a susceptible-infected-susceptible (SIS) framework to capture the dynamics of pneumococcal carriage acquisition and clearance. I have used data from a longitudinal household-based nasopharyngeal (NP) swabbing study in South Africa where individuals were swabbed twice weekly for approximately 10 months each year during 3-year study period (PHIRST study). In the PHIRST study, a total of 1,684 individuals were enrolled from 327 households from rural and urban sites where a total of 115,595 NP samples were collected [74,75]. The HMM also allows estimation of misclassification probability (false negative pneumococcal samples) of a real-time quantitative polymerase chain reaction (qPCR) that was used for carriage detection.

To assess social mixing patterns and the role of HIV infection status in it , I designed and implemented a social contacts survey in urban Blantyre[76], Malawi between April and July 2021, where 1,201 individuals of all ages were enrolled and interviewed on their social contacts in the previous day, resulting in 12,540 total reported contact events. Using these data, I have constructed and fitted a negative binomial mixed effects model, with household as a random effect, to determine factors associated with contact frequency. Additionally, I have computed age-specific contact rates via contacts matrices based on the ratio of the measured probability of a contact event between individuals based on age group to a null model of the probability under an assumption of random mixing. Contact probabilities under the null hypothesis are determined by the proportion of the population in each given age group in the study setting. Further, contact matrices are stratified by HIV infection status to explore potential differential social contacts between HIV-infected and uninfected adults which may impact pneumococcal carriage transmissibility and susceptibility.

I have used generalised additive modelling framework (GAM) to assess risk factors for pneumococcal carriage in HIV-infected adults on ART in infant PCV era. GAM models are fitted to age and time-specific trajectories of pneumococcal carriage to allow flexibility in capturing nonlinear carriage dynamics. Penalised B splines for age and time smoothers are used to construct basis functions, and a penalised log-likelihood maximisation is used to fit a non-parametric binomial model with complementary log-log link function defined by log-hazard of carriage as function of risk factors and age and time splines. Pneumococcal carriage data are based on a previous study (PCVPA study) that collected NP swabs from 2,067 adults aged 18-40 years attending ART clinic during the rolling, cross-sectional surveys in Blantyre, Malawi between 2015 and 2019 [2].

To determine the optimal age-targeting for pneumococcal vaccines in older adults aged ≥55 years, I first collate age- and serotype group (serogroup)-specific IPD data with varying surveillances periods in a mature infant PCV era from collaborators in Brazil, England, Malawi and South Africa [3,8,77–80]. Then, I fit an exponential growth model to observed age group incidence to estimate annual age incidence. Together with each setting's smoothed population demographics, I compute age and serogroup-specific expected number of IPD cases. On the other hand, vaccine parameters including waning rates and initial vaccine efficacy are estimated using a piecewise constant model fitted to vaccine effectiveness/efficacy data from previous studies. Lastly, I use a cohort model with data on expected number of cases and vaccine parameters to estimate (1) optimal preventable cases per vaccinated age cohort or (2) the efficiency of the vaccination program.

To inform additional benefits of pneumococcal vaccines against coinfection with other viruses that cause similar respiratory tract inflammation, I conducted a non-systematic review, through literature search, of SARS-CoV-2 and pneumococci coinfection to inform the risk-benefit of expanding or implementing new pneumococcal vaccination programs during COVDI-19 pandemic to avert severe COVID-19 outcomes due to coinfections. I conducted this research work during the early phases of COVID-19 pandemic when data on coinfections were sparse, and several assumptions were made about the transmission dynamics of SARS-CoV-2 based on initial data from Wuhan in China.

The output of my PhD research in this thesis is organised as research paper style into six new research chapters excluding introduction and discussion under the following titles:

1. Vaccine strategies to reduce the burden of pneumococcal disease in HIV-infected adults in Africa. This study has been published in Expert Review of Vaccines journal.
2. Estimating the contribution of HIV-infected adults to household pneumococcal transmission in South Africa, 2016-2018: A hidden Markov modelling study. This study has been published in PLOS Computational Biology journal.
3. Social mixing patterns relevant to infectious diseases spread by close contact in urban Blantyre, Malawi. This study has been published in Epidemics journal.
4. Risk factors for pneumococcal carriage in adults living with HIV on antiretroviral therapy in the infant pneumococcal vaccine era in Malawi. This study is under review at AIDS journal.
5. Optimal age targeting for pneumococcal vaccination in immunocompetent older adults; a modelling study. This study is in MedRxiv pre-print server (at submission).
6. Use of seasonal influenza and pneumococcal polysaccharide vaccines in older adults to reduce COVID-19 mortality. This study has been published in Vaccines journal.

In research paper 1, I discuss the mechanism that facilitates increased susceptibility of HIV-infected adults on ART to pneumococcal carriage and disease. I also discuss pneumococcal burden and vaccination in African HIV-infected adults. Since the circulation of VTs persists in the infant PCV era in some low-income countries and results in a continued high and vaccine-preventable burden of pneumococcal disease in HIV-infected adults, compounded by non-existing pneumococcal vaccination programs for HIV-infected adults in low-income countries [10], I propose new strategies to help mitigate VT disease burden.

In research paper 2, I have estimated the contribution of South African HIV-infected adults to household pneumococcal transmission, and therefore evaluate potential indirect effects of

their direct vaccination if such pneumococcal programs are to be introduced in Africa [81]. I also uncover the proportion of pneumococcal negative swabs that were false negatives after detection by real-time qPCR targeting autolysin gene.

Since the transmission of pneumococcus requires close contact with infectious respiratory droplets, secretions or inhalation, in research paper 3, I collected primary social contacts data to quantify mixing rates between age groups and investigate the role of adult HIV status in social contacts in low-income settings where such data are limited [82]. Since this was conducted during COVID-19 pandemic, the study also evaluates the impact of COVID-19 restrictions on social contacts in Malawi. These results are relevant for modelling pneumococcal transmission dynamics, and optimising disease control strategies such as vaccination, particularly among the vulnerable adults.

HIV-infected adults remain at high risk of pneumococcal carriage and subsequent disease, yet their risk factors for residual VT carriage in the infant PCV era are not known. In research paper 4, I assess the association between carriage and potential risk factors to help inform targeted-vaccination for HIV-infected adults along with other public health measures to further reduce preventable carriage and therefore disease [83].

In research paper 5, I address a conundrum for identifying the optimal age at which to offer pneumococcal vaccination in older adults aged ≥55 years given that IPD incidence increases with age while the population benefitting from pneumococcal vaccines and immune responses to vaccines decreases. Thus, I estimate the total preventable IPD cases per vaccinated age-cohort as well as the efficiency of vaccination in Brazil, England, Malawi, and South African, and show the age of vaccination that prevents maximum IPD cases.

In research paper 6, I discuss the potential benefit of using pneumococcal polysaccharide vaccines in older adults to avert the worst clinical consequences of co-infections with SARS-CoV-2 [84]. This review was undertaken during the early phases of COVID-19 pandemic in the pre-COVID-19 vaccines period, to help inform risks and benefits of increasing PPV23 vaccination coverage where PPV23 programs existed or introducing new PPV23 programs where it was non-existent amid a pandemic.

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Chapter 2: Research paper 1

Vaccine strategies to reduce the burden of pneumococcal disease in HIV-infected adults in Africa.

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Vaccine strategies to reduce the burden of pneumococcal disease in HIV-infected adults in Africa.

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Abstract

Introduction*: Streptococcus pneumoniae* is the leading cause of invasive bacterial disease, globally. Despite antiretroviral therapy, adults infected with human immunodeficiency virus (HIV) are also at high risk of pneumococcal carriage and disease. Pneumococcal conjugate vaccines (PCVs) provide effective protection against vaccine serotype (VT) carriage and disease in children, and have been introduced worldwide, including most HIV-affected low-middle income countries. Unlike high-income countries, circulation of VT persists in the PCV era in some low-income countries and results in a continued high burden of pneumococcal disease in HIV-infected adults. Moreover, no routine vaccination that directly protects HIV-infected adults in such settings has been implemented.

Areas covered: Non-systematic review on pneumococcal burden in HIV-infected adults and vaccine strategies to reduce this burden.

Expert opinion: We propose and discuss the relative merit of: changing the infant PCV programme to use (1a) a 2 prime plus booster dose schedule, (1b) a 2 prime plus booster dose schedule with an additional booster dose at school entry, to directly vaccinate (2a) HIV-infected adults, or vaccinating (2b) HIV-infected pregnant women for direct protection, with added indirect protection to the high-risk neonates. We identify key knowledge gaps for such an evaluation and propose strategies to overcome them.

Keywords: Pneumococcus, HIV, PCV, Vaccination strategy

1. Introduction

Streptococcus pneumoniae is a major cause of global childhood mortality [1,2], particularly in <5 year-olds, and also causes a high burden of disease among the elderly and human immunodeficiency virus (HIV) infected adults [3–5]. In the last two decades, infant pneumococcal conjugate vaccine (PCV) programmes have substantially reduced the burden of invasive pneumococcal disease (IPD) and mortality in vaccinees [2,6–13]. In contrast to high income countries though [14,15], routine infant PCV programmes in most low-income sub-Saharan African (sSA) countries have led to a less pronounced herd effect with continued circulation of vaccine serotypes (VT), especially in the unvaccinated adult population [12,16–20] including those with HIV infection and thus those at high risk for pneumococcal disease [21]. For instance, over 3.5-year study in Malawi, post-PCV VT carriage in HIV-infected adults only declined from 15.2% 95%CI 10.8-20.9 in survey 1 to 8.9% 95%CI 5.7-13.7 in survey 7 [20]. While the underlying reasons have not been fully established they may include a higher infection pressure as a result of more frequent human contacts and lower vaccine uptake [18].

HIV infection can substantially increase the risk of IPD among otherwise healthy older children or adults on antiretroviral therapy (ART) [5,22–24]. This is in part related to impairment of both the cell-mediated and humoral arms of the immune system [25,26]. Capsule-specific immunoglobulin G (IgG) antibodies as well as T and B cell mediated protein-specific responses play a central role in the control of pneumococcal colonisation and infection [27–29]. However, HIV affects both T and B cell functions, resulting in the impairment of humoral responses to extracellular pathogens such as pneumococci [30–32] and control of pneumococcus at the mucosal level. ART only partially reconstitutes the immune system of HIV-infected individuals by increasing B and T-lymphocyte number and

functionality [25,27]. Deficiencies in humoral response due to depleted or persistent defects in memory cell function persist after ART initiation and disproportionately so at the mucosal level [33,34]. Thus, HIV-infected individuals on ART remain with impaired antibody responses to natural pneumococcal infections and vaccination [35,36].

In this article we present a review of the pneumococcal burden in HIV-infected adults in the presence of mature PCV infant programmes, particularly in sub-Saharan Africa (sSA). We highlight four options for vaccine strategies that could be implemented to address this disease burden and discuss the key evidence gaps to enable a solution to be identified.

2. Pneumococcal burden in African HIV-infected adults

Without ART, the risk of IPD in HIV-infected adults is reported to be 30-300 times higher than in HIV-uninfected individuals, and with an about 6-fold higher risk of recurrence [25,37–39]. Although ART has reduced the risk of IPD and subsequent mortality [3,40], the risk remains more than 30-fold higher than in HIV-uninfected adults [41] with an incidence of >50 cases per 100,000 person-years [3,5,42]. The introduction of infant PCV programmes in South Africa and Kenya has led to further reduction in VT-IPD and pneumococcal pneumonia incidence in HIV-infected adults [9,43,44].

HIV prevalence in African adults varies widely, with Swaziland reporting the highest at 27.2% [45]. In 2017, all sSA countries reported >10% national or sub-national adult HIV prevalence [45]. It has been observed that countries with sub-optimal PCV herd protection and substantial residual vaccine serotype circulation, like Malawi and Mozambique also report high prevalence of HIV [46]. HIV prevalence amongst children has fallen as a consequence of effective prevention of vertical transmission of HIV and ART use [47–50].

Only a small proportion of infants are infected with HIV, and are already included in the PCV infant programs. HIV prevalence remains high because of improved survival with ART in adults. Thus, a large proportion of adults at high risk of pneumococcal disease attributable to HIV infection will remain a concern in the years to come in sSA.

3. Pneumococcal vaccines in HIV-infected adults

Since the 1980s, the 23-valent pneumococcal polysaccharide vaccine (PPV23) has been approved for use in HIV-infected adults for direct protection against a wide range of serotypes, in most high-income countries where it is reported to be safe, including in HIV-infected but otherwise healthy adults [51–54]. However, evidence of PPV23's efficacy in HIV-infected adults is somewhat controversial [53,55–60], with suggestion of potential hyporesponsiveness in individuals with advanced immunosuppression, and a reported increase , albeit not statistically significant, in the incidence of all-cause pneumonia when given to HIV-infected Ugandan adults not on ART [61]. Estimates of PPV23 efficacy in HIV-infected adults are highly heterogeneous which may be linked to differences in HIV viral load and ART status at the time of vaccination [25,61–64].

PCVs are more immunogenic than PPV23 in HIV-infected adults [23,65] and are highly efficacious in preventing VT-disease in HIV-uninfected children and adults [6,66]. Two formulations, a 10 and a 13-valent product, are currently in use worldwide. They have comparable effectiveness and have been licensed based on their non-inferiority to a previous 7-valent formulation (PCV7) [67]. While the efficacy of PCVs against VT-disease in HIV-infected children is somewhat inferior to that of HIV-uninfected children (51% vs 77%) [6], the efficacy against carriage is similar irrespective of HIV status [68]. PCV7 has been shown to be immunogenic [69] and 74% efficacious against VT-IPD in HIV-infected adults, with

highest efficacy within the first 12 months of vaccination even in those with CD4+ count <200 cells/mm^3 and with unsuppressed HIV viral load at vaccination [65,70]. Further evidence on PCV13 efficacy of 75% against VT-IPD and 72.8% against VT community acquired pneumonia in older adults (aged ≥65 years) have been reported in Netherlands and the United States, respectively [66,71,72].

In many high-income countries PCV is recommended for use as priming of HIV-infected adults followed by a PPV23 booster [52,73,74], which acts only against IPD. This is despite the limited PCV serotype disease incidence in these settings as a result of effective herd effects from infant PCV programmes [75]. However, no such pneumococcal immunisation programme for HIV-infected adults exists in low-income African countries [76], where the highest disease burden exists [2]. Implementation barriers include the high costs of PCV [77], and a limited amount of evidence on effective and cost-effective vaccine strategies to address the high pneumococcal disease burden among HIV-infected adults in Africa.

4. Optimal vaccination strategies

We propose two potential approaches for reducing the disproportionate burden of pneumococcal disease in HIV-infected African adults: through (1) expanded indirect protection or (2) introduction of direct protection. For expanded protection, options include either (1a) changing the three-dose infant PCV schedule to a 2 prime plus boost schedule with potentially longer lasting protection and greater herd protection against IPD in HIV-infected adults, or (1b) using a 3-dose prime-boost strategy but with a 4^{th} dose given as an additional booster at school entry to further enhance the duration of protection and thereby limit onward transmission. Direct protection could be achieved by (2a) vaccinating all HIV-infected adults to confer direct protection, or (2b) vaccinating HIV-infected pregnant women

which has the additional benefit of protecting the young infant via transplacental transfer of antibody and reduced maternal exposure (Figure 1).

Option	Approach	New vaccine doses needed	Potential impact	Certainty of impact
1a	PCV switch from 3p+0 to 2p+1		⊕⊕⊕	???
1b	PCV switch from 3p+0 to 2p+1(+1)		⊕⊕⊕	??
2a	1 dose PCV (+ 1 PPV boost) to all HIV-infected adults		⊕⊕	?
2b	1 dose PCV (+ 1 PPV boost) to all HIV-infected pregnant women		⊕	?

Figure 1. Schematic of potential pneumococcal vaccine strategies against invasive pneumococcal disease (IPD) in HIV-infected adults through indirect (1) and direct (2) approaches. Change the infant PCV schedule from 3p+0 to 2p+1 to enhance herd immunity against IPD in HIV-infected adults through a single booster dose (1a), change the infant PCV schedule from 3p+0 to 2p+1(+1) to enhance herd immunity against IPD in HIV-infected adults through double booster doses (1b), vaccinate HIV-infected adults for direct protection (2a), vaccinate HIV-infected pregnant women for direct protection, with some indirect protection for their neonates (2b). Option 1a will not require any additional vaccine doses as it simply rearranges the timing of the three-dose schedule. Option 1b will need additional vaccine doses equivalent to the number of 5-year-old children in a country per year (e.g., about 300,000 doses per annum for Malawi). Option 2a will need one additional dose of PCV and one of PPV for each HIV-infected adult (e.g., assuming revaccination of the 970,000 HIV-infected adults in Malawi (http://aidsinfo.unaids.org/) every 10 years would use about 200,000 doses per annum, although the rate of new HIV infections is lower than that). The

last option 2b will need one additional dose of PCV and one of PPV for each HIV-infected pregnant woman (e.g., 90,000 doses per annum for the about 45,000 HIV-infected pregnant women in Malawi each year). Options 1a and 1b are likely to have large impact because of their potential to elicit herd immunity, however, to date it is not well established that herd immunity would indeed be enhanced through a booster dose schedule (several trials are under way to assert this). Option 1b offers less uncertainty due to extra dose included. Option 2a only provides direct protection against vaccine serotypes to HIV-infected adults while 2b will see only a small subset of that vaccinated. There is limited uncertainty for the impact of the latter two strategies as PCV's efficacy is relatively well established in the two groups

(1a) Switch from 3p+0 to 2p+1 PCV schedule to potentially increase herd protection

The World Health Organization currently recommends a 3 dose schedule administered either as three doses in early infancy (3p+0) or as 2 infant priming doses followed by a booster typically at 9 to 12 months (2p+1) [67]. In contrast to high income countries, the vast majority of Africa opted for a 3p+0 schedule based on prioritisation of direct protection against the high disease burden in early childhood, alignment with other routine immunisations and concerns about potentially low booster dose coverage in a 2p+1 schedule. A notable exception is South Africa where 2p+1 PCV schedule was introduced in 2009 with a booster dose at 9 months to align with measles vaccine dose 1 [8,9,78].

In theory, a 3rd dose given as a booster to 9-12 month olds elicits high levels of antibody that extend protection against VT carriage acquisition into early or pre-school age and hence further interrupt transmission in one of the key age groups for pneumococcal spread [79,80]. While trials to test this hypothesis are ongoing [81,82], there is currently no clear evidence to

confirm that a 2p+1 schedule would induce superior herd protection in those African countries that have been using a 3p+0 with unsatisfactory indirect effects [67].

For now, a conclusive comparison of the differential impact of the two vaccine schedules across countries is hindered by the strong correlation between vaccine schedule and pneumococcal transmission intensity. Most high-income countries have been using 2p+1, and most African countries, typically with higher overall carriage prevalence, have been using 3p+0. Exceptions to this include South Africa introducing PCV in a 2p+1 schedule and Australia using a 3p+0 (but switching to a 2p+1 as a result of breakthrough disease in the PCV13 era) [83,84]. South Africa has experienced substantial reductions in VT-carriage and IPD in unvaccinated populations including HIV-infected adults [44]. Other low-income African countries like Malawi [16,20], Mozambique [19], and the Gambia [85] have substantially less evidence of herd immunity from their mature PCV infant programmes with overall residual VT-carriage prevalence of 13.9%, 19.7%, and 11.4%, respectively [46], at a minimum 3rd dose vaccine coverage rate of ≥81% [20,86,87].

(1b) Switch from 3p+0 to 2p+1(+1) PCV schedule to increase herd protection

A switch from 3p+0 to a 2p+1 schedule would not have major cost implications. Also, if indeed with the addition of a booster dose herd effects can be enhanced, the impact of such schedule change extends beyond just HIV-infected adults and will benefit other unvaccinated individuals as well. However, herd immunity is the result of a complex interplay of factors including bacterial physiology, booster dose coverage, average age of pneumococcal carriage, duration of vaccine protection against carriage and social mixing patterns [88–90]. Additionally, the high average age of carriage, intense social mixing and the waning of PCV protection against carriage (estimated half-life is 4-6 years) may imply that, in some settings,

older children are a key source of pneumococcal transmission and are not fully protected in a 2p+1 schedule [91,92]. A school entry PCV booster dose may be necessary to interrupt transmission and increase herd protection [91].

(2a) Vaccinating HIV-infected adults

PCV is more immunogenic than PPV23 [23,57,65,69], and efficacious in preventing recurrent episodes of VT-IPD in HIV-infected adults [65]. As per existing recommendations in many high-income countries [51,52], a single dose of PCV followed by a PPV23 booster for expanded serotype coverage could be given to HIV-infected adults in low-income countries to prevent VT-IPD [73,74]. As PCV is efficacious in vaccinees with low CD4+ cell count [65], it could be given immediately at HIV diagnosis to increase PCV coverage [93]. Since most sSA countries have considerably high ART coverage between 65-85% [94], adoption of this strategy will require a carefully considered integration of the proposed HIV-infected adult pneumococcal vaccine programme into the mature ART programmes to achieve a similar high coverage in the midst of competing health priorities [49,50,95,96]. In order to optimise local resources, PCV/PPV23 could concurrently be given with ART to HIV-infected adults [97].

PCV-mediated protection against IPD in HIV-infected adults has been reported to wane rapidly beyond 12 months, especially in those with low CD4+ cell count [65]. Revaccination with PCV or PPV is feasible [98], but of unproven clinical value. Choosing a PPV booster repeated may seem more rational as it is a cheaper vaccine and has higher serotype coverage, but also carries theoretical risks of generating hyporesponsiveness. This approach may also have additional indirect effect benefits if a PCV + PPV strategy could be shown to reduce carriage in this population. HIV-infected adults typically have higher pneumococcal carriage

prevalence than HIV-uninfected adults [99,100], and may be part of a reservoir for residual VT circulation in high HIV prevalence sSA settings. Whilst there is no substantial evidence to suggest they sustain transmission, they consequently represent a disproportionate health burden [101–103].

(2b) Vaccinating HIV-infected pregnant women

Where there are insufficient resources for targeting all HIV infected adults, HIV-infected pregnant women could be prioritised for PCV protection. Their vaccination would come with the added benefit of indirect protection of their infant and hence would be particularly relevant in settings where the benefits of herd immunity from PCV paediatric programmes are limited or neonatal acquisition of VT pneumococcal carriage commonly occurs before the infant can be directly protected by vaccination [46]. Transmission of pneumococci from HIV-infected mothers to their children has been reported [101,102], and this is also likely to be seen in infants not yet eligible for PCV vaccination; e.g. > 40% of infants in the Gambia [104,105], and Kenya [106,107] were reported to acquire pneumococci by the age of 4 weeks. Although HIV infection is reported to reduce the efficiency of maternal antibody transfer to the infant [108], maternal vaccination may still be useful since the (reduced) transfer ratio is applied to a higher vaccine-induced anti-pneumococcal capsular IgG in pregnancy. Thus, vaccination may directly protect the mother and foetus against pneumococcal carriage and disease [105,107,109], and interrupt VT transmission between mother and neonate, thereby providing cocooning immunity during neonatal life.

Maternal PCV vaccination has been shown to be safe. No serious adverse pregnancy associated outcomes have been reported from clinical trials where the average gestation at vaccination was between 27-38 weeks [110]. However, data on the IPD burden in neonates

and mothers, as well as the benefits of maternal immunization from low-income countries are limited. A Cochrane systematic review highlighted that there is insufficient evidence to assess whether pneumococcal vaccination during pregnancy could reduce infant infections [110].

National antenatal programmes in most low-income countries are well-established, with substantial service coverage [48]. Vaccine doses along with other services could be given to HIV-infected pregnant women who attend antenatal clinic or otherwise ART clinics.

5. Expert opinion

PCV is widely used in global infant immunisation programmes and has been recommended for use in HIV-infected adults in high-income countries along with a PPV23 booster dose. In parts of Africa, there is a combination of substantial residual VT circulation among adults despite mature infant PCV programmes, still relatively high adult HIV prevalence and persistent high risk of IPD in HIV-infected adults. An adapted vaccination strategy could reduce the risk of IPD in HIV-infected adults. Here, we have presented a few options through direct and indirect vaccine protection to enable identification of an effective way forward.

We define the optimal vaccination strategy as one that maximises the reduction in pneumococcal disease burden in HIV-infected adults in Africa. There are of course other factors as well that may determine whether a theoretically optimal strategy is indeed programmatically feasible. Important evidence gaps exist to enable evaluation of the optimal pneumococcal vaccine strategy. It is uncertain if a 2p+1 dosing schedule will work to achieve better herd protection than a 3p+0 in settings where it has not yet been implemented, or whether an additional booster at school entry 2p+1(+1) may be needed if protection against

carriage wanes considerably in early childhood. Two cluster randomised trials in Malawi and Vietnam, in which 3p+0 and 2p+1 schedules are being compared head to head in each trial, can be used to evaluate their impact on pneumococcal carriage [81,82], and could provide crucial information on their relative merits for providing herd protection.

While PCV7 vaccine efficacy against IPD in HIV-infected adults has been previously estimated at 74% [65], efficacy against VT-carriage is unknown. Moreover, the duration of protection against both carriage and disease in HIV-infected adults is unknown, with some evidence for the latter pointing to rapid decline after 12 months of vaccination [65]. Data on interaction between ART (which may improve efficacy) and PCV shows no major impact of ART [25], but since PPV23 effectiveness/efficacy against IPD is contentious [60], dosing intervals to optimize efficacy and protection remain uncertain. More importantly, it is uncertain whether in the era of routine PCV use in infants, HIV-infected adults substantially contribute to the residual VT transmission because of their elevated rates of carriage. Despite the importance of social interactions for pneumococcal transmission [111,112], only a few social mixing patterns studies have been conducted in low-income countries [112–116]. Moreover, data on whether HIV-infected adults have differential social mixing behaviour compared to HIV-uninfected adults is not available. Thus, limiting our ability to precisely quantify transmission dynamics in HIV-infected adults.

Uncertainties around the benefits of maternal immunization with PCV also need to be addressed. The efficacy of maternal vaccination in protecting the neonate from carriage acquisition and the duration of vaccine-induced protection in the new-born need to be established [105,110]. Also, there are concerns that maternal vaccination could interfere with the benefits of infant priming doses by inhibiting the antibody responses particularly when

high residual concentration of maternal placentally transferred antigen-specific antibodies are present at the time of infant immunisation [117,118].

Article highlights

- Circulation of VTs persists in the PCV era in some low-income countries and results in a continued high and potentially vaccine preventable burden of pneumococcal disease in HIV-infected adults.
- Routine pneumococcal vaccination programmes for HIV-infected adults are not implemented in low-income countries.
- Mitigation of the VT disease burden in HIV-infected adults in low-income countries may be achieved either by added direct protection or increased indirect protection from the infant programme (via increased coverage or a change in vaccine schedule).
- For added direct protection both PCV and PPV are licensed and used in high income countries. PCV is more immunogenic but also substantially more expensive and has the inferior serotype coverage.
- For added indirect protection a change in infant immunisation schedule to stipulate longer lasting protection may largely mitigate the risk for vaccine preventable pneumococcal disease in the HIV-infected.
- Both strategies will need formal evaluation of their likely effectiveness and cost-effectiveness.

Articles of considerable interest

- Swarthout TD, Fronterre C, Lourenço J, Obolski U, Gori A, Bar-Zeev N, et al. High residual carriage of vaccine-serotype Streptococcus pneumoniae after introduction of

pneumococcal conjugate vaccine in Malawi. Nature Communications 2020;11:2222. https://doi.org/10.1038/s41467-020-15786-9.

- Klugman KP, Rodgers GL. Population versus individual protection by pneumococcal conjugate vaccination. The Lancet 2019;393:2102–4. https://doi.org/10.1016/S0140-6736(19)30039-X.

  These articles provide evidence of residual carriage of VT after introduction of PCV in low-income sSA countries which may imply that HIV-infected adults remain at high risk of VT pneumococcal disease

- Dwyer-Lindgren L, Cork MA, Sligar A, Steuben KM, Wilson KF, Provost NR, et al. Mapping HIV prevalence in sub-Saharan Africa between 2000 and 2017. Nature 2019;570:189. https://doi.org/10.1038/s41586-019-1200-9.

  This article reports on changes in HIV prevalence in sSA over 15 years. The results indicate that HIV prevalence is still high at country and sub-country levels underlining the importance of control of pneumococcal disease in this group through optimal pneumococcal vaccination strategies as proposed in this paper.

- Flasche S, Lipsitch M, Ojal J, Pinsent A. Estimating the contribution of different age strata to vaccine serotype pneumococcal transmission in the pre vaccine era: a modelling study. BMC Medicine 2020;18. https://doi.org/10.1186/s12916-020-01601-1.

  This study stresses on the importance of pre-school children vaccination but also highlights the significance of vaccinating school-aged children for substantial herd immunity, particularly in high pneumococcal transmission settings where their

contribution to transmission is high. This aligns with our proposal in this paper for a switch from 3p+0 to a 2p+1 or 2p+1(+1) schedule.

- French N, Gordon SB, Mwalukomo T, White SA, Mwafulirwa G, Longwe H, et al. A Trial of a 7-Valent Pneumococcal Conjugate Vaccine in HIV-Infected Adults. New England Journal of Medicine 2010;362:812–22. https://doi.org/10.1056/NEJMoa0903029.
- Bonnave C, Mertens D, Peetermans W, Cobbaert K, Ghesquiere B, Deschodt M, et al. Adult vaccination for pneumococcal disease: a comparison of the national guidelines in Europe. Eur J Clin Microbiol Infect Dis 2019;38:785–91.

  The first article reports on substantial vaccine efficacy of PCV7 against IPD in HIV-infected adults in sSA in a trial setting. The second article provides data on different pneumococcal vaccination schedules (PCV and PPV) against pneumococcal disease in HIV-infected adults in high-income countries. Both articles support our proposal for scheduling and effectiveness of direct vaccination in HIV-infected adults against pneumococcal disease with a PCV13 followed by PPV23.

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Author Contribution

DT, NF, SF conceived the idea for the manuscript. DT wrote the first manuscript draft with support from AP, OJ, KEG, NF and SF. All authors contributed to, and approved the final draft. All authors declare that they meet the ICMJE criteria for authorship.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Chapter 3: Research paper 2

Estimating the contribution of HIV-infected adults to household pneumococcal transmission in South Africa, 2016-2018: A hidden Markov modelling study.

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Estimating the contribution of HIV-infected adults to household pneumococcal transmission in South Africa, 2016-2018: A hidden Markov modelling study.

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Abstract

Human immunodeficiency virus (HIV) infected adults are at a higher risk of pneumococcal colonisation and disease, even while receiving antiretroviral therapy (ART). To help evaluate potential indirect effects of vaccination of HIV-infected adults, we assessed whether HIV-infected adults disproportionately contribute to household transmission of pneumococci. We constructed a hidden Markov model to capture the dynamics of pneumococcal carriage acquisition and clearance observed during a longitudinal household-based nasopharyngeal swabbing study, while accounting for sample misclassifications. Households were followed-up twice weekly for approximately 10 months each year during a three-year study period for nasopharyngeal carriage detection via real-time PCR. We estimated the effect of participant's age, HIV status, presence of a HIV-infected adult within the household and other covariates on pneumococcal acquisition and clearance probabilities. Of 1,684 individuals enrolled, 279 (16.6%) were younger children (<5 years-old) of whom 4 (1.5%) were HIV-infected and 726 (43.1%) were adults (≥18 years-old) of whom 214 (30.4%) were HIV-infected, most (173, 81.2%) with high CD4+ count. The observed range of pneumococcal carriage prevalence across visits was substantially higher in younger children (56.9-80.5%) than older children (5-17 years-old) (31.7-50.0%) or adults (11.5-23.5%). We estimate that 14.4% (95% Confidence Interval [CI]: 13.7-15.0) of pneumococcal-negative swabs were false negatives. Daily carriage acquisition probabilities among HIV-uninfected younger children were similar in households with and without HIV-infected adults (hazard ratio: 0.95, 95%CI: 0.91-1.01). Longer average carriage duration (11.4 days, 95%CI: 10.2-12.8 vs 6.0 days, 95%CI: 5.6 - 6.3) and higher median carriage density (622 genome equivalents per millilitre, 95%CI: 507-714 vs 389, 95%CI: 311.1-435.5) were estimated in HIV-infected vs HIV-uninfected adults. The use of ART and antibiotics substantially reduced carriage duration in all age groups, and acquisition rates increased with household size. Although South African HIV-infected adults

on ART have longer carriage duration and density than their HIV-uninfected counterparts, they show similar patterns of pneumococcal acquisition and onward transmission.

Author summary

We assessed the contribution of HIV-infected adults to household pneumococcal transmission by applying a hidden Markov model to pneumococcal cohort data comprising 115,595 nasopharyngeal samples from 1,684 individuals in rural and urban settings in South Africa. We estimated 14.4% of sample misclassifications (false negatives), representing 85.6% sensitivity of a test that was used to detect pneumococcus. Pneumococcal carriage prevalence and acquisition rates, and average duration were usually higher in younger or older children than adults. The use of ART and antibiotics reduced the average carriage duration across all age and HIV groups, and carriage acquisition risks increased in larger household sizes. Despite the longer average carriage duration and higher median carriage density in HIV-infected than HIV-uninfected adults, we found similar carriage acquisition and onward transmission risks in the dual groups. These findings suggest that vaccinating HIV-infected adults on ART with PCV would reduce their risk for pneumococcal disease but may add little to the indirect protection against carriage of the rest of the population.

Introduction

Streptococcus pneumoniae (pneumococcus) caused an estimated 3.7 million cases of invasive pneumococcal disease (IPD) and 317,300 deaths in children <5 years-old, globally in 2015 [1,2]. While severe disease is largely concentrated in young children and older adults, human immunodeficiency virus (HIV)-infected adults are also at an increased risk of both colonisation and IPD [3–7]. HIV affects the T and B cell function, resulting in impaired responses to control pneumococcal carriage at mucosal level [8–10]. Although the universal scale-up of antiretroviral therapy (ART) [11,12] has successfully reduced IPD risk in HIV-infected adults [13,14], the IPD risk remains elevated if compared to HIV-uninfected adults [5,6]. ART partially reconstitutes mucosal immunity by increasing B and T cell quantity and functionality [8,15], but deficiencies in humoral mucosal response due to depleted or persistent defects in memory cell function persist after ART initiation [16–18].

Despite mature pneumococcal conjugate vaccine (PCV) infant immunisation programmes, continued circulation of vaccine preventable serotypes in adults has been observed throughout Africa [19–25]. In some countries, such as Malawi, Mozambique, and Kenya, this intersects with areas of high HIV prevalence. Adult HIV prevalence in Africa remains high [26] as a consequence of improved survival with ART use [11,12] and persistently high HIV incidence [27], thus the high risk of pneumococcal carriage and IPD in HIV-infected adults in Africa remains a concern.

Presently, no pneumococcal immunisation program for HIV-infected adults exist in South Africa and low-income African countries [28]. Vaccination of African HIV-infected adults with PCV, similar to the recommendations in many high-income countries, may not only reduce their disease burden but also vaccine serotype pneumococcal acquisition and hence

onward transmission and may thus benefit non-vaccinated populations [29]. We hypothesised that children living with HIV-infected adults have higher rates of pneumococcal carriage acquisition due to increased exposure from frequently colonised HIV-infected adults who usually have a prolonged higher carriage prevalence [5]. In this study, we assessed whether HIV-infected adults contribute more to pneumococcal transmission within the household than their HIV-uninfected counterparts.

Methods

Ethics Statement

The longitudinal pneumococcal carriage data described in this study were obtained from South African children and adults through a written consent as part of the PHIRST study. For a child participant, written consent was obtained from a parent or guardian. The use of data was granted by the University of Witwatersrand, Human Research Ethics Committee (HREC) and the Protocol Review Committee (PRC) under approval #150808, the US CDC's Institutional Review Board relied on the local review (#6840), and the London School of Hygiene & Tropical Medicine Observational Research Ethics Committee under approval #17902.

Data description

The temporal dynamics of pneumococcal colonisation were observed in a cohort study (Prospective Household Observational Cohort Study of Influenza, Respiratory Syncytial Virus and Other Respiratory Pathogens Community Burden and Transmission Dynamics - PHIRST) conducted between 2016 and 2018 in a rural (Agincourt) and an urban (Klerksdorp) community in South Africa. Households were randomly selected, and were eligible for the study if they had ≥3 household members and the household members resided in the

household for ≥1 year prior to study commencement, had no plan to relocate during study duration, and consented to participate in the study. Also, enrolment ensured that more than half of the households included at least one child aged <5 years, and a new cohort was enrolled every study year [30,31].

A total of 1,684 individuals from 327 households were enrolled and followed up from May to October in 2016 and January to October in 2017 and 2018. The median household size was 5 (interquartile range 4-7). Nasopharyngeal (NP) swabs were taken twice weekly, resulting in 115,595 total NP samples from 1,684 individuals. The swabs were tested for the presence of pneumococci using real-time quantitative polymerase chain reaction (qPCR), targeting the autolysin (*lytA*) gene [32]. Serotyping was not performed. On enrolment, the demographic characteristics of the study participants were recorded, and household members were tested for HIV infection according to the double rapid test algorithm in South Africa [33]. Participants were considered HIV infected if they had two positive rapid HIV tests, evidence of a positive HIV laboratory result or evidence of ART treatment. Participants were considered HIV uninfected if they had a documented negative HIV test result. A documented HIV negative status for the mother confirmed HIV negative status for a child aged <10 years. HIV infection was confirmed by PCR in children aged <18 months. In all HIV infected individuals, specimens were collected for CD4+ T cell and quantitative HIV viral load testing. Newly HIV diagnosed patients were referred to the local HIV/ART clinic [30].

Modelling framework

We used a continuous time, time homogeneous, hidden Markov model (HMM) which assumed a Susceptible – Infected – Susceptible (SIS) framework [34–40], to fit to individual level trajectories of colonisation during the study period. An individual can be either infected

(I or 2) and currently carrying pneumococci or be susceptible (S or 1). Thus, the model can be described by transition intensities between S and I for acquisition (q_{12}) and clearance (q_{21}) in the transition intensity matrix $Q = \begin{pmatrix} -q_{12} & q_{12} \\ q_{21} & -q_{21} \end{pmatrix}$. The effect ($\beta$) of i^{th} individual covariate (z_i) for acquisition and clearance rates over all transitions (T) are incorporated via proportional hazard models $q_{12}(z_i(t)) = q_{12}^{(0)} exp\left(\beta_{12}^T z_i(t)\right)$ and $q_{21}(z_i(t)) = q_{21}^{(0)} exp\left(\beta_{21}^T z_i(t)\right)$, respectively. To obtain the transition probabilities, matrix $P = \begin{pmatrix} 1-p_{12} & p_{12} \\ p_{21} & 1-p_{21} \end{pmatrix}$ is defined and explicitly calculated through matrix exponential, $P = \exp\left(Q(t)\right)$, where p_{12} is the probability of being in state 2 (I) at time $t > 0$, given that the previous state was 1 (S). A more detailed description of the Markov transition process is provided in the Supplement.

In the hidden Markov modelling (HMM) framework [36,41–46], the states S and I of the Markov Chain ($X_i(t)$) for individual i at time t are not observed directly, but approximated by the results of a NP swab. The link between the modelled, true infection status and observed pneumococcal carriage states in the model ($Y_i(t)$) is governed by emission probabilities conditional on the unobserved state. We assumed 100% specificity of the NP swab and the PCR (no false positive) while estimating the proportion of false negative results (e) probabilistically (observed vs hidden/truth states). Hence, the emission matrix is given as $E = \begin{pmatrix} 1 & 0 \\ e_{21} & 1-e_{21} \end{pmatrix}$ where $e_{21} = \Pr(Y_i(t) = 1 \mid X_i(t) = 2)$.

We assumed that the observed states are conditionally independent given the values of the unobserved states and that the future Markov chain is independent of its history beyond the current state (Markov property) (Fig 1). Thus, the likelihood is the product of the emission

probability density and the transition probability of hidden Markov chain summed over all possible paths of the hidden states (explicitly defined in the Supplement).

Our model assumed that carriage acquisition at the current observation point was a function of individual age group (younger child aged <5 years, older child aged 5-17 years, or adult aged ≥18 years), HIV status (infected or uninfected), number of HIV-infected adult(s) in the household, place of carriage exposure (household or community), and household size. Carriage duration was modified by individual age, HIV status, ART status, and antibiotic use. The place of carriage exposure is generally unknown without fine-scale serotype data. Crudely, we assumed that if a household member is currently infected while all other household members were susceptible at the last observation point, then current carriage acquisition of that member was attributable to community transmission [34]. Otherwise, we assumed that the transmission was from within the same household (Fig 1).

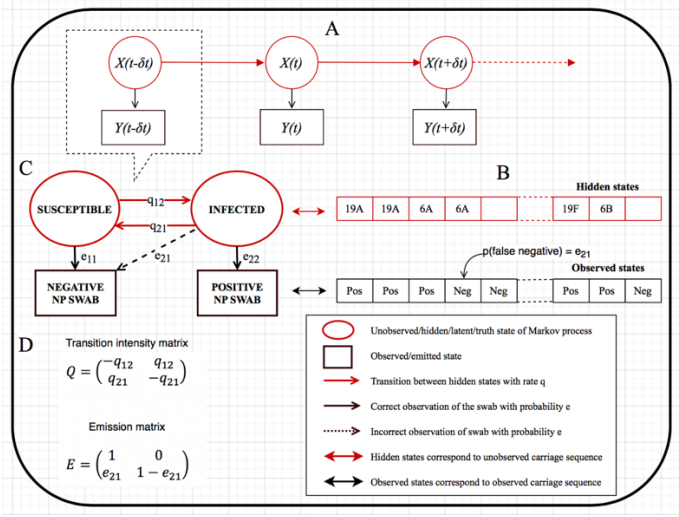

Fig 1. Susceptible-infected-susceptible (SIS) hidden Markov model schemas of pneumococcal carriage dynamics in South African households between 2016–2018. Continuous-time time-homogeneous hidden Markov model where $X(t)$ represents hidden states, and $Y(t)$ observed states, and in which $Y(t)$ is conditionally independent given $X(t)$ and

the Markov property holds (A). Pneumococcal nasopharynx (NP) carriage sequence of a specified individual representing hidden and observed states, with a probability that an individual truly carrying a pneumococcal serotype may be detected negative by a real-time quantitative polymerase chain reaction test (B). An SIS hidden Markov model structure that captures a snapshot of part A and carriage sequence of part B in order to estimate transition rates and probability of misclassification/false negative (C). Transition intensity matrix, Q, and emission matrix, E, respectively capture the SIS model transition rates and emission or misclassification probability in part C to compute the maximum likelihood estimates of transition intensities and misclassification probability (D).

Model fit, convergence and prediction

The model was fitted to longitudinal data of pneumococcal carriage dynamics in a maximum likelihood framework using Bound Optimisation By Quadratic Approximation optim algorithm facilitated by msm R package [36,47]. To ascertain convergence of the model, we purposefully selected five unique pairs of initial transition intensities {S, I} for the Q matrix, then refitted the model five times, each time starting a Markov chain with a unique dyad and iterating 1,000 times to obtain similar final transition intensities and -2log-likelihood. Model predictions were assessed by comparing infection and susceptibility prevalence in 14-day intervals for the observed data to the fitted values. (S1 Fig in S1 File) [36].

Decoding the underlying carriage sequence

After fitting the HMM, a Viterbi algorithm with the msm function was used to recursively construct the sequence of pneumococcal carriage with the highest probability through the hidden states [48]. The probability of each hidden state at each observation point, conditionally on all the data was computed using Baum-Welch forward/backward algorithm.

Thus, an overall misclassification probability of the observed states given the hidden states was computed. Model estimates of carriage transition intensity and probability were adjusted for misclassification probability (S2 Fig in S1 File).

Sensitivity analysis

In a sensitivity analysis, three alternative and potentially more parsimonious models were fitted separately to the data. Fits of these models were compared to the main model using Akaike Information Criterion (AIC) [49] and checked whether they yielded qualitatively different results to the main model. Each of the four fitted models assumed the same number of covariates to modify carriage acquisition intensity but varying number of covariates assumed to modify carriage duration. Potential modifiers of carriage duration included age and HIV status for model 1; age, HIV status and antibiotic use for model 2; age, HIV status and viral load-based ART status for model 3; and age, HIV status, antibiotic use and viral load-based ART status for main model 4 (S1 Table).

Further, we examined the impact of alternative stratification of covariates on the changes in carriage transition probabilities: (i) while the main analysis estimated age- and HIV-stratified carriage acquisition rates comparing households with ≥1 HIV-infected adult(s) versus households without HIV-infected adults, in the sensitivity analysis, we estimated age- and HIV-stratified carriage acquisition rates comparing households with 0,1, 2, 3, 4 and 5 HIV-infected adult(s) and (ii) rather than assuming time-homogeneous intensities throughout the study period, we relaxed this assumption by fitting a time-inhomogeneous model with yearly piecewise follow-up periods; 2016, 2017, and 2018 (S3 Fig in S1 File).

Statistical significance was set at <0.05. All analyses were conducted in R v3.5.0 [36,50] and are available via https://github.com/deusthindwa/hmm.pneumococcus.hiv.south-africa.

Results

Descriptive analysis

A total of 327 households were recruited in the PHIRST study of which 166 (50.8%) had at least one member living with HIV infection. At enrolment, of 1,684 individuals included in the study, 279 (16.6%) were younger children aged less than 5 years old of whom 4 (1.5%) were HIV-infected, and 679 (40.3%) were older children aged between 5-17 years old of whom 31 (4.7%) were HIV-infected. Among the 726 (43.1%) study participants aged 18 years or older ("adults"), 214 (30.4%) were HIV-infected, and 505 (69.6%) were females. Among those HIV-infected adults, 196 (86.7%) self-reported to be on ART, although only 151 (79.5%) had CD4+ cell count of more than 350. Most adults were non-smokers (69.6%) and did not regularly consume alcohol (57.4%). A similar proportion of children lived in households with (50.6%) and without (49.4%) at least one HIV-infected adult. Among 231 younger children with vaccine information available, 227 (98.3%) received first PCV dose at 6 weeks, 225 (97.4%) second dose at 14 weeks and 216 (93.5%) third dose at 9 months of age (Table 1).

Table 1. Baseline demographic and clinical characteristics of children and adults who were followed up twice weekly for ten months for nasopharynx swabbing for pneumococcal carriage in South African households between 2016 and 2018.

Description	Total N=1,684	Younger children <5 years n=279 (16.6%)	Older children 5-17 years n=679 (40.3%)	Adults ≥18 years n=726 (43.1%)
Mean age (SD)	22.1 (±19.8)	2.2 (±1.3)	10.5 (±3.7)	40.5 (±16.7)
Study site Agincourt (rural) Klerksdorp (semi-urban)	 849 (50.4) 835 (49.6)	 171 (61.3) 108 (38.7)	 376 (55.4) 303 (44.6)	 302 (41.6) 424 (58.4)

Sex				
Female	1,009 (59.9)	137 (49.1)	367 (54.1)	505 (69.6)
Male	675 (40.1)	142 (50.9)	312 (45.9)	221 (30.4)
HIV status				
Negative (-)	1,379 (84.7)	256 (98.5)	634 (95.3)	489 (69.6)
Positive (+)	249 (15.3)	4 (1.5)	31 (4.7)	214 (30.4)
Viral-load based ART status†				
Not on ART	93 (40.8)	1 (50.0)	13 (52.0)	79 (39.3)
On ART	135 (59.2)	1 (50.0)	12 (48.0)	122 (60.7)
Self-reported ART status				
Not on ART	30 (13.2)	0 (0.0)	1 (3.8)	29 (14.5)
On ART	198 (86.8)	2 (100.0)	25 (96.2)	171 (85.5)
Mean CD4 count (SD)	673 (±430)	1,210 (±13.4)	857 (±418)	645 (±426)
CD4+ cell count‡				
Low	49 (22.8)	0 (0.0)	10 (43.5)	39 (20.5)
High	166 (77.2)	2 (100.0)	13 (56.5)	151 (79.5)
Living with ≥1 HIV+ adults				
No	818 (48.7)	133 (47.8)	346 (51.1)	339 (46.9)
Yes	860 (51.3)	145 (52.2)	331 (48.9)	384 (53.1)
PCV13 doses received#				
At 6 weeks	227 (98.3)	227 (98.3)	N/A	N/A
At 14 weeks	225 (97.4)	225 (97.4)	N/A	N/A
At 9 months	216 (93.5)	216 (93.5)	N/A	N/A
Smoking (≥18 years)				
No	505 (69.6)	N/A	N/A	505 (69.6)
Yes	221 (30.4)	N/A	N/A	221 (30.4)
Alcohol use (≥18 years)				
No	417 (57.4)	N/A	N/A	417 (57.4)
Yes	309 (42.6)	N/A	N/A	309 (42.6)

† ART use status based on viral load results (on ART = Undetected; Not on ART = <20 copies per ml)
‡ Low CD4+ count ≤350 cells/mm^3 and high CD4+ count >350 cells/mm^3 in adults, and low CD4+ count ≤750 cells/mm^3 and high CD4+ count >750 cells/mm^3 in children, in HIV-INFECTED only
# Pneumococcal conjugate vaccine (PCV13) vaccination status in younger children from available records
Standard deviation (SD)
N/A not applicable

Carriage prevalence and density

We estimated carriage prevalence by dividing the number of PCR positive samples by the number of swabs taken per visit per age or HIV group. Among HIV-uninfected participants,

observed pneumococcal carriage prevalence was higher in younger children (range across visits: 56.9-80.5%, n=256) than older children (31.7-50.0%, n=634) and was lowest in adults (11.5-23.5%, n=489) (Fig 2A). Among HIV-infected participants, pneumococcal carriage prevalence fluctuated in younger children (0-100%, n=4), in older children (30-77%, n=31), and in adults (14-34%, n=214) (Fig 2A). The likelihood of detecting pneumococcal carriage during visits was higher for children than adults and for HIV-infected younger children or older children or adults than their HIV-uninfected counterparts (Fig 2B). Carriage prevalence among younger HIV-uninfected children was lower in households with less than 6 members (65.5%, 95%CI: 64.5-66.5) than in households with 6-10 (72.5%, 95%CI: 71.5-73.5) or household more than 10 members (85.6%, 95%CI: 82.4-88.8) but it was similar in HIV-infected children across household size groups (Fig 2C). Carriage prevalence fluctuated across visits by HIV-infection and sex in adults, with similar ranges between HIV-uninfected male adults 10.8-25.3% and HIV-uninfected female adults 10.2-24.0%, and between HIV-infected male adults 6.3-40.7% and HIV-infected female adults 12.3-34.6% (S5A Fig in S1 File).

Median pneumococcal carriage density, in genome equivalents per millilitre (GE/ml), was significantly higher in younger children (24,341, 95%CI: 22,638-26,122) than older children (3,490, 95%CI: 3,168-3,754) or adults (476, 95%CI: 429-522). Also, median carriage density was higher in HIV-infected than HIV-uninfected older children (11,156, 95%CI: 8,681-13,948 vs 3,221, 95%CI: 2,911-3,472) or adults (622, 95%CI: 507-714 vs 389, 95%CI: 311-435), and not in younger children (33,050, 95%CI: 22,690-42,293 vs 24,124, 95%CI: 22,547-25,838) (Fig 2D). Conversely, median carriage density was similar between those not on ART compared to those on ART in older children (9,624, 95%CI: 5,289-11,843 vs 8,818, 95%CI: 5,102-12,720) or adults (861, 95%CI: 508-1,001 vs 499, 95%CI: 382-586), and not

in younger children (25,430, 95%CI: 13,138-40,245 vs 91,566, 95%CI: 43,355-265,628) (Fig 2E). About 14.4%, 95%CI: 13.7-15.0 of negative NP swab results were estimated probabilistically to be false negatives.

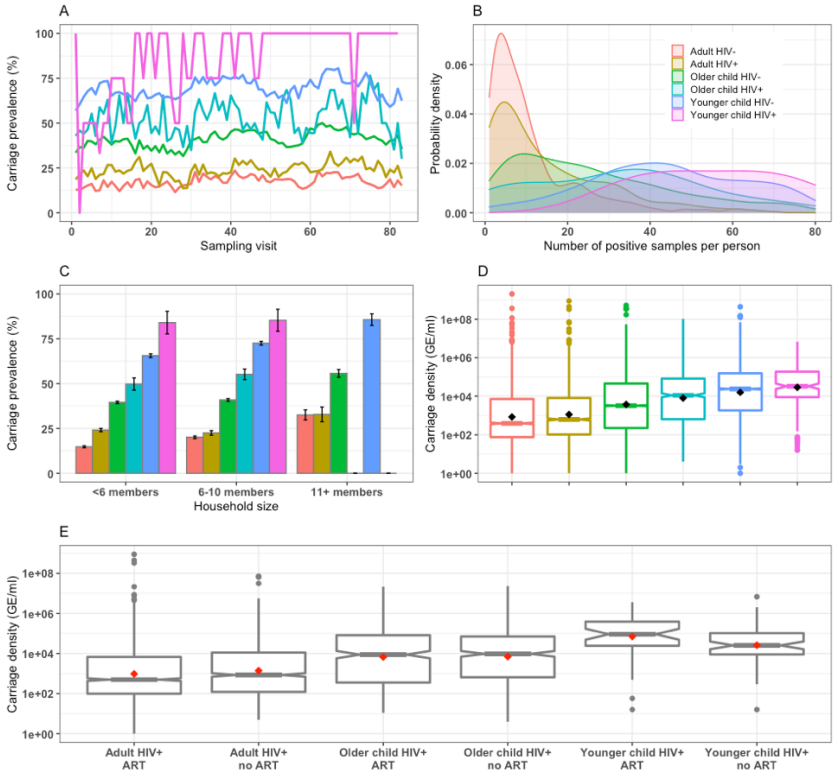

Fig 2. Human immunodeficiency virus (HIV)-stratified pneumococcal carriage dynamics in younger children (<5 years-old), older children (5–17 years-old) and adults (≥18 years-old) in South African households between 2016–2018. Age and HIV-stratified pneumococcal carriage prevalence by different nasopharyngeal sampling visits (A), the likelihood of detecting pneumococcal carriage during visits (B), pneumococcal carriage prevalence by household sizes with 95% confidence intervals (CI) (C) and carriage densities with mean (black diamond), median and associated 95%CI of median, 25th and 75th percentiles, minimum and maximum, and outlier where carriage density is measured as genome equivalents per millilitre (GE/ml) (D). Age and antiretroviral therapy (ART) stratified

carriage density with mean (red diamonds), median and associated 95%CI of median, 25th and 75th percentiles, minimum and maximum, and outlier (notched boxplot) (E).

Pneumococcal carriage acquisition

Overall, compared to adults, daily pneumococcal carriage acquisition rates were 1.15 (95%CI: 1.08-1.23) times higher in older children and 1.52 (95%CI: 1.38-1.68) times higher in young children, respectively.. Acquisition of carriage was more frequently observed when at least another household member was infected half a week before (and hence attributed to household transmission) than in previously uninfected households (1.80, 95%CI: 1.68-1.93). Irrespective of age and HIV status, acquisition rates from within the household increased with household size; by 1.05 (95%CI: 1.00-1.10) in households with 6-10 members and by 1.41 (95%CI: 1.24-1.60) in households with 11 or more members compared to households with less than 6 members. However, within household carriage acquisition rates in children, irrespective of age group and HIV status, were not higher in the households with at least one HIV-infected adult (0.95, 95%CI: 0.91-1.01) (Fig 3 and Table 2). In addition, daily carriage acquisition rates in HIV-uninfected younger children did not significantly vary between households with HIV-infected female adults (0.14, 95%CI: 0.12-0.17) and those with HIV-infected male adults (0.13, 95%CI: 0.11-0.15) (S5 Fig in S1 File).

We estimated 3.8 carriage acquisition episodes per year, (95%CI: 3.4-4.2) for HIV-infected younger children, 5.9 (95%CI: 5.4-6.3) for HIV-uninfected younger children, 7.4 (95%CI: 6.7-8.1) for HIV-infected older children and 10.6 (95%CI: 10.2-11.0) for HIV-uninfected older children from households with at least one HIV-infected adult, and these were similar to their counterparts from households without HIV-infected adults (3.8, 95%CI: 3.3-4.2 and

5.8, 95%CI: 5.4-6.3, and 7.3, 95%CI: 6.6-8.0 and 10.3, 95%CI: 9.9-10.8, respectively) (Fig 3 and Table B in S1 File).

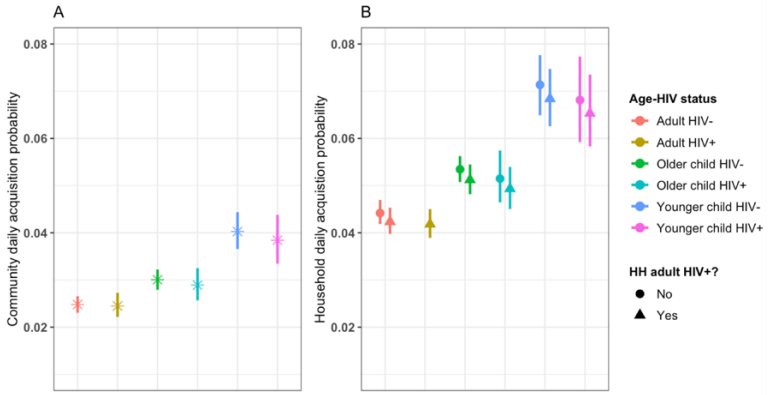

Fig 3. Community and within household (HH) acquisitions of pneumococcal carriage in younger children (<5 years-old), older children (5–17 years-old) and adults (≥18 years-old) in South African households between 2016–2018. Age and human immunodeficiency virus (HIV) stratified estimates of community carriage acquisition probability per day (A) and within household carriage acquisition probability per day over the total follow-up period (B), comparing household without HIV-infected adult(s) (HIV-) to households with HIV-infected adult(s).

Table 2. Effects of included covariates on pneumococcal acquisition and clearance rates estimated in the hidden Markov model.

Description	**Hazard Ratio (95%CI)**‡
Pneumococcal carriage acquisition	
Age in years (y) Adult, ≥18y Older child, 5-17y Younger child, <5y	 Reference 1.15 (1.08-1.23) 1.52 (1.38-1.68)
HIV status Negative Positive	 Reference 0.95 (0.87- 1.04)
Children living with ≥1 HIV-infected adults	

No	Reference
Yes	0.95 (0.91- 1.01)
Place of carriage exposure	
Community	Reference
Within household	1.80 (1.68- 1.93)
Household size	
<6 members	Reference
6-10 members	1.05 (1.00-1.10)
11+ members	1.41 (1.24-1.60)
Pneumococcal carriage clearance	
Age in years (y)	
Adult, ≥18y	Reference
Older child, 5-17	0.34 (0.31-0.36)
Younger child, <5y	0.10 (0.09-0.12)
HIV status	
Negative	Reference
Positive	0.52 (0.46-0.59)
Antibiotic use	
No	Reference
Yes	1.47 (0.67-3.25)
Viral load-based ART status†	
Not on ART	Reference
On ART	1.29 (1.13-1.47)
† ART use status based on viral load results	
‡ 95% confidence interval (95%CI)	

Pneumococcal carriage duration

The average duration of pneumococcal carriage was highest in HIV-infected and HIV-uninfected younger children (107.9 days, 95%CI: 92.1-124.7 and 56.3 days, 95%CI: 51.1-62.1) followed by HIV-infected and HIV-uninfected older children (33.9 days, 95%CI: 29.9-38.6 and 17.9 days, 95%CI: 16.8-18.5), and HIV-infected and HIV-uninfected adults (11.4 days, 95%CI: 10.2-12.8 and 6.0 days, 95%CI: 5.6-6.3) (Fig 4C and 4D and Table C in S1 File).

Pneumococcal carriage cleared slower in older children (Hazard Ratio [HR]: 0.34, 95%CI: 0.31-0.36) and younger children (HR: 0.10, 95%CI: 0.09-0.12) when compared to adults. Carriage clearance was slower in HIV-infected than in HIV-uninfected individuals (HR: 0.52, 95%CI: 0.46-0.59), and faster in HIV-infected individuals with successfully suppressed viral load than in those without successful viral suppression (HR: 1.29, 95%CI: 1.13-1.47) (Fig 4B and Table 2). Antibiotic use may have accelerated pneumococcal clearance; however, the effect was not statistically significant (HR: 1.47, 95%CI: 0.67-3.25) (Fig 4A and Table 2).

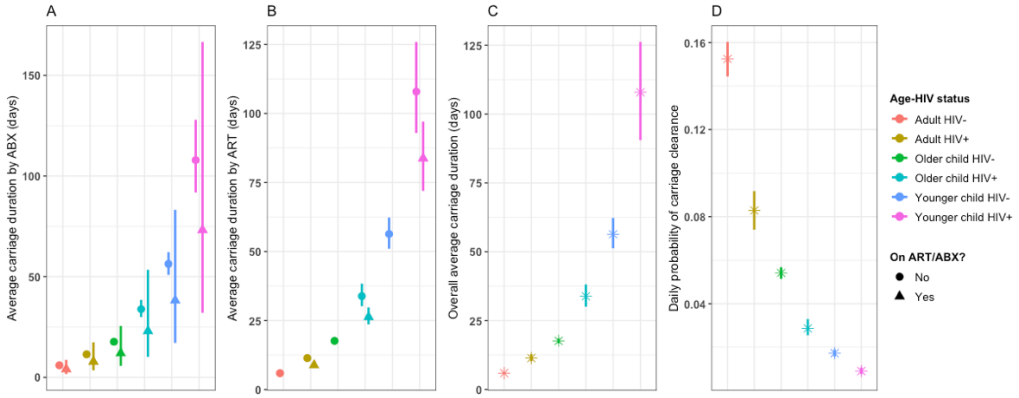

Fig 4. Duration of pneumococcal carriage in younger children (<5 years-old), older children (5–17 years-old) and adults (≥18 years-old) in South African households between 2016–2018. Age and human immunodeficiency virus (HIV) stratified average carriage duration in days comparing individuals on antibiotics (ABX) (triangular shape) to those not on ABX (circular shape) (A), and individuals on antiretroviral therapy (ART) (triangle shape) to those not on ART (circle shape) (B). Age and HIV stratified overall average carriage duration in days (C). Age and HIV stratified daily probability of carriage clearance (D).

Sensitivity analysis

In the sensitivity analysis, a model that included age, HIV status, antibiotic use, and ART status as potential modifiers for pneumococcal carriage duration had the lowest AIC score as

well as for including both antibiotic use and ART status (Table A in S1 File). Increasing the number of HIV-infected adults within household to 1, 2, 3, 4, and 5 resulted in similar estimates of pneumococcal carriage acquisition in younger or older children (S3A Fig in S1 File). Our results were also robust when instead of assuming a time homogeneous hidden Markov model, we allowed for the estimation of time varying transition probabilities (S3B Fig in S1 File)

Discussion

We used a HMM to better understand pneumococcal carriage dynamics, and the role of HIV-infected adults in it, using data from a densely sampled longitudinal South African cohort using data from 115,595 nasopharyngeal swabs. We estimated that children have higher acquisition rates and duration of carriage than adults, and that, within a household, HIV-infected adults are not more likely to transmit pneumococci to children than HIV-uninfected adults. Pneumococcal acquisition events increased with larger household size irrespective of age and HIV status. Although ART use reduced pneumococcal carriage duration in HIV-infected children and adults, they still carry pneumococci for longer than their HIV-uninfected counterparts.

Heterogeneous household acquisition rates higher in children than adults have been reported previously [34,51–55], reflecting setting-specific population mixing behaviour and immunisation levels. Similarly, and for the first time in the presence of a mature infant PCV routine vaccination programme, we find that children both have higher acquisition rates than adults and carry pneumococci for longer, making them a likely key source for pneumococcal transmission in and beyond the household [56,57]. Moreover, adults simply have far lower carriage duration than children. So, even though HIV-infected adults have slightly longer

carriage duration, the risk of carriage acquisition in children from an adult is far lower than from another child or in the community.

We postulated that HIV-infected adults were more likely to carry pneumococci and may have higher carriage density which individually or in combination may increase their risk for pneumococcal transmission compared to HIV-uninfected adults. Thus, carriage density was not controlled in this model for being on the causal pathway. Moreover, if carriage density indeed influences carriage transmission, then false negatives in low density carriers are partially captured because individuals who are more transmissible are more likely to be correctly detected. Prior to infant PCV introduction, a study in Malawi showed that HIV-infected adults on ART had higher carriage prevalence than those not on ART [5], and two studies in South Africa also found that HIV-infected adults (mothers) had higher carriage prevalence than their HIV-uninfected counterparts, irrespective of ART status [34,51]. In addition, HIV-infected adults (mothers) were found to transmit pneumococci to their children more often than HIV-uninfected peers [34]. We generated additional evidence showing that, in the PCV era, carriage prevalence is slightly increased in HIV-infected adults on ART compared to HIV-uninfected adults as a result of reduced carriage clearance rates. We also show that median carriage density is higher in HIV-infected than HIV-uninfected adults. However, we find no evidence that carriage density is modified by ART status in HIV-infected adults (Fig 2). Further research may need to investigate whether differential effects of ART on pneumococcal carriage density in adults by country may be driven by types of ART regimens used.

Furthermore, our model estimates that the presence of an HIV-infected adult in the household does not increase the risk for pneumococcal carriage acquisition in co-habiting children.

Although it is possible that there may have been other HIV-infected adults within households who were not enrolled into the study, it is unlikely this would alter the results given the insensitive acquisition estimates with increasing number of HIV-infected adults within household (S3A Fig in S1 File). These findings support the notion that ART largely, but not completely, reconstitutes the anti-pneumococcal mucosal immune response in HIV-infected adults [8]. This would imply that HIV-infected adults do not contribute disproportionally to pneumococcal transmission when on ART and hence that their vaccination is unlikely to substantially add to the herd protection already induced by the childhood immunisation programme although vaccination will provide direct protection against IPD in HIV-infected adults.

Our observation of increasing pneumococcal carriage acquisition rates with higher household size has also been reported previously [38] and suggests density dependent transmission in the household [58]. In line with evidence before infant PCV introduction [34,38], we find that pneumococcal carriage acquisition probabilities from the community were higher in children than in adults irrespective of HIV status, likely in part due to frequent effective contacts among playschool children [51,59] and immature immunity in children relatively to adults. We also estimate that children were twice as likely to get infected from within the household than from the community. However, we base this inference on the identified pneumococcal carriage in a household member at the previous visit. On the other hand, unlike previous household transmission models [34,38], our main model did not explicitly account for the number of other house members with carriage when estimating individual probability to carriage acquisition. However, it included a household size covariate to adjust for the contribution to carriage acquisition from housemates. Since pneumococcal infection rates usually increase with household size [38], this ensured that an individual living in a

household with more members and likely to spread pneumococci has higher probability to carriage acquisition than smaller households with potentially fewer carrying individuals. A potential caveat could be if only a relatively small number of persons in a large household are indeed carrying which could overestimate infection contribution (S6 Fig in S1 File).

In the absence of serotyping of the pneumococcal isolates, our inferences may be prone to overestimation within household transmission by linking family members who in fact were infected with different pneumococcal serotypes. Similarly, serotyping would enhance our ability to differentiate a single and long carriage episode from almost immediate re-acquisition or the clearance of the dominant serotype while the previously subdominant serotype persists. This may have led to an overestimation of carriage duration and underestimated clearance rates. However, the mean carriage duration of 56 days (51-62) in HIV-uninfected children estimated in this study aligns with studies that used serotype data [34,37,51,60]. While both the estimates for duration of carriage and the contribution of household transmission may be somewhat exaggerated, the lack of serotyping should not have affected our primary outcome, the relative contribution of HIV infected adults to pneumococcal transmission.

The use of ART, as inferred from measured viral load in study participants, reduced pneumococcal carriage duration by 22% compared to no ART use within each age group of HIV-infected participants. However, mean pneumococcal carriage duration remained slightly higher than their HIV-uninfected counterparts (Fig 4). Our model also estimated the sensitivity of the swabbing and qPCR testing regime for the detection of pneumococcal carriage. We estimate that about 1 in 7 swabs were misclassified as pneumococcal negative. False negatives might have arisen as a result of the sampling technique or if samples

contained insufficient quantities of bacteria to successfully amplify and detect [58]. We assumed 100% specificity of an assay targeting the autolysin gene as the probability of false positives is seemingly very low [32,60]. However, lower specificity would yield slightly lower acquisition rates than estimated in this study. Our estimated misclassification probability in this study is within 10-20% range of values that were reported elsewhere [60,61].

In conclusion, we used one of the most densely sampled longitudinal pneumococcal carriage studies to infer the role of HIV-infected adults in pneumococcal transmission in the PCV and ART era. We find that the transmission risk from HIV-infected adults largely aligns with that of their uninfected counterpart. This implies that PCV use in HIV-infected adults who have access to ART would reduce their risk for pneumococcal disease but may have little added benefit over vaccinating other adults to the indirect protection against carriage of the rest of the population.

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Disclaimer

The findings and conclusions in this publication are those of the authors and do not necessarily represent the official position of the United States Centers for Disease Control and Prevention, the NIHR or the Department of Health and Social Care.

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Supplementary or supporting information

Multi-state Markov model of pneumococcal carriage dynamics

A continuous-time time-homogeneous Markov model of pneumococcal carriage dynamics consists of susceptible (S) and infected (I) states, and 1,684 individuals, each of whom is in S or I state at any observation point. S or I state occupied by i^{th} individual at time *t* is denoted by $X_i(t)$, and movement of individuals between S and I states is governed by a set of transition intensities, (q_{12}) or (q_{21}) where {1,2}={S,I}, which may depend on the time and a set of potential individual covariates. The transition intensity represents instantaneous risk of moving from state S to I or I to S per unit time, e.g.

$$q_{12}(t;z) = \lim_{\delta_t \to 0} \Pr\left(X_i(t+\delta_t) = I \mid X_i(t) = S\right)/\delta_t \qquad (1)$$

Transition intensities form a 2X2 matrix, Q, whose rows sum up to 0 so that the diagonal entries are

$q_{22} := -q_{21}$ *or* $q_{11} := -q_{12}$. Thus, multi-state model fitting to observed individual pneumococcal carriage sequence data enables the Q matrix below to be estimated as follows.

$$Q = \begin{pmatrix} q_{11} & q_{12} \\ q_{21} & q_{22} \end{pmatrix} \rightarrow \begin{pmatrix} -q_{12} & q_{12} \\ q_{21} & -q_{21} \end{pmatrix} \qquad (2)$$

In this framework, the future state evolution of the Markov chain only depends on the current pneumococcal carriage state and not pneumococcal carriage history (H_t) before time *t*. It's assumed that all individuals in S have the same probability to move to I and back regardless of H_t. However, this probability is modified by individual covariates, z, so that $q_{12}(t;z;H_t) = q_{12}(t;z)$ or $q_{21}(t;z;H_t) = q_{21}(t;z)$. Moreover, our time-homogeneous model assumes that a transition intensity is constant over follow-up time and pneumococcal

carriage duration is distributed exponentially at a rate of $-q_{22}$ so that the mean pneumococcal carriage duration is $1/q_{21}$.

Covariates of pneumococcal carriage dynamics in a multi-state model

Pneumococcal carriage acquisition could be modified by age, human immunodeficiency virus (HIV), household adult HIV status, source of pneumococcal infection or household size. On the other hand, pneumococcal carriage duration may be altered by age, HIV status, antiretroviral therapy (ART) or antibiotic use. Proportional hazards model is used to estimate the effect (β) of i^{th} individual covariate (z_i) on transition intensity over all transitions (T) e.g. $q_{12}(z_i(t)) = q_{12}^{(0)} exp\left(\beta_{12}^T z_i(t)\right)$ and $q_{21}(z_i(t)) = q_{21}^{(0)} exp\left(\beta_{21}^T z_i(t)\right)$ for pneumococcal carriage acquisition and clearance respectively. The Q matrix with covariates is used for likelihood estimation, and is maximised over the baseline intensities $q_{12}^{(0)}$ and $q_{21}^{(0)}$, and the log-hazard ratios β_{12}^T and β_{21}^T.

Converting the transition intensity matrix into a transition probability matrix

A transition probability matrix (P) is derived from Q matrix using matrix exponentiation, such that $P = \exp\left(Q(t)\right)$, and used for likelihood estimation. In time-homogeneous intensities, entry of P matrix, $p_{12}(t)$, defines the probability of being in state I at time *t*, given that the system was in state S at a previously time, and vice versa for $p_{21}(t)$.

The transition probabilities form a 2X2 matrix, P, whose rows sum up to 1 so that the diagonal entries are $p_{22} := 1 - q_{21}$ *or* $p_{11} := 1 - q_{12}$. The P matrix is thus defined as follows

$$P = \begin{pmatrix} p_{11} & p_{12} \\ p_{21} & p_{22} \end{pmatrix} \rightarrow \begin{pmatrix} 1 - p_{12} & p_{12} \\ p_{21} & 1 - p_{21} \end{pmatrix} \quad (3)$$

Hidden Markov model of pneumococcal carriage dynamics

We extend the Markov model to a hidden Markov model (HMM) where S and I states are not directly observed. Observed nasopharyngeal (NP) swab results are governed by probability distribution (emission probability) conditionally on unobserved state. The evolution of the hidden Markov chain is governed by Q matrix and the observed NP swab results are states assumed to be misclassifications of the hidden states. If $X_i(t)$ is the hidden Markov chain of pneumococcal carriage dynamics of individual i at time t only known through realisations of NP swab result $Y_i(t)$, then the sensitivity of the quantitative polymerase chain reaction (qPCR) test used to detect pneumococcus was measured by the probability that the observed state is equal to a hidden state when carriage is detected. Thus, misclassification probability = 1-sensitivity e.g., $e_{21} = \Pr(Y_i(t) = S \mid X_i(t) = I)$.

Misclassification probabilities form a 2X2 matrix, E, whose rows sum up to 1 so that the diagonal entries are $e_{22} := 1 - e_{21}$ *or* $e_{11} := 1$ since we assume 100% specificity (no false positive tests). The E matrix is thus defined as follows

$$E = \begin{pmatrix} e_{11} & e_{12} \\ e_{21} & e_{22} \end{pmatrix} \rightarrow \begin{pmatrix} 1 & 0 \\ e_{21} & 1-e_{21} \end{pmatrix} \quad (4)$$

Likelihood contribution from uncensored pneumococcal carriage states

The likelihood estimation of the HMM is computed through forward algorithm based on matrix product, assuming the observed states are conditionally independent given the values of unobserved states and the future Markov chain is independent of past history. Thus, the individual (i) likelihood is integrated over all possible hidden states ($X_{i,j}$) at all observation points (j) adjusted for false negative NP swabs

$$L_{i,j} = \sum_{X_{i,1}} \Pr\left(Y_{i,1} \middle| X_{i,1}\right) \Pr\left(X_{i,1}\right) \ldots \ldots \sum_{X_{i,j}} \Pr\left(Y_{i,j} | X_{i,j}\right) \Pr\left(X_{ij} | X_{i,j-1}\right) \quad (5)$$

Likelihood contribution from censored pneumococcal carriage states

Missing NP swab result is assumed to be censored at each observation point they occurred as its exact value is unknown but largely known to be either I or S. If $Y(t_{i,j+1})$ is the pneumococcal carriage censored state Y of individual i at observation time $(j+1)$, then individual likelihood is given by

$$L_{i,j} = \sum_{m \in \{I,S\}} \Pr\left(Y(t_{i,j})\right) | m\left(t_{i,j+1} - t_{i,j}\right) \quad (6)$$

The maximum likelihood estimation is computed using Bound Optimization By Quadratic Approximation, a derivative-free iterative optim algorithm for finding the minimum -2log-likelihood of a HHM through construction of quadratic models by interpolation.

Sensitivity on hidden Markov models (fitting and comparison)

Four HMMs were fitted to the same observations using Akaike Information Criterion (AIC) defined by equation 7. AIC estimated a relative distance between the unknown true likelihood function of the data and the likelihood function of each HHM such that a lower AIC value was an indication that the fitted model was close to the true model. "Model 4" was selected because not only was its AIC score close to "Model 3" but also accounted for both antiretroviral therapy and antibiotics use.

$$AIC = -2L(\theta) + 2k \quad (7)$$

Where L is the log-likelihood of a fitted HMM with parameter set θ, and k is the number of parameters in the fitted HMM.

Table A. Multistate model comparisons between hidden Markov models of specified degree of freedom (*df*) using Akaike Information Criterion (AIC) after fitting the models to longitudinal pneumococcal carriage data in South African households, 2016-2018.

Model	Covariates for pneumococcal carriage acquisition	Covariates for pneumococcal carriage duration	*df*	AIC
1	Age + HIV status + household adult HIV status[&] + Carriage exposure[‡] + household size	Age + HIV status	14	95604.11
2	Age + HIV status + household adult HIV status[&] + Carriage exposure[‡] + household size	Age + HIV status + Antibiotic use	15	95605.36
3	Age + HIV status + household adult HIV status[&] + Carriage exposure[‡] + household size	Age + HIV status + ART status[#]	15	95592.17
4	Age + HIV status + household adult HIV status[&] + Carriage exposure[‡] + household size	Age + HIV status + Antibiotic use + ART status[#]	16	95593.38*

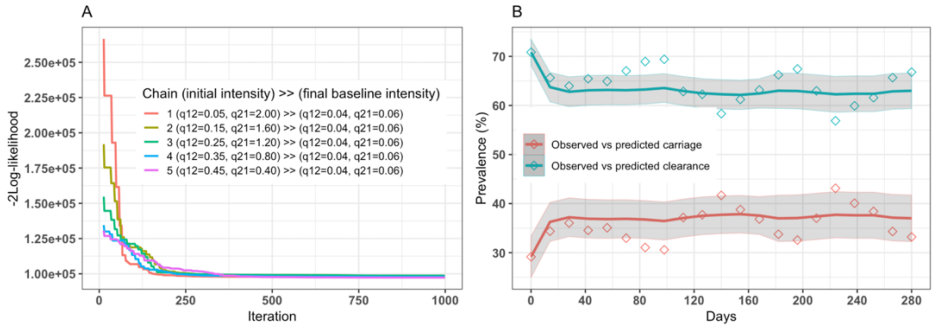
& Whether an individual is living in a household with HIV-infected adult(s) or HIV-uninfected adult(s) only.
‡ Whether carriage exposure may have come from within household or community (outside household).
# Antiretroviral (ART) status determined by viral load results.
* The main model 4 has AIC score close to model 3 but also accounts for both ART and antibiotic use.
HIV - Human immunodeficiency virus.

Table B. Maximum likelihood parameter estimates and 95% confidence intervals (95%CI) for acquisition probabilities within household and from community from a hidden Markov model that is fitted to pneumococcal carriage data in South African households, 2016-18.		
Age and HIV-specific estimates (per day)	Household with ≥1 HIV+ adult(s) (95%CI)	Household without HIV+ adult (95%CI)
Carriage acquisition within household		
Younger child HIV+	0.065 (0.058 - 0.073)	0.068 (0.060 - 0.078)
Younger child HIV-	0.068 (0.062 - 0.075)	0.071 (0.065 - 0.078)
Older child HIV+	0.049 (0.045 - 0.054)	0.051 (0.046 - 0.058)
Older child HIV-	0.051 (0.048 - 0.054)	0.053 (0.051 - 0.056)
Adult HIV+	0.042 (0.039 - 0.045)	NA
Adult HIV-	0.042 (0.040 - 0.045)	0.044 (0.042 - 0.047)
Carriage acquisition from community		
Younger child HIV+	0.038 (0.033 - 0.044)	
Younger child HIV-	0.040 (0.037 - 0.044)	
Older child HIV+	0.029 (0.026 - 0.033)	
Older child HIV-	0.030 (0.028 - 0.032)	
Adult HIV+	0.024 (0.022 - 0.027)	
Adult HIV-	0.025 (0.023 - 0.027)	
Human immunodeficiency virus infected (HIV+) or uninfected (HIV-)		

Table C. Maximum likelihood parameter estimates and 95% confidence intervals (95%CI) for carriage duration and by antibiotic use and antiretroviral therapy (ART) from a hidden Markov model that is fitted to pneumococcal carriage data in South African households, 2016-18.		
Age and HIV-specific estimates	Estimate (95%CI)	Estimate (95%CI)
Carriage duration (days)	Antibiotics use	No antibiotics use
Younger child HIV+	73.2 (34.2 - 157.5)	107.9 (92.4 - 125.8)
Younger child HIV-	38.2 (18.5 - 82.8)	56.3 (50.9 - 62.1)
Older child HIV+	23.0 (9.6 - 52.8)	33.9 (29.6 - 38.4)
Older child HIV-	12.0 (5.5 - 25.7)	17.7 (16.8 - 18.5)
Adult HIV+	7.7 (3.4 - 17.1)	11.4 (10.2 - 12.9)
Adult HIV-	4.0 (1.8 - 8.9)	6.0 (5.6 - 6.3)
Carriage duration (days)	On ART	Not on ART
Younger child HIV+	83.8 (72.3 - 95.5)	107.9 (92.5 - 125.4)
Younger child HIV-	NA	56.3 (50.9 - 62.3)
Older child HIV+	26.3 (23.4 - 29.6)	33.9 (29.8 - 38.7)
Older child HIV-	NA	17.7 (16.9 - 18.6)
Adult HIV+	8.9 (8.0 - 9.7)	11.4 (10.1 - 12.7)
Adult HIV-	NA	6.0 (5.6 - 6.3)
Carriage duration (days)	Overall	
Younger child HIV+	107.9 (92.1 - 124.7)	
Younger child HIV-	56.3 (51.1 - 62.1)	
Older child HIV+	33.9 (29.9 - 38.6)	
Older child HIV-	17.9 (16.8 - 18.5)	
Adult HIV+	11.4 (10.2 - 12.8)	
Adult HIV-	6.0 (5.6 - 6.3)	
Carriage clearance probability per day	Overall	
Younger child HIV+	0.009 (0.008 - 0.011)	
Younger child HIV-	0.017 (0.016 - 0.019)	
Older child HIV+	0.029 (0.025 - 0.032)	
Older child HIV-	0.054 (0.052 - 0.057)	
Adult HIV+	0.083 (0.074 - 0.092)	
Adult HIV-	0.152 (0.144 - 0.160)	

Checking convergence and predictions of a fitted Hidden Markov model

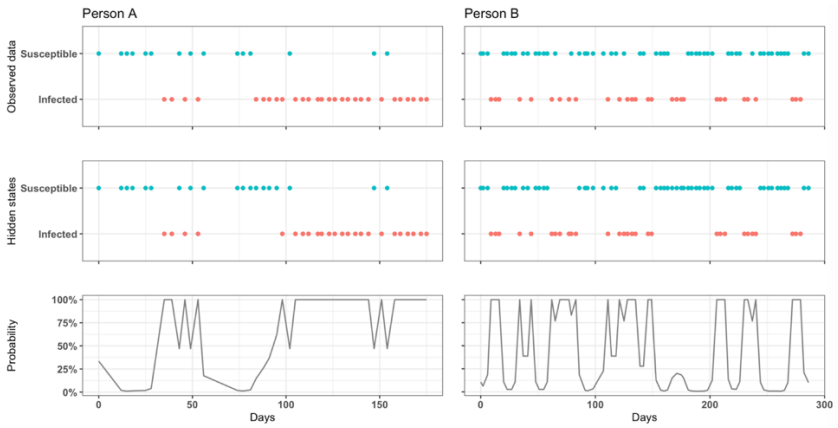
Convergence of the selected HMM was assured by running 5 Markov chains, each with 1000 iterations. Each chain was a unique pair of initial transition intensities converging to similar final baseline intensities and -2log-likelihood. To show how the HMM predicted the irregularly-observed process, we compared the proportions of pneumococcal carriage observed with predicted, grouped over 14-days intervals. We assumed (a) individual's state at arbitrary time was the same as the state at their previously observation time given high frequent pneumococcal carriage sampling and (b) the Markov process began at a common time for all individuals. If $n(t)$ individuals are under observation at time t, then the predicted number of individuals in I state at time t is $n(t)P(t)_{0,I}$, where $P(t)$ is the transition probability matrix.



S1 Fig. Hidden Markov model (HMM) convergence and predictions. HMM convergence estimated using maximum likelihood, given 5 Markov chains each with 1000 iterations. Each chain is a unique pair of initial infected (q_{12}) and susceptible (q_{21}) intensities converging to similar final baseline transition intensities, and 2*log-likelihood (A). HMM fitting assessment comparing the observed (diamond) to predicted (line) pneumococcal carriage and clearance with 95% predictive intervals of the model-fitted line, where observed data are grouped into 14-days intervals to compute fitted values (B).

Viterbi algorithm

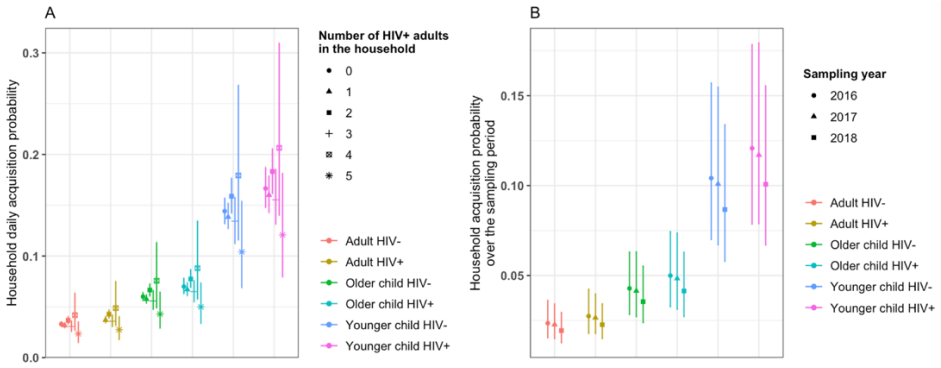
We used msm Viterbi function to recursively construct the sequence of pneumococcal carriage with the highest probability through the hidden states. The probability of each hidden state at each observation point, conditionally on all the data was also computed using Baum-Welch forward/backward algorithm.



S2 Fig. The probabilities of the underlying states and the most likely path through them. Observed pneumococcal carriage results from NP swabs of two randomly selected persons A and B (first row). The underlying sequences of a fitted HMM given the observed sequence, found by the Viterbi algorithm through a recursive construction of the path with the highest probability (second row). For each observed infected state (first row), if the probability of the hidden infected state (third row) at each observation point is <100% then it reflects misclassification. The probability of the hidden infected state is conditionally on all the data and computed using Baum-Welch forward/backward algorithm.

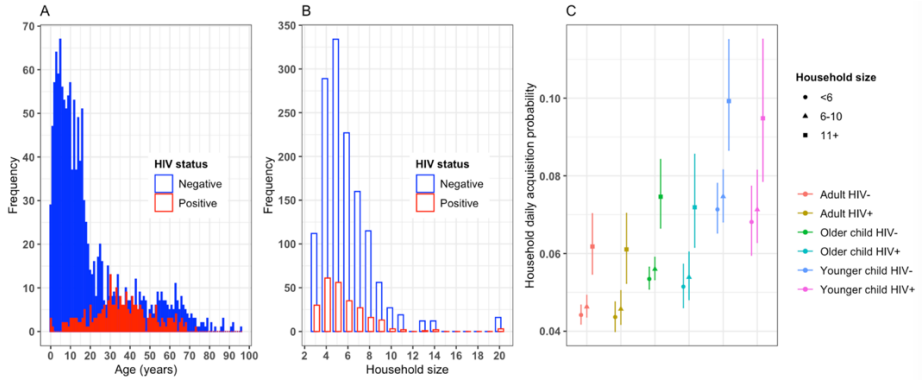
Sensitivity on the number of HIV+ adults within household and time-homogeneous HMM

We conducted a sensitivity analysis to check if varying covariate values affects pneumococcal acquisition within household. The HMM was refitted with different numbers of HIV+ adults in the household and different sampling periods.



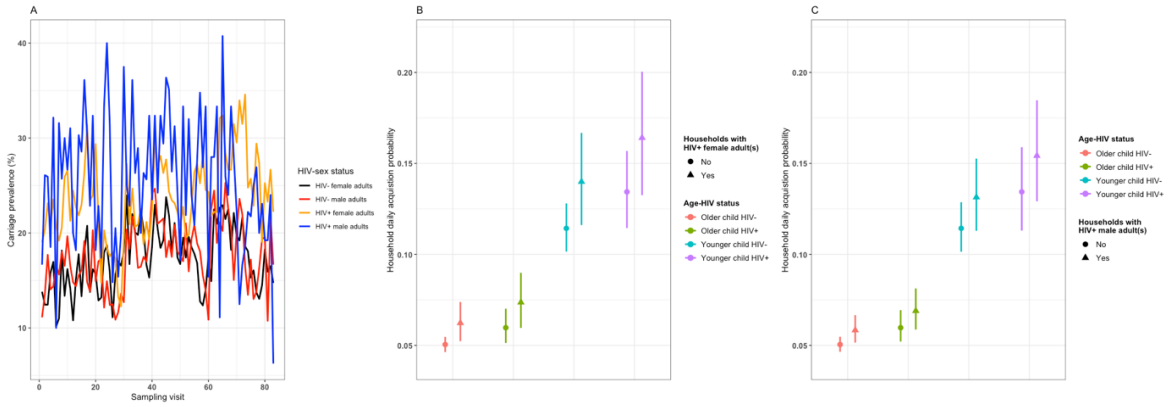
S3 Fig. Sensitivity analysis of varying covariate values in younger children (<5 years-old), older children (5-17 years-old) and adults (≥18 years-old). The main analysis computed within household HIV+ and age-stratified acquisition per day comparing households with HIV+ adult(s) to those without, whereas here, we compare households with 0,1,2,3,4 or 5 HIV+ adult(s) (A). Similarly, the main analysis estimated acquisition probabilities for entire study follow-up period (0-289 days), whereas here, we estimate acquisition probability comparing samples collected between different periods.

HIV-age distribution, and pneumococcal carriage acquisition dynamics by household size

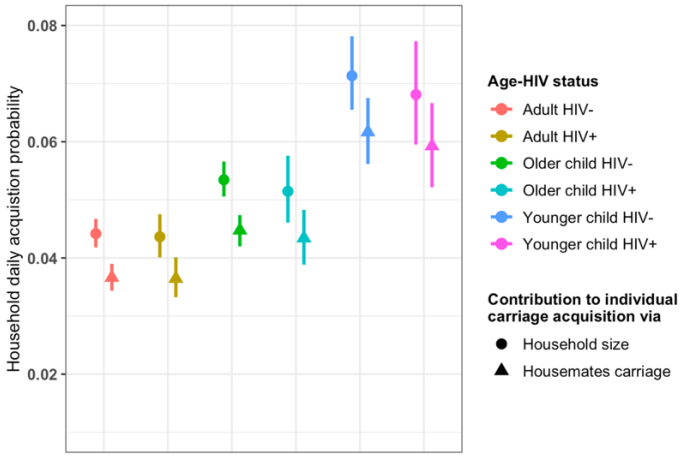


S4 Fig. HIV and Age distribution of study participants, and household size carriage acquisition dynamics in younger children (<5 years-old), older children (5-17 years-old) and adults (≥18 years-old). Overall HIV and age distribution of study participants (A). HIV and age distribution of study participants by their household size (B). HIV and age-stratified carriage acquisition probability per day by household size (C).

Sensitivity on the contribution of HIV+ female adults to household pneumococcal transmission in children



S5 Fig. Pneumococcal carriage prevalence in adults (≥18 years-old) (A), household pneumococcal acquisition in younger children (<5 years-old) and older children (5-17 years-old) by HIV status of household female adults living with these children (B), and household pneumococcal acquisition in younger and older children by HIV status of household male adults living with these children (C).



S6 Fig. The contribution to individual pneumococcal carriage acquisition by age groups and HIV status. Within household individual carriage acquisition probability estimated by accounting for infections through household size or daily contribution from household members.

Chapter 4: Research paper 3

Social mixing patterns relevant to infectious diseases spread by close contact in urban Blantyre, Malawi.

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Candidate's role: I worked with Professor Stefan Flasche, Professor Neil French, and Dr Amy Pinsent to conceive the idea for the work. I developed the field study protocol, conducted the study in Malawi, monitored the data collection and quality, developed analysis methods using socialmixr R package, and generated results. I wrote the first draft of the manuscript. I reviewed and responded to all comments from co-authors and those from the journal reviewers to generate the published manuscript.

Social mixing patterns relevant to infectious diseases spread by close contact in urban Blantyre, Malawi.

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Abstract

Introduction: Understanding human mixing patterns relevant to infectious diseases spread through close contact is vital for modelling transmission dynamics and optimisation of disease control strategies. Mixing patterns in low-income countries like Malawi are not well known.

Methodology: We conducted a social mixing survey in urban Blantyre, Malawi between April and July 2021 (between the 2nd and 3rd wave of COVID-19 infections). Participants living in densely-populated neighbourhoods were randomly sampled and, if they consented, reported their physical and non-physical contacts within and outside homes lasting at least 5 minutes during the previous day. Age-specific mixing rates were calculated, and a negative binomial mixed effects model was used to estimate determinants of contact behaviour.

Results: Of 1,201 individuals enrolled, 702 (58.5%) were female, the median age was 15 years (interquartile range [IQR] 5-32) and 127 (10.6%) were HIV-positive. On average, participants reported 10.3 contacts per day (range: 1-25). Mixing patterns were highly age-assortative, particularly those within the community and with skin-to-skin contact. Adults aged 20-49y reported the most contacts (median:11, IQR: 8-15) of all age groups; 38% (95%CI: 16-63) more than infants (median: 8, IQR: 5-10), who had the least contacts. Household contact frequency increased by 3% (95%CI 2-5) per additional household member. Unemployed participants had 15% (95%CI: 9-21) fewer contacts than other adults. Among long range (>30 meters away from home) contacts, secondary school children had the largest median contact distance from home (257m, IQR 78-761). HIV-positive status in adults >18 years-old was not associated with changed contact patterns (rate ratio: 1.01, 95%CI (0.91-1.12). During this period of relatively low COVID-19 incidence in Malawi, 301

(25.1%) individuals stated that they had limited their contact with others due to COVID-19 precautions; however, their reported contacts were 8% (95%CI 1-13) higher.

Conclusion: In urban Malawi, contact rates, are high and age-assortative, with little reported behavioural change due to either HIV-status or COVID-19 circulation. This highlights the limits of contact-restriction-based mitigation strategies in such settings and the need for pandemic preparedness to better understand how contact reductions can be enabled and motivated.

Keywords: Social contacts, Transmission, Mixing data, Infectious disease, Malawi, Africa

Introduction

Globally, respiratory tract pathogens carry a substantial burden of morbidity and mortality at all ages [1–3], with incidence highest in low- and middle-income countries and in populations where human immunodeficiency virus (HIV) prevalence is high. For instance, an estimated 318,000 pneumococcal deaths occurred in 2015 of which 23,300 were among HIV-positive individuals [1]. In 2019, there were an estimated 1.5 million deaths from tuberculosis (TB), with HIV a major risk factor for the development of active TB and mortality [2]. By November 2021, 5.2 million deaths from Coronavirus disease (COVID-19) have been reported globally [4], and with detrimental impact on healthcare delivery, particularly in low-income countries (LICs) [5].

Transmission of respiratory tract pathogens requires close contact with infectious respiratory droplets, secretions or inhalation, making understanding of human social mixing patterns an essential part of the design of effective disease control strategies [6]. Social contact type, frequency, duration and place have shown to vary substantially between different settings [7,8]. Local built environment, population characteristics, and social activities such as traditional, political, religious and leisure events are likely to play important roles in explaining contact patterns variations between countries [9–11]. However, relatively little is known about social mixing patterns in LICs [8], including how these are affected by age, occupation, household size, HIV status, and non-pharmaceutical interventions (NPIs) during COVID-19 pandemic.

Social mixing studies in middle (MICs) and high (HICs) income countries have shown that individuals in the same age groups tend to have higher contact rates than with other age groups (age-assortative mixing) [7,8], yet not much is known about contact patterns in LICs in the era of fairly high urbanisation [12–14]. Intergenerational mixing between younger children

and adults was evident in Zimbabwe, reflecting parental or guardian roles played by adults [13], though age-sex mixing patterns are not well known [12,13]. Commonly, people tend to make high number of contacts within a short distance of their homes, with this being most pronounced for people living close to their usual place of work [9,15]. Where commuting long distances to work is common through mass transport, outbreak containment becomes more difficult due to greater ease of wide spatial spread of respiratory infections [16].

Physical distancing and lockdown NPIs to limit the number and geographical spread of close contacts have been used extensively during the COVID-19 pandemic, especially in HICs and MICs where relatively; mobility is usually high, per capita hospitalisation and mortality during the first wave was high, and lockdowns were strictly observed [17–20]. In LICs, the impact of NPIs on social contacts is less clear, with added uncertainty on whether individual contacts are affected by COVID-19 vaccination status due to perceived attitude of being protected from severe COVID-19 [21]. However, this is unlikely due to relatively very low current COVID-19 vaccination coverage in LICs [22]. Moreover, despite the 3 pandemic waves in a LIC like Malawi, NPIs were only restricted to face mask wearing, rotational working, limited transit vehicles, self-quarantine for returning travellers, restricted gatherings, closure of non-essential businesses, social distancing, and reduced public transportation capacity, without implementation of a formal countrywide lockdown.[23]

Unlike in HICs, urban neighbourhoods in LICs are predominantly comprised of high-density informal settlements, relatively larger households (extended families), have low rates of formal employment, and often high HIV prevalence [24,25]. Contact patterns may then differ substantially having, for example, much higher rates within than outside households, and a higher ratio of skin-to-skin to verbal contacts [7,13]. Despite these anticipated differences, there

are only two studies of social contacts from LICs (Uganda and Somaliland) [10,14] and six studies from LMICs (Kenya, South Africa, Zambia and Zimbabwe) [9,12,13,17,26,27]. Also, understanding how contact patterns vary by HIV status is important to inform targeted interventions to mitigate risks both to HIV-positive individuals and to their social contacts.

The main objectives of this study in urban Malawi was to (1) estimate age-specific daily rates of social contacts, (2) investigate factors associated with social contact rates, (3) explore the influence of sex, household, community, HIV status and distance of contact event place in social contact patterns and (4) explore self-reported changes in social contact behaviour during the COVID-19 pandemic in the context of Malawi not having had a formal "lockdown" at any stage during the pandemic.

Methods

Study design

A cross-sectional study was undertaken in Ndirande, Blantyre, Malawi between April and July 2021. Ndirande mainly comprises high-density informal residential neighbourhoods, with minimal town-planning, building regulations or access to municipal services such as roads, electricity, water or refuse collection. Buildings tend to be single storey, built by unqualified local artisans using low-cost and sometimes locally-made materials like fired bricks. The road network is extremely limited, making access by motor vehicle impassable for most parts of the suburb.

Our sampling frame was based-on a previous Blantyre household TB prevalence survey, conducted in 2018-2019, where adult HIV status was ascertained using Government-approved rapid diagnostic tests [28]. The TB prevalence survey mapped high density

neighbourhoods in Blantyre city into 72 clusters where 12,865 adults from randomly selected households were recruited proportional to cluster size. A cluster was defined as a physical location whose boundaries were based on existing community health workers combined catchment areas with about 4000 adults aged 18+ years. Ndirande, the site for the present social mixing study, contributed 14 clusters and 2,626 adults to the TB prevalence survey.

The targeted sample size for the present social mixing study was ≥1,080 participants from 393 households across 14 clusters, of whom 490 were adults aged ≥18 years-old (y), and 190 were HIV-positive adults taking ART. A randomly sample (proportional to cluster size) of household members from Ndirande clusters of TB prevalence survey was taken, aiming to recruit equal number of participants across six age groups of <1y (infants), 1-4y (preschool children), 5-14y (primary school children), 15-19y (secondary school children), 20-49y (adults), and 50+y (older adults) to give adequate power of ≥80% to measure the number of social contacts with standard deviation of no more than 50% of the mean number of daily social contacts, and to detect the true differences in the mean contact rates between age groups if in excess of 30% [10,29]. Age groups were chosen based on transmission patterns of a typical respiratory infection [7,12,30].

A household was defined as a group of family members or unrelated individuals living in the same compound and sharing food from the same kitchen [31]. Household size was split into <4, 4-6, >6 members during analysis based on interquartile range of measured household size in the study. Using the sampling frame of households in the 14 Ndirande clusters, handheld geographical positioning system (GPS, Garmin ETrex 30) devices were used to identify previously enrolled households. After visiting and validating each household, the household head aged ≥18 years was invited to participate, along with their <18 years-old household

members. If a household or an adult household member who participated in the TB prevalence survey was not found after two visits, they were replaced by next household on the list. If a particular age-group had reached it's required sample size, recruitment was restricted to households with at least one member in the age-groups that had not reached saturation.

COVID-19 dynamics during field study

To date, Malawi has experienced three COVID-19 waves (May to August 2020, January to March 2021, and June to September 2021) [23]. Our social mixing study was conducted after the end of the second wave (April-May 2021) and during the first half of the third wave (June-July 2021). During our study period, Malawi had initially implemented Level 1 COVID-19 policies, which included social distancing, recommended face mask wearing, rotational working, limited transit vehicles, self-quarantine for returning travellers, and restrictions of gatherings to100 people (From April-May 2021). From June-July 2021, Level 3 COVID-19 policies were enacted, including: restricted movements, enforced facemask wearing, closing of non-essential businesses, enforced social distancing, reduced public transportation capacity, and 10 people restricted gatherings. Throughout the study period between April and July 2021, school closures were not implemented.

Data collection

The study outcomes were retrospectively reported physical (participant's skin to skin touch with a contact) and non-physical contacts (participant's two-way close verbal conversation lasting for ≥5 minutes and with ≥3 words exchanged with a contact) during the time period between waking up in the morning and going to bed in the evening [10]. The household head was interviewed on household characteristics and composition on behalf of other household

members, and responded to their own individual demographic characteristics, travel history, COVID-19 behavioural change, and social mixing events, and those of younger (<7 years-old) household members. Older children mostly reported their contacts with help of an adult. A house was considered well-ventilated if it had open windows, doors, and ventilation within the cooking area (Supplementary Questionnaire).

Survey interviews were conducted across all days of the week to ensure representation of weekdays and weekends. Repeated contacts with the same individual were recorded once, noting the frequency and cumulative time. The age of a contact was not always known, in which case it was guessed and approximated to nearest annual age unit. We defined the "hypothesised" number of contacts as additional number of people the participants would have encountered the day before, had there been no COVID-19 pandemic. Open data kit (ODK, Nafundi, Seattle, USA) was used to capture participant's responses electronically, with an embedded electronic physical address locator (ePAL, Tripod Software, Salford, UK) for geolocating places of contacts [25].

Characteristics and determinants of social contact events

We tabulated the number and distribution of participants and their contacts by age, and the proportion and distribution of contact events by the day of the week when contacts occurred and number of contacts per participant, respectively. The number and proportion of physical and non-physical contact events were also tabulated by contact duration, frequency, location, relationship of participant to contact, and sex of contact.

Social contact patterns were characterised by computing the median and mean number of contact events for a set of potential factors (age, sex, occupation, education, HIV, day of the

week, COVID-19 restriction, and household size), with bootstrap confidence intervals based on 1000 bootstrap replicates. Factors associated with the mean number of mixing events at $p<0.10$ in univariable analysis were retained in multivariable analysis if they reduced the Akaike Information Criterion (AIC) [32]. To investigate factors associated with contact rates, a negative binomial mixed model with household random intercept terms was constructed, and the ratio of mean number of contact events in each category of a factor relative to reference category was calculated [10]. Detailed methods are described in Supplementary Text 1.

Age-specific social mixing rates

Age-stratified contact matrices were generated to investigate interactions between age groups. Age-specific contact rates through contact matrices were constructed from the mean number of daily contacts between participants and their contacts using the 'socialmixr' R package [33]. Age-based contact matrices were estimated based on the ratio of the measured probability of a contact event between individuals based on age group to a null model of the probability of that contact event under an assumption of random mixing. Contact probabilities under the null model were determined by proportion of the population in each given age category in Ndirande [25,31]. Our analyses were weighted by days of the week as well as reciprocity in contact patterns such that the total number of contacts from age group i to j were equal to the total number of contacts from age group j to i ($m_{ij}w_i = m_{ji}w_j$), where the elements m_{ji} make up a contact matrix and w_i is the population size in age group i. Thus, c_{ij} is the daily mean contact rate given as $c_{ij} = m_{ji}/w_i$ [10,33].

For each contact matrix, the assortativity index Q was computed. The Q index is defined as the coefficient of degree between pairs of linked age groups and quantifies the weight of mixing between individuals of the same age groups. A Q value close to 0 represents little

dependence of mixing patterns on age while Q=1 implies exclusivity of contacts within age groups [27]. Age-specific contact matrices were stratified by physical vs. non-physical contact, sex, within vs. outside household, within vs. outside Ndirande community, and adult HIV-positive vs. HIV-negative status, as well as affected vs. unaffected by COVID-19 and sex interactions.

Spatial distance distribution of contact events

We used longitude and latitude GPS coordinates to calculate the Euclidian distance in metres between participants' houses and places of contact events. The inverse cumulative distance distributions for physical and non-physical contacts and for the stratification by age groups in relation to the distances away from homes were estimated [34]. All analyses were conducted in R v4.1. Results can be reproduced using the data and code in the GitHub repository [35]

Ethics

Ethical approval was granted by the College of Medicine Research Ethics Committee, University of Malawi (P.01/21/3244), and the London School of Hygiene and Tropical Medicine Research Ethics Committee (#22913). Informed consent was obtained from each participant aged ≥16 years, or from the parent or guardian of each individual aged <6 years, or from each participant aged 6-15 years with additional informed assent.

Results

Study area, participants and their contacts

A total of 378 (85.9% of all who were approached) households participated in the survey from across 14 clusters in Ndirande, Blantyre City. Non-participation was mostly due to relocation, and with only 3% refusals. The proportion of study households within each cluster

(relative to total census-counted cluster households) and across clusters varied between 7.9-19.7% and 4.0-10.0%, respectively. The most common number of rooms per house was four, of which two or three were commonly used as bedrooms. The median household size was 6 members (interquartile [IQR] range 4-7), with 53 (14.2%) households reporting having at least one smoker (cigarette, marijuana, or local cigar; chingambwe). Charcoal was predominantly used as source of energy in 366 (96.8%) households, of which 200 (52.9%) reported indoor cooking, and of which 23 (11.5%) were not well ventilated (Figure S1).

Overall, 1,201 participants were recruited, including 65 (5.4%) infants, 230 (19.2%) preschool children, 265 (22.1%) primary school children, 188 (15.7%) secondary school children, 301 (25.1%) adults and 152 (12.7%) older adults. Of enrolled participants, 702 (58.5%) were female, 138 (30.0% of adults) were unemployed, and the median age was 15 years (IQR 5-32). Among all adults aged 18 years or older, 200 (43.3%) had primary education, 18 (3.9%) had no formal education, and 124 (26.8%) self-reported HIV-positive status, all of whom were taking ART. In total, there were 12,540 reported contacts of whom 213 (1.7%) were infants, 1,161 (9.3%) preschool children, 3,239 (25.8%) primary school children, 2,165 (17.3%) secondary school children, 4,765 (38.0%) adults, and 997 (7.9%) older adults. The median age of contacts was 18 years (IQR 10-32). 9,341 (74.5%) contacts occurred during Monday to Friday. The average number of contacts per person was 10.43, with 25%, 50% and 75% of participants reporting at most 7, 10 and 13 contacts, respectively (Figure 1, Table 1, Table S1).

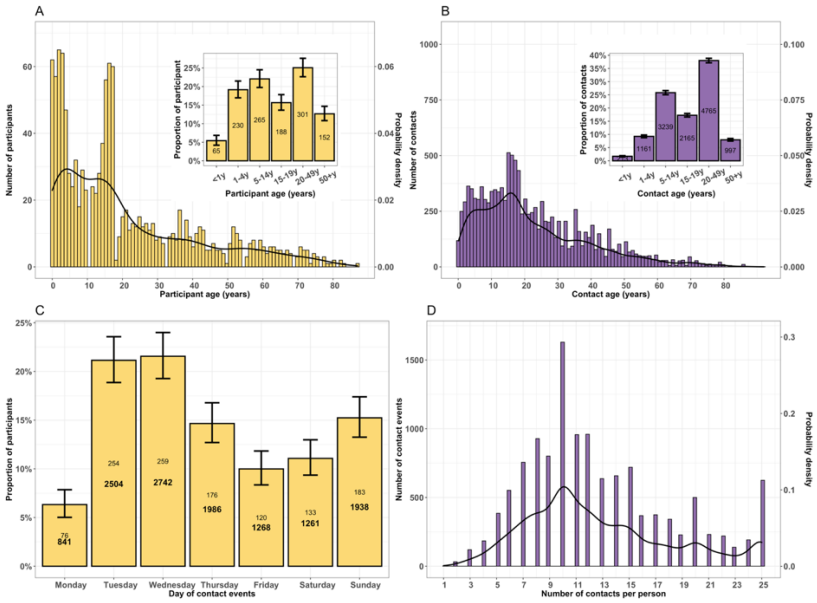

Figure 1. The probability distribution, number and proportion of study participants and reported contact events during the social contact patterns study in urban Blantyre, Malawi between April, and July 2021. The frequency and probability distribution of participants, with proportion of participants in age groups of infants (<1 years-old), preschool (1-4 years-old), primary school (5-14 years-old), secondary school (15-19 years-old), adults (20-49 years-old) and older adults (50+ years-old) (insert) (A); The age frequency and probability distribution of contacts, with proportion of contacts by age groups (insert) (B); The number of contacts (bold font face) and participants (roman font face), and proportion of participants by day of the week when the contact event occurred (C); and the total number and probability distribution of reported contact events for a given number of contacts reported by the participant (D). Throughout the plots, the black line represents the probability density with values on secondary y-axis whereas yellow and purple colour represent participants and contacts, respectively. The 95% confidence interval for each bar is shown as vertical line.

Travel history and COVID-19 impact

Approximately one quarter of participants (n=281, 23.4%) had travelled more than 5km outside of Ndirande community in the last 24 hours. However, of 1,041 (86.7%) participants

who travelled outside Ndirande anytime in the past, 81 (7.8%) reported that they made similar travel daily and 161 (15.5%) at least once a week; 840 (80.7%) spent at most 24 hours outside Ndirande, and 913 (87.7%) used public transport during similar travels.

A total of 301 (25.1%) participants, almost exclusively adults, reported to have reduced their social contacts due to COVID-19 pandemic, with home (n=225, 74.8%) and market (n=183, 60.8%) being the main localities where contact was reportedly reduced. Among all participants, we estimated that preventive measures against the COVID-19 pandemic contributed 9.1% (95%CI 0-13) to social contacts reduction e.g. from the median of 11 (IQR 7-18) daily contacts, actual and hypothesised (additional contacts that could have occurred in absence of COVID-19 pandemic), to 10 (IQR 7-13) actual contacts. However, the actual contacts of participants affected by COVID-19 were 8% (95% CI: 1-13) higher than their counterparts who reported no reduced social contacts due to COVID-19 (Table 1, Figure S2, Figure S3).

Table 1. Characteristics of participants and their reported daily in Blantyre, Malawi, April-July 2021. The relative numbers of mean daily contacts (contacts rate ratio, CRR) were obtained from a negative binomial mixed model.

Characteristic	Number of participants %	Median number of contacts (95%CI)	Mean number of contacts (95%CI)	Crude CRR (95%CI)	Adjusted CRR[#] (95%CI)
Age	(N = 1,201)				
<1y	65 (5.4)	8.00 (6.39-9.84)	8.14 (7.26-9.15)	Ref	Ref
1-4y	230 (19.1)	9.00 (8.35-10.26)	8.63 (8.18-9.08)	1.14 (1.03-1.25)	**1.13 (1.03-1.25)**
5-14y	265 (22.0)	10.00 (9.60-10.51)	10.24 (9.72-10.82)	1.29 (1.17-1.42)	**1.23 (1.07-1.41)**
15-19y	188 (15.7)	10.00 (9.30-10.83)	10.88 (10.18-11.61)	1.40 (1.27-1.54)	**1.31 (1.14-1.50)**
20-49y	301 (25.1)	11.00 (10.42-12.38)	11.75 (11.17-12.38)	1.50 (1.37-1.63)	**1.38 (1.16-1.63)**
50+y	152 (12.7)	10.00 (9.38-11.53)	10.18 (9.43-11.15)	1.38 (1.24-1.53)	**1.30 (1.08-1.56)**
Sex					
Female	702 (58.5)	10.00 (9.73-10.32)	10.45 (10.08-10.8)	Ref	Ref
Male	499 (41.5)	10.00 (9.44-11.35)	10.06 (9.64-10.49)	0.94 (0.90-0.97)	0.97 (0.94-1.01)
Occupation					
Business[‡1]	206 (17.2)	10.50 (9.38-11.55)	12.13 (11.31-12.95)	Ref	Ref

Workers‡2	79 (6.6)	11.00 (8.67-13.14)	11.27 (10.13-12.63)	0.96 (0.89-1.05)	1.00 (0.92-1.08)
Pre-school child	267 (22.2)	9.00 (8.34-9.64)	8.74 (8.31-9.16)	0.70 (0.66-0.74)	0.90 (0.77-1.05)
Schoolers	479 (39.9)	10.00 (9.42-10.96)	10.28 (9.87-10.76)	0.86 (0.82-0.91)	0.95 (0.85-1.06)
Retired	28 (2.3)	9.00 (7.60-11.06)	8.79 (7.26-10.50)	0.84 (0.73-0.97)	0.91 (0.78-1.05)
Unemployed	138 (11.5)	10.00 (9.28-10.79)	10.34 (9.68-11.08)	0.85 (0.79-0.91)	**0.85 (0.79-0.91)**
Other	4 (0.33)	7.50 (5.75-12.63)	9.50 (6.00-15.25)	0.88 (0.62-1.25)	0.91 (0.64-1.28)
Education level†					
University/college	17 (3.7)	10.00 (6.97-14.57)	9.76 (7.35-12.23)	Ref	-
No education	18 (3.9)	9.50 (6.87-11.91)	11.00 (8.94-14.24)	1.03 (0.76-1.40)	-
Primary school	200 (43.3)	11.00 (10.33-12.40)	11.48 (10.66-12.24)	1.04 (0.83-1.32)	-
Secondary school	227 (49.1)	10.00 (9.57-10.36)	11.22 (10.54-11.99)	1.03 (0.82-1.29)	-
HIV status†					
Negative	338 (73.2)	10.00 (9.19-10.53)	11.28 (10.70-11.88)	Ref	-
Positive on ART	124 (26.8)	10.00 (8.95-10.68)	11.13 (10.26-12.17)	1.01 (0.91-1.12)	-
Interview day					
Weekday (Mon-Fri)	885 (73.7)	10.00 (9.82-10.21)	10.43 (10.12-10.78)	Ref	-
Weekend (Sat-Sun)	316 (26.3)	9.00 (7.65-9.73)	9.90 (9.27-10.45)	0.99 (0.92-1.06)	-
COVID-19 restrictions*					
No	900 (74.9)	10.00 (9.42-11.01)	10.04 (9.74-10.40)	Ref	Ref
Yes	301 (25.1)	10.00 (9.78-10.23)	11.03 (10.50-11.55)	1.21 (1.16-1.27)	**1.08 (1.01-1.13)**
Household size					
1-3 people	90 (7.5)	8.00 (3.35-9.78)	8.81 (7.70-10.07)	Ref	Ref
4-5 people	305 (25.3)	9.00 (7.87-9.67)	10.40 (9.69-11.24)	1.20 (1.04-1.39)	**1.24 (1.07-1.43)**
6 people	230 (19.2)	9.00 (7.60-9.57)	10.13 (9.50-10.84)	1.21 (1.03-1.42)	**1.26 (1.07-1.47)**
7+ people	576 (48.0)	10.00 (9.91-10.09)	10.80 (10.43-11.19)	1.29 (1.12-1.49)	**1.36 (1.18-1.57)**

‡1 Business refers to individuals involved in the exchange of goods and services to earn profits usually struggling self-employed traders

‡2 Workers include all persons involved in agricultural, domestic, manual, and office activities

† Only applicable to adults 18 years and older (N=462)

95%CI - 95% bias-corrected and accelerated bootstrap confidence intervals based on 1000 bootstrap replicates

* Whether or not individual reported that they had modified their social mixing behaviour due to the COVID-19 pandemic

Estimates in multivariable model were adjusted for age, sex, occupation status, whether social contacts were restricted by COVID-19, and household size.

ART: Antiretroviral therapy; Ref: refers to reference category; Crude CRR: refers to univariable analysis of the relative effect of each variable category on mean # of contacts; Adjusted CRR: refers to multivariable analysis of the relative effect of each variable category on mean # of contacts accounting for other variables simultaneously; Bold font: refers to statistically significant effects at significance level of $p<0.05$.

Characteristics and determinants of reported mixing events

About 74% (8,266/1,1175) of contacts longer than 15 minutes involved physical contact whereas 60% (547/1,365) of shorter contacts did not. Contacts were likely physical if they occurred daily (7,648/10,058) compared to less frequent contacts. More than 80% (4,681/5,626) of contacts with family members were physical and only 30% (487/1,554) of contacts with unknown (random) people were physical. About 75% (8,183/10,966) of contacts at school, home, leisure or in transport were physical whereas less than 50% (552/1,409) of contacts at church, market or work were. More than 95% (12,136/12,540) of all contacts happened within than outside the community (Figure 2).

Data on spatial distances between participant house and place of mixing was available for 12,449 (99.3%) social mixing events. Overall, the median Euclidian distance meters (m) away from home to where mixing events occurred was 121.6m (IQR 57.2-369.5), ranging from 30.0m to 12,358.8m. Secondary school children travelled furthest on average for their physical contacts (256.8m, IQR 78.3-760.7), primary school children had the most localised physical contacts (82.1m, IQR 51.4-169.3). (Figure 2).

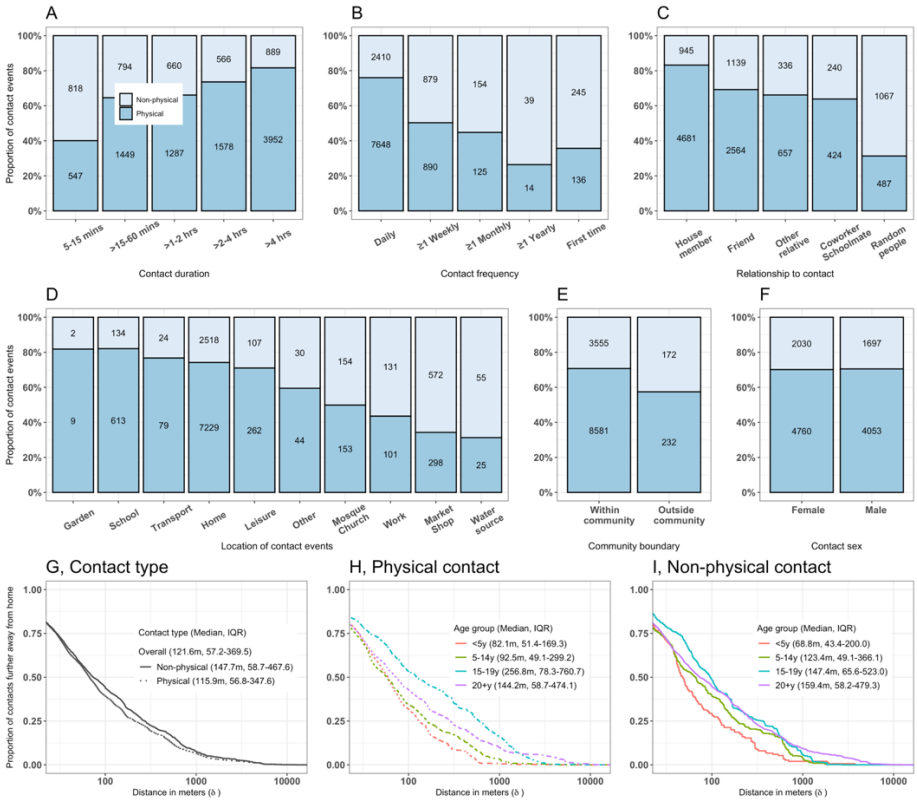

Figure 2. Characteristics of reported physical and non-physical social contacts in urban Blantyre, Malawi between April and July 2021. The proportion of physical and non-physical contacts by the duration of contacts (A), frequency of contacts (B), relationship of participant to contacts (C), the exact location of contacts (D), contacts within or outside community (E) and contact sex (F). The number in each bar plot indicates absolute number of reported contacts. Physical contact refers to participant's skin to skin touch with a contact whereas non-physical contact refers to participant's two-way close verbal conversation lasting for ≥5 minutes and with ≥3 words exchanged. The inverse cumulative distance distribution showing the proportion of contacts in relation to the distance (in metres) further away from the participant home by physical and non-physical contact type (G), for physical contact events by age group (H), and for non-physical contact events by age group (I).

The mean number of contacts varied significantly by age, with infants and preschool children reporting lower contacts (95%CI: 7.26-9.15) than those in older age groups (95%CI: 9.72-

12.38). Similarly, households with at most three members had significantly lower contacts (95%CI: 7.70-10.07) than those with at least seven members (95%CI: 10.43-11.19). On the contrary, the mean number of contacts did not significantly differ by sex, education status, HIV status or interview day (Table 1).

In a multivariable analysis, age, occupation status, and household size were significantly associated with daily number of contacts. Adults had the highest contact frequency among all ages, over 30% more than infants (1.38, 95%CI 1.16-1.63). Unemployed adults (less active community members) had 15% (9-21) fewer contacts than business adults, usually self-employed traders (more active counterparts). Household contact frequency increased by 3% (95%CI 2-5) per additional household member. Members of households of at least 7 members had 36% (95%CI: 18-57) more contacts than participants from households with 1-3 members (Table 1).

Age-specific mixing patterns

Social contacts were highly age-assortative, with the most intense contacts clustered among primary school children and secondary school children compared to infants, preschool children, or adults. Non-physical contacts were less age-assortative (Q=0.076) than physical contacts (Q=0.118) and were mostly reported among adults, whereas children mostly reported physical contacts (Figure 3).

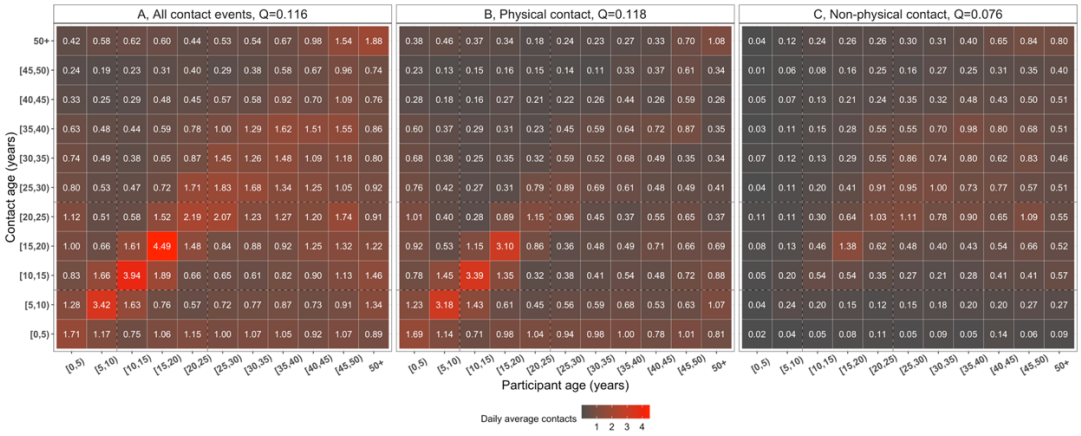

Figure 3. The daily mean number of reported contacts between age groups, in urban Blantyre, Malawi between April and July 2021. The number in each cell represents the daily mean number of contacts between two age groups from 1000 bootstrap replicates, corrected for reciprocity between participants and contacts, and weighted for day of the week. The matrices show the daily mean number of all contacts (A), physical contacts (participant's skin to skin touch with a contact) (B) and non-physical contacts (participant's two-way close verbal conversation lasting for ≥5 minutes and with ≥3 words exchanged with a contact) (C).

Age-assortativity was particularly pronounced for male-gender mixing patterns (Q =0.142), with women being more involved in intergenerationally mixing (Q =0.103). Participant-contact mixing between male-male (Q =0.420) was more intense and highly assortative than female-female (Q =0.163) or male-female (Q =0.106) or female-male (Q =0.096). Mixing outside household (Q =0.266) and Ndirande community (Q =0.196), was more age-assortative than within household (Q =0.073) and community (Q =0.113). No differential age-assortativity was seen on social contacts behaviour between HIV-positive adults taking ART (Q =0.056) and HIV-negative adults (Q =0.071) (Figure 4, Figure S4, Figure S5).

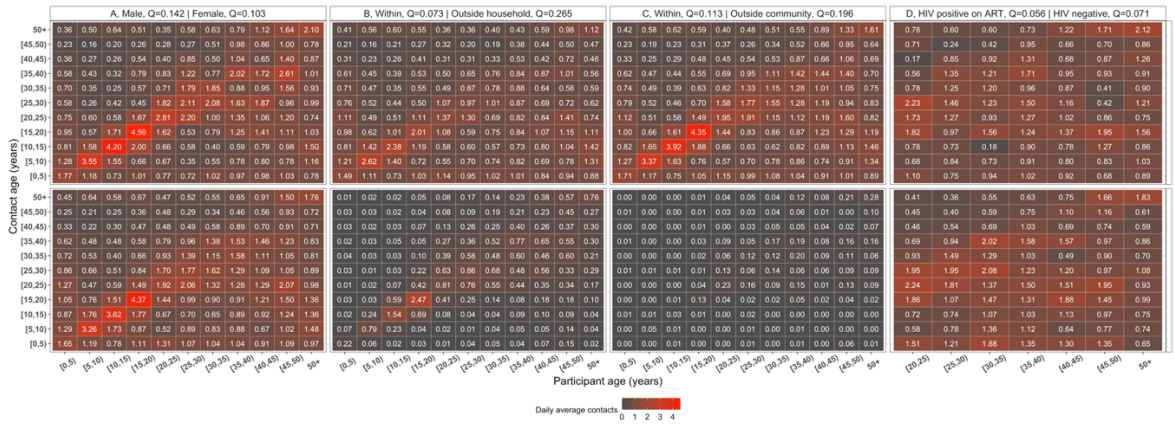

Figure 4. Daily mean number of reported contacts between age groups, in urban Blantyre, Malawi between April and July 2021. The number in each cell represents the daily mean number of contacts between two age groups from 1000 bootstrap replicates, corrected for reciprocity between participants and contacts, and weighted for day of the week. The top and bottom matrices show the daily mean number of contacts respectively stratified by male and female sex (A), within and outside household contacts (B), within and outside community contacts (C), Human Immunodeficiency Virus (HIV) positive adults (20+ years old) and HIV-negative adults (D). The assortativity index Q quantifies the weight of mixing between individuals of the same age groups and is estimated on the square matrix. For the HIV-stratified matrices, the index Q is estimated on the square matrix between pairs of adult participants and adult contacts aged at least 20 years old.

Discussion

Surveying 1,201 individuals in high-density informal urban suburb in Malawi, the median number of contacts was higher than previously reported in Zambia [12], but similar to Zimbabwe and Somaliland and many MICs and HICs [7,13,14]. Older age, employment, and bigger households were significantly associated with an increased number of contacts in this setting, consistent with previous social contacts studies [7,8]. Reported social contacts were strongly age-assortative and intergenerational by sex, mostly physical and occuring within household and geographically localised. Notably, neither HIV status, ART use nor COVID-19 pandemic restrictions significantly reduced population-level social contacts behaviour.

The reported median number of contacts of 10 is similar to reported contacts among internally displaced people in Digaale camp in Somaliland [14], but higher than the median of 4 contacts reported in a LIC in Zambia [12], and lower than the 24 reported in Thailand [36] or 18 in rural Kenya [26], highlighting the substantial role local context play in social contacts. The completeness of contacts capture was strengthened by conducting participant's interview only on second visit with advanced notice to remember contacts on the day, guided interview process collecting only contacts initials to start with and aiding participant's memory by structuring the interview to prompt participants to the different typical parts of the day. Unlike some LIC, MICs and HICs where the number of daily contacts usually are highest among school age children [7,13,14,26,37], our finding that working age adults had the largest number of increasing daily contacts aligns with results from upper MICs [7]. This suggests that schools may play a less prominent role in the transmission of infectious diseases in this setting than they do in other parts of the world; albeit that this may be counter-balanced by children comprising a generally larger share of the population in LICs.

The 15% relatively higher average number of contacts among workers (often self-employed traders in this setting) than among unemployed individuals is in line with evidence from several previous studies irrespective of location [7], and reflects the influence of human mobility and trading activities on social contacts [16], which in part has motivated lockdowns in some MICs and HICs during the COVID-19 pandemic [38]. Increasing number of contacts with household size has also been reported in some MICs and HICs [7], with household density suggested to be a driving factor particularly in this setting where extended families sharing a compound is common. We also report higher proportion of home contacts similar to other LICs and MICs than those reported in HICs, and by contrast, the proportion of school and work contacts were substantially lower than those in HICs [7]. This implies that household may be a key site of transmission for respiratory diseases [39], and public preventive measures may only be efficacious at reducing the speed for spatial spread outside homes. However, the relevance of contact location on transmission will also depend on, among other things, specific pathogen and transmission routes e.g. droplet, fomite or aerosol [7].

The strong age-assortative contacts in this study are consistent with widespread evidence globally [7,8], and support adjusting for age-heterogeneity when calibrating models for predictions [40,41]. Approximately 80% of contacts in this study were skin-to-skin, falling on the higher side of the reported range of 19-84% globally [7]. While the predominance of physical contacts in children compared to adults is similar across all settings, substantial physical contacts in our study align with reports in LICs and MICs but not HICs [7]. Social interactions by women were less strongly age-assortative than for men, consistent with a greater role for intergenerational mixing between mothers or female guardians with younger children, as also reported in Zimbabwe and Kenya [13,26]. This finding may imply that shielding older adults as a public health policy during pandemics may substantially reduce the spread

of infectious respiratory pathogens. Age-sex interactions showed relatively high age-assortativeness among male-male contacts than other sex combinations, implying that relatively small underlying biological or behavioural difference in susceptibility by sex may be amplified by assortative social networks, as hypothesised for TB [12]. Moreover, relatively high (97%) frequency of contacts occurring within rather than outside community in this study may imply that epidemics would mostly be localised. However, adults >15 years-old reported the highest intense physical contacts including minibus travel with potential to disseminate outbreaks outside of the local community.

Ours is the first study to evaluate whether HIV-positive status modulates contact behaviour. In this high HIV prevalence population with good access to ART, we found no evidence that HIV status *per se* influences contact rates or age-assortativeness. Given that immunosuppressed individuals may be at increased risk of prolonged COVID-19 infectiousness and generation of new variants as well as increased pneumococcal carriage [42,43], this suggests that HIV-positive individuals may have equivalent or increased potential for contributing to respiratory disease transmission in this setting [44]. We have not, however, assessed the other drivers of pathogen transmissibility, such as carriage density and duration of infection, and so cannot confirm a likely disproportionate role in transmission. Of note, reported adult HIV prevalence in this setting is slightly higher (26.8%) compare to that from the impact HIV assessment in Blantyre in 2015-16 (17.7%) [45], due to undersampled HIV-negative adults in our study since our sampling procedure was not aimed at estimating HIV prevalence but rather comparing age-specific contact rates from representative sample of HIV-positive and HIV-negative adults.

Contrary to MICs and HICs who reported substantial reduction in social contacts due to NPIs [17,18,20], only 25% of participants in our study reported to have changed their contact behaviour between the second and third COVID-19 waves in Malawi. However, in this study, behavioural changes are self-reported and entirely hypothetical and the actual changes in social contact behaviour cannot be reliably measured, and that little is known about contact patterns in Malawi prior to the pandemic. Moreover, contacts among younger children reported by their parents or guardians may also be underreported affecting estimation of average contacts in this age group. Nevertheless, we did not find reduced contact rates among participants who reported to have reduced their social contacts due to COVID-19 pandemic restrictions compared to those who reported to not have changed their behavior. Additional analysis of average contacts between the COVID-19 waves (level 1 policies) compared to during the COVID-19 wave (level 3 policies) consistently showed little contact behavioural change similar to participants responses about their hypothetical contact behaviour (Supplementary Table 2 and Supplementary Table 3). This may suggest sub-optimal adherence to COVID-19 prevention measures such as restricted movements, closing of non-essential businesses, enforced social distancing, reduced public transportation capacity, and limited numbers (recommended 10 people per gathering) in this setting, which may reflect the day-to-day demands in the context of pressing economic hardship [46–48]. Economic implications of policy options aimed at limiting transmission of respiratory diseases need to be considered in order to make pragmatic recommendations that can be adhered to in the local context. Of note, relatively few *per capita* hospitalisations and deaths from COVID-19 occurred during the first wave in Malawi despite evidence of widespread transmission, and this may explain low compliance with recommendations to reduce social contacts during the second and third waves of COVID-19 pandemic in urban Malawi.

The strengths of this study include a sufficiently large sample size to detect significant differences in contact rates between age groups, although small numbers limited our precision for infants. We sampled households from 14 clusters making up a high proportion of residential Blantyre. Substantial number of participants were recruited during weekdays (75%) and weekends for representation and contact matrices were weighted for weekdays and weekends and accounted for reciprocity. This study collected novel data on social contacts in Malawi, adding insights to limited primary datasets on contact patterns in LICs in Africa, with only 3 countries represented. Limitations include that reported contacts by participants may be subject to recall bias [49]. This bias was partially addressed, however, by conducting two visits within three days; asking participants on the first visit to remember all their contacts during waking up and going to bed, and on the second visit, asking participants to report those contacts. Prospective reporting of cases reduces bias, but can lead to overreporting [50]. Data on contacts within schools and other indoor spaces were not collected at fine scale, hence are difficult to assess. Social contacts may change over time [19,20], and our cross-sectional design did not include longitudinal sampling of mixing patterns. Our results may not be generalisable to rural settings of Malawi that have relatively low household density and socio-economic activities but large school sizes compared to urban communities [51]. Thus, it remains uncertain whether or not contacts would be low given mixed results from rural Zimbabwe and Kenya [13,26].

In conclusion, high rates of physical, age-assortative, and localised contacts were observed, particularly among secondary school children and adults. With the demographic shift that many LICs are undergoing this raises the potential for adults in this and similar settings to play a more prominent role in the transmission of respiratory diseases than typically the case in HICs. In addition, the lack of change in contact behavior in response to the ongoing

pandemic highlights specific challenges for mitigation strategies in poor communities with no social protection mechanisms. For pandemic planning, it will be crucial to better understand what factors would enable and encourage poor urban populations to reduce their contacts to slow pandemic spread if the need arises.

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Declaration of interest

None

Author contribution

Conceptualization; DT, SF, NF, AP

Data curation; DT

Formal analysis; DT

Funding acquisition; DT, RSH

Investigation; DT

Methodology; DT, SF, AP

Project administration; DT, KJ

Resources; DT, RSH

Software; DT

Supervision; SF, NF, KJ

Validation; DT, KCJ, JO, PM, MDP, AP, MK, LC, KEG, RSH, ELC, NF, SF

Visualization; DT

Roles/Writing - original draft; DT

Writing - review & editing; DT, KCJ, JO, PM, MDP, AP, MK, LC, KEG, RSH, ELC, NF, SF

All authors read and approved the final manuscript.

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Supplementary or supporting information

Supplementary Text 1

Statistical modelling framework for factors associated with social contacts

Social contact patterns were characterised by computing the median and mean number of contact events for a set of potential factors which included age, sex, occupation, education, HIV, day of the week, COVID-19 restriction, and household size. Bias-corrected and accelerated bootstrap confidence intervals for the mean and median number of contacts were based on 1000 bootstrap replicates. Factors associated with the mean number of mixing events at $p<0.10$ in univariable analysis included age, occupation, COVID 19 restrictions, and household size, with sex considered *a priori*, and were retained in multivariable analysis if they reduced the Akaike Information Criterion (AIC) e.g. All possible combinations of the retained factors/variables (model variants) were fitted to the same dataset and compared using AIC to identify a model with the lowest AIC value (final model). Final model estimate of each potential factor was adjusted by the final model variables in a multivariable analysis, which included age, sex, occupation, COVID 19 restrictions, and household size.

To obtain a contact rate ratio (CRR), a negative binomial mixed model with household random intercept terms was constructed, and the ratio of the mean number of contact events in each category of the factor relative to the reference category was calculated in both univariable and multivariable analysis. Statistical or mathematical description of the model specification is shown below;

Assume there are n households present for the social mixing survey, and n_i participants for the ith household. For each j participant, we measure their counts for m contacts, C_{ijh}, where

h = 1, …, m. The total number of contacts is given by T_{ij}, and some potential factors is given by X_{ij}. The aim is to identify if there are factors that are associated with contact frequency. Since counts of contacts outcome is over-dispersed (mean not equal to variance), we use negative binomial to analyse each contact. The function *glmm.nb* (https://github.com/nyiuab/NBZIMM) allows analysis of the data for contact h using negative binomial mixed models (NBMM).

$C_{ijh} \sim NB(C_{ijh}|\mu_{ijh}, \theta_h)$

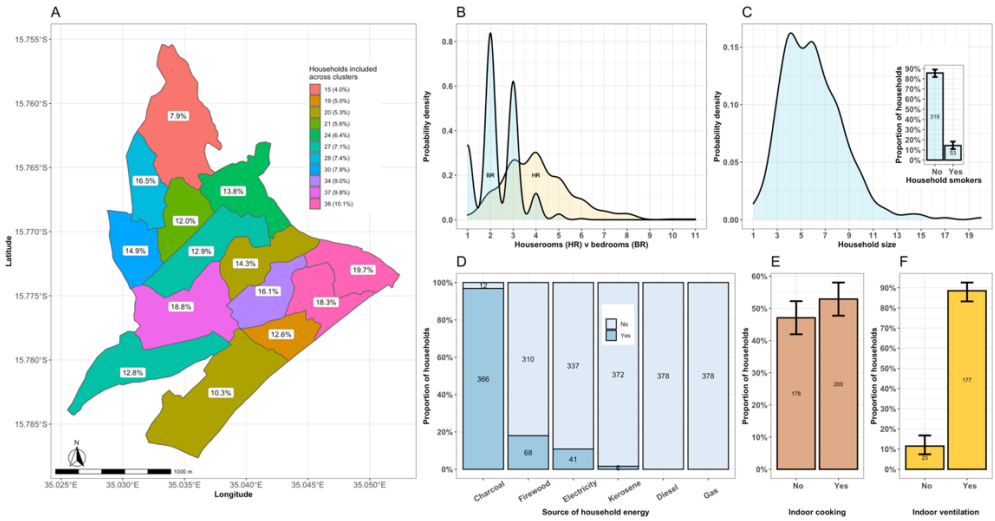
$log(\mu_{ijh}) = log(T_{ij}) + X_{ij}\beta_h + G_{ij}b_{ih}$, where $b_{ih} \sim N(0, \tau_h)$

Where μ_{ijh} is the mean number of contacts, the dispersion parameter θ_h determines the over-dispersion, the offset $log(T_{ij})$ accounts for the varying total contacts, β_h is a vector of fixed effects, b_{ih} are random effects, G_{ij} denotes the vector of group-level covariates, τ_h is the standard deviation of the random effects. The function *glmm.nb* iteratively approximates the NBMMs by fitting a linear mixed model using the function *lme* from the R package *nmle*. The dispersion parameter θ_h is then updated using Newton Raphson algorithm as in the function *glm.nb* of *MASS* R package.

Supplementary Table 1. Ndirande community total population versus total sampled population and their respective proportions per age group.			
Age group, years old (y)	Population size†	Sample size	Proportion
<1y	2414	65	2.7%
1-4y	10182	230	2.3%
5-14y	25780	265	1.0%
15-19y	11150	188	1.7%
20-49y	42417	301	0.7%
50+y	5388	152	2.8%
Total	97,331	1,201	1.2%
† Data on the total population in each age group from previous census in Ndirande community (STRATAA study) (Thindwa et al., 2020)			

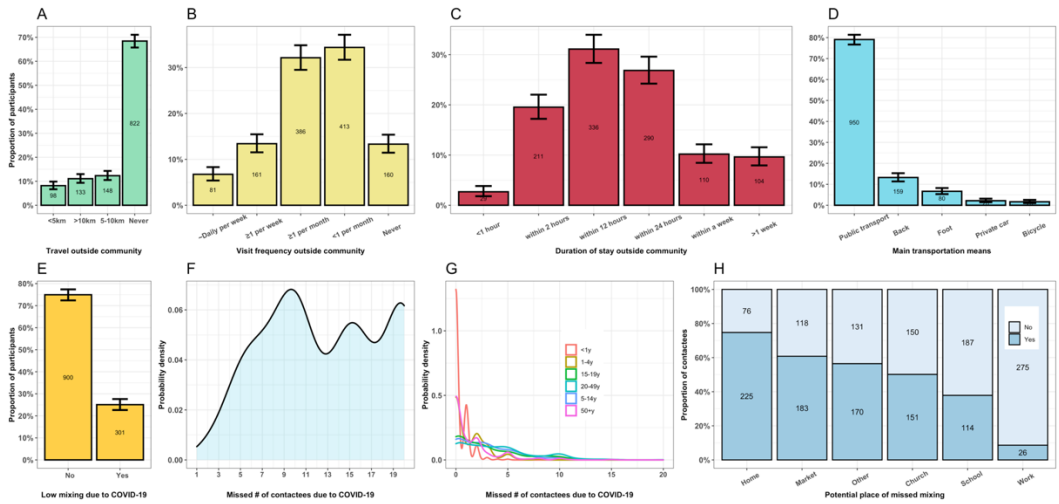
Supplementary Table 2. Mean number of contacts OUTSIDE homes during different levels of COVID-19 control policies, and participant's responses about their hypothetical additional contacts if COVID-19 did not occur in Ndirande community, Blantyre, Malawi.			
COVID-19 control policy	Number of participants	Number of contacts	Mean number of contacts (95%CI)
Level 1 (Apr-May) †1	300 (50.9)	1228 (44.1)	1.93 (1.71, 2.16)
Level 3 (Jun-Jul) †2	289 (49.1)	1559 (55.9)	2.76 (2.49, 3.08)
COVID-19 control policy	Avoided contacts due to COVID-19	Had contacts despite COVID-19	Chi-square test
Level 1 (Apr-May) †1	91 (42.3)	209 (55.9)	$X^2 = 10.04$, p = 0.002
Level 3 (Jun-Jul) †2	124 (57.7)	165 (44.1)	
†1 Social distancing, recommended face mask wearing, rotational working, limited transit vehicles, self-quarantine for returning travellers, and restrictions of gatherings to100 people †2 Restricted movements, enforced facemask wearing, closing of non-essential businesses, enforced social distancing, reduced public transportation capacity, and 10 people restricted gatherings.			

Supplementary Table 3. Mean number of ALL contacts during different levels of COVID-19 control policies, and participant's responses about their hypothetical additional contacts if COVID-19 did not occur in Ndirande community, Blantyre, Malawi.			
COVID-19 control policy	Number of participants	Number of contacts	Mean number of contacts (95%CI)
Level 1 (Apr-May) †1	636 (53.0)	6241 (49.8)	9.81 (9.46, 10.20)
Level 3 (Jun-Jul) †2	565 (47.0)	6291 (50.2)	11.13 (10.77, 11.63)
COVID-19 control policy	Avoided contacts due to COVID-19	Had contacts despite COVID-19	Chi-square test
Level 1 (Apr-May) †1	144 (47.8)	492 (54.7)	$X^2 = 4.22$, p = 0.040
Level 3 (Jun-Jul) †2	157 (52.2)	408 (45.3)	
†1 Social distancing, recommended face mask wearing, rotational working, limited transit vehicles, self-quarantine for returning travellers, and restrictions of gatherings to100 people †2 Restricted movements, enforced facemask wearing, closing of non-essential businesses, enforced social distancing, reduced public transportation capacity, and 10 people restricted gatherings.			

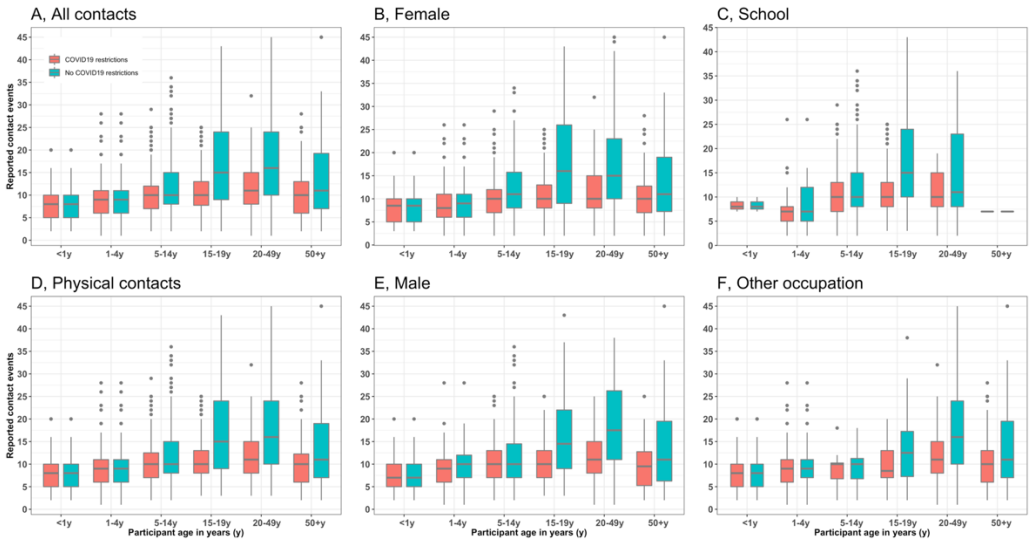


Supplementary Figure 1. Community and household composition in urban setting of Blantyre, Malawi 2021. Map of sampled study households by cluster, where the absolute number and proportion in the legend represents number of households sampled and the proportion of households in that cluster relative to all households, respectively, and the proportions in the map are the proportion of study households by clusters (A); The

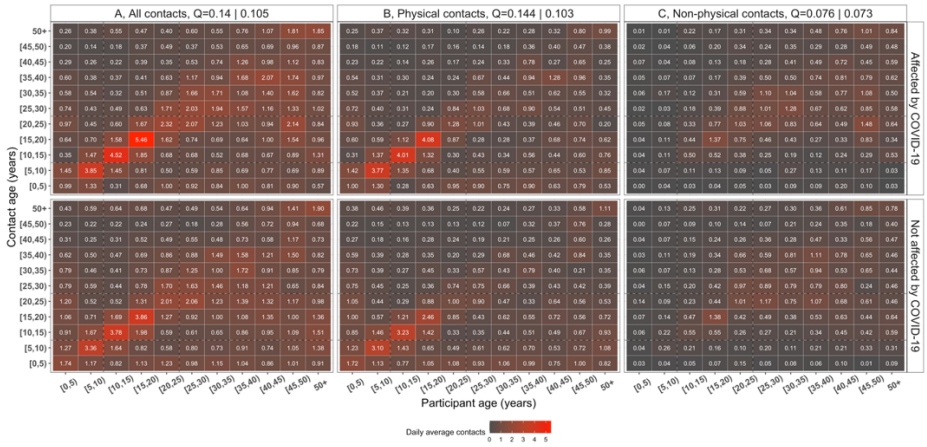
probability distribution of the number of all household rooms compared to sleeping rooms (B); The probability distribution of the number of members in the household, with insert plot showing the proportion of smokers in all sampled households (C); Proportion of households using different sources of household energy (D); Proportion of households with indoor cooking (E); and proportion of households with indoor ventilation among households with indoor cooking (F).



Supplementary Figure 2. Travel history and COVID-19 related social behaviour. Proportion of participants: who travelled unique distances in the last 24 hours before initial study visit (A); with different visiting frequency outside Ndirande community (B); with different lengths of stay outside Ndirande community among those who make visits (C); using different means of travelling during visits outside Ndirande (D); and who reported having reduced number of contact events due to COVID-19 pandemic (E). The probability distribution of the number of missed contacts due to COVID-19 pandemic by overall (F) and age group (G). The proportion of hypothetical contacts and potential places where those contacts could have occurred in the absence of COVID-19 pandemic (H).

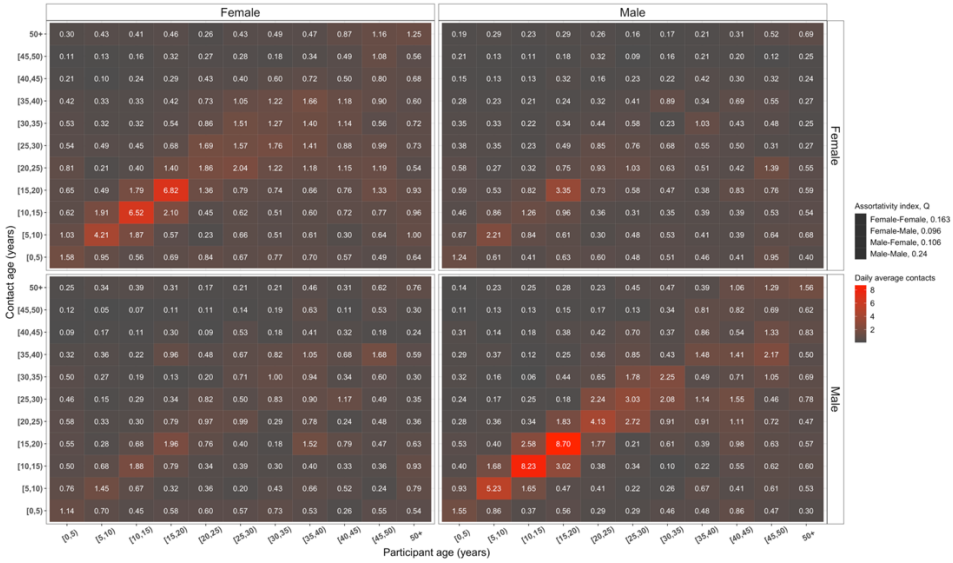


Supplementary Figure 3. Distribution of contacts and contact events in those whose contact behaviour is affected or not affected by COVID-19 pandemic. The median, interquartile range, minimum and maximum number of contacts in those with/without restrictive social contact behaviour due to COVID-19, stratified by all mixing events (A); physical mixing events only (B); female sex (C); male sex (D); schoolers (E); and other occupation (F).



Supplementary Figure 4. Social contact matrices by COVID-19 contacts behaviour change. The daily average rate of mixing between different age groups comparing participants who reported their social contact behaviour being affected and not affected by COVID-19 pandemic for all the contact events (A); physical contact events (B); and non-physical contact events (C). The number in each cell represents the daily mean number of contact events

between two given age groups, corrected for mixing reciprocity between participants and contacts and weighted by day of the week. The assortativity index Q quantifies the weight of mixing between individuals of the same age groups.



Supplementary Figure 5. Social contact matrices by gender interactions. The daily average rate of mixing between different age groups comparing interactions between female participants and female contacts (top-left panel), male participants and female contacts (top-right panel), female participants and male contacts (bottom-left panel) and male participants and male contacts (bottom-right panel). The number in each cell represents the daily mean number of contact events between two given age groups, corrected for mixing reciprocity between participants and contacts and weighted by day of the week. The assortativity index Q quantifies the weight of mixing between individuals of the same age groups.

Chapter 5: Research paper 4

Risk factors for pneumococcal carriage in adults living with HIV on antiretroviral therapy in the infant pneumococcal vaccine era in Malawi.

Author(s): Deus Thindwa, Thandie S Mwalukomo, Jacquline Msefula, Kondwani C Jambo, Comfort Brown, Arox Kamng'ona, Charles Mwansambo, John Ojal, Stefan Flasche, Neil French, Robert S Heyderman, Todd D Swarthout.

Journal/publisher: AIDS

Type of publication: Original contribution

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Academic peer reviewed: Yes

Candidate's role: I helped to reshape an original concept for the manuscript by Professor Neil French, Professor Robert S Heyderman, and Dr Todd D Swarthout. I helped to curate the data. I developed analysis methods using mgcv R package and generated results. I wrote the first draft of the manuscript. I reviewed and responded to all comments from co-authors and those from the journal reviewers to generate the published manuscript.

Risk factors for pneumococcal carriage in adults living with HIV on antiretroviral therapy in the infant pneumococcal vaccine era in Malawi.

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Abstract

Objective

Adults living with HIV (ALWHIV) on antiretroviral therapy (ART) are at high risk of pneumococcal carriage and disease. To help evaluate carriage risk in African ALWHIV at least 4-years after infant pneumococcal conjugate vaccination introduction in 2011, we assessed association between pneumococcal carriage and potential risk factors.

Methods

Nasopharyngeal swabs were collected from adults aged 18-40 years attending an ART clinic during rolling, cross-sectional surveys in Blantyre, Malawi between 2015-2019. We fitted generalised additive models to estimate the risk of sex, social economic status (SES), living with a child <5y, and ART duration on carriage.

Results

Of 2,067 adults, median age was 33y (range 28-37), 1,427 (69.0%) were females, 1,087 (61.4%) were in low-middle socio-economic-status (SES), 910 (44.0%) were living with a child <5y, and median ART duration was 3.0 years (range 0.004-17). We estimated 38.2% and 60.6% reductions in overall and vaccine-serotype carriage prevalence. Overall carriage was associated with low SES, living with a child <5y and shorter duration on ART. By contrast, vaccine-type carriage was associated with living without a child <5y and male sex.

Conclusion

Despite temporal reductions in overall and vaccine-serotype carriage, there is evidence of incomplete vaccine-serotype indirect protection. A targeted-vaccination campaign should be

considered for ALWHIV, along with other public health measures to further reduce vaccine-serotype carriage and therefore disease.

Key words: Pneumococcal carriage, pneumococcal conjugate vaccine, human immunodeficiency virus, herd immunity, antiretroviral, risk factors, Malawi

Running title: Pneumococcal carriage in adults with HIV on ART

Introduction

Pneumococcus is a common coloniser of the human nasopharynx, particularly in young children and populations with human immunodeficiency virus (HIV) [1]. Pneumococcal colonisation is a prerequisite for transmission and the development of disease, including otitis media, sinusitis, pneumonia, meningitis, and bacteraemia [2]. The pneumococcus is associated with a large burden of disease in adults living with HIV (ALWHIV) compared to adults without HIV [3–5]. Adult HIV prevalence remains high (>10%) in many sub-Saharan African countries, with Malawi reporting a national prevalence of 10.6% [6–8]. The use of antiretroviral therapy (ART) has substantially increased survival and reduced the incidence of invasive pneumococcal disease (IPD) [9]. However, despite >85% of ALWHIV in Malawi receiving ART [10–12], ALWHIV remain at greater risk of IPD than adults without HIV [3].

Pneumococcal conjugate vaccines (PCVs) are widely used in infant schedules in low- and middle-income countries (LMICs), generally targeting the most commonly invasive serotypes in this age group [1]. To date, in contrast to high-income settings, immunisation of vulnerable adults with pneumococcal vaccines has not been adopted in most LMICs such as Malawi, nor are pneumococcal vaccines available outside the Expanded Program on Immunisation (EPI) [13]. In November 2011, Malawi introduced the 13-valent PCV (PCV13) into the national EPI using a three-primary-dose schedule without booster (3+0; one dose at 6, 10 and 14 weeks of age). Despite nearly 10 years of >80% PCV13 three-dose coverage among age-eligible children, there is evidence of a sub-optimal reduction in both vaccine-serotype (VT) carriage prevalence and VT-IPD incidence in children and ALWHIV in Malawi [14–16]. Similar evidence of residual VT carriage prevalence is also reported in the Gambia and Mozambique after 5 and 2 years of implementation, respectively, [17] despite both countries also reporting >80% PCV three-dose coverage under a 3+0 schedule [18,19]. There is

increasing evidence that the indirect protection offered by an infant PCV against VT carriage, especially in ALWHIV, is sub-optimal [14,18].

The most effective strategy to reduce residual VT-IPD burden in ALWHIV depends on the factors shaping VT carriage and disease risk. Before introducing infant PCV in Malawi and South Africa, risk factors for IPD in ALWHIV included younger age, female sex, cotrimoxazole resistance, underlying medical conditions and living in a densely populated area [3,4]. Conversely, risk factors for carriage of any pneumococcal serotype included exposure to infants exposed to HIV [20,21], low socio-economic status (SES), high density living in housing with inadequate ventilation and with intense social contacts [22–25]. Moreover, among Malawian ALWHIV, VT and non-VT (NVT) carriage prevalence was found to be higher in those on ART than not on ART [26,27].

In the PCV era, however, there are important gaps in our understanding of the relative importance of key factors for pneumococcal carriage and disease among ALWHIV. These include duration on ART, PCV vaccination status among children in the household, and SES. Following our recent data from Blantyre, Malawi showing high residual VT carriage and its determinants in PCV13-vaccinated and unvaccinated children and in ALWHIV [15,16], we extend the analysis to identify age- and time-dependent risk factors for pneumococcal carriage in ALWHIV on ART using generalised additive modelling.

Methods

Study design

Blantyre spans 2,025 km^2, with an urban (population density 3,334/km^2) and rural (253/km^2) population of approximately 800,000 and 451,000 people, respectively. [28]. As described

elsewhere [15], rolling, prospective cross-sectional pneumococcal nasopharyngeal (NP) carriage surveys were conducted between 29 June 2015 and 9 August 2019 in Blantyre to investigate temporal change of pneumococcal colonisation in ALWHIV on ART. The majority (98.6%) of sampled individuals were on a first line ART regimen containing either i) Zidovudine, Lamivudine and Efavirenz, ii) Tenofovir, Lamivudine and Efavirenz or iii) Tenofovir, Lamivudine and Nevirapine [29]. Eight pneumococcal carriage surveys (each approximately 6 months in duration) were conducted, as per study protocol, from 3.6 to 7.9 years after infant PCV13 introduction into the EPI schedule. Thus, ≥2 carriage surveys per year except in 2019 when only one carriage survey was conducted. ALWHIV aged 18-40 years were recruited from the Queen Elizabeth Central Hospital (QECH) ART clinic in Blantyre using a systematic sampling approach. Exclusion from the study included being currently on treatment for tuberculosis, hospitalisation within two weeks of recruitment and previously enrolled in the survey.

Nasopharyngeal sample collection and processing

An NP swab sample was collected from each participant and processed at the Malawi-Liverpool-Wellcome Programme laboratory, co-located to QECH, to ascertain the presence of pneumococci. Samples were collected and processed according to World Health Organisation guidelines [30]. Serotyping was done using latex agglutination, based on picking a single colony, to identify serotypes targeted by PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F). Non-typeable and NVT isolates were both classified as NVT. Pneumococcal carriage was further evaluated using DNA microarray techniques, a technique which, in the case of co-carriage of multiple pneumococcal serotypes, differentiates all individual serotypes and reports relative abundance of each serotype in carriage [31–33]. Microarray was implemented only in surveys 1 through 4 and with samples having latex-

confirmed pneumococcal carriage. Further details of sample processing was reported earlier [15,32].

Data collection and analysis

Participant data collected at recruitment included age, sex, cohabitation with a child <5y, social economic status (SES), duration of ART use, CD4+ T-cell count, current ART regimen and cotrimoxazole use. A multiple imputation random forest-based method, using MissForest R package [34], was conducted to impute 1 (0.0005%), 297 (14.4%), and 537 (26.0%) missing data points on cohabitation with a child <5y, SES, and duration of ART use, respectively. Though reported in the descriptive analysis, CD4+ cell count was excluded from model-based analyses because 46.0% of its data points were missing, a proportion above the acceptable standard threshold for imputation [34]. Duration on ART was not used as a continuous variable because of data sparsity in age- or time-stratified analyses but was categorised as short (<3 years) or long (≥3 years) duration based on (1) a previous study in rural Malawi which showed strong evidence of high pneumococcal carriage during the first 2 years of ART use [26], and (2) the median value of ART duration in this study.

Individual fitted carriage prevalence estimates were categorised into 18-24y, 25-29y, 30-34y, and 35-40y age groups reflecting their distinct IPD incidence [3]. Time was stratified into year of survey initiation (2015, 2016, 2017, 2018 and 2019). Seasonality in carriage was captured using an indicator variable with values ranging from January to December based on NP sample collection month [26].

Generalised additive modelling framework

We used a generalised additive modelling (GAM) framework to fit to age- and time-specific trajectories of pneumococcal carriage, and allow flexibility in capturing nonlinear carriage dynamics. In brief, we used penalised B splines (P-splines) for the age and time spline smoothers to avoid knot selections which usually introduce under- and over-fitting biases when trading-off model fit to the data and the smoothness of the curve [35]. A penalized log-likelihood maximization was used to fit a non-parametric binomial model with complementary log-log link function defined by log-hazard of carriage as a function of the risk factors and a spline in age and time. No time-series autocorrelation structure was included in the model fits because ALWHIV were independently sampled without replacement and with no evidence to suggest strong autocorrelation across time.

Age- and time-dependent carriage prevalence estimation

We modelled age- and time-dependent carriage trajectories separately for overall (VT+NVT) and VT carriage as outcome variables for a set of potential risk factors. Due to reported poor immunogenicity and effectiveness of PCV13 against serotype 3 [36,37], we also modelled VT carriage without serotype 3 (VT-st3) to explore changes in carriage prevalence. A model with age and time smoothers and potential risk factors including sex, seasonality, duration on ART, cohabitation with a child <5 years old, and SES were fitted to the carriage data to estimate the overall or VT carriage prevalence and risk factor-specific effects on carriage prevalence dynamics.

A 'gam' function in the 'mgcv' R package facilitated model fitting [38], based on a model formulated as $g\big(P(Y_i = 1|a_i, t_i)\big) = g\big(\pi(a_i, t_i)\big) = \eta(a_i, t_i)$, where Y_i is a binomial outcome on whether an individual i is carrying pneumococcus (1) or not (0); g is the complementary log-log link function; $\pi(a_i, t_i)$ is the carriage prevalence estimate for individuals of age (a_i)

at time (t_i); $\eta(a_i, t_i)$ is a nonparametric linear predictor as function of individual age and time, and a set of risk factors. The linear predictor on a predictor scale is further expanded using the equation $\eta(a_i, t_i) = \beta_0 + \sum_k \beta_k G_i + te(a_i) + te(t_i)$, where β_0 is a model intercept, G_i refers to individual risk factor category, β_k is the risk factor coefficient, $te(a_i)$ and $te(t_i)$ denote tensor product P-spline of predictor age (a_i) and time (t_i).

The relative difference in carriage prevalence was computed by subtracting the GAM carriage prevalence estimate for each age or time category from the reference category and then dividing the difference by the reference category and then multiplying by 100%. The 95% confidence interval (95%CI) of the relative difference was estimated using $(\rho + 1) * [1 \pm 1.96 * \sqrt{\delta_1^2 + \delta_2^2 - (1.96^2) * \delta_1^2 * \delta_2^2}/(1 - 1.96 * \delta_1^2)] - 1$, where ρ is the relative difference, δ_1 and δ_2 are the coefficient variations of the reference and comparator categories, respectively, and coefficient variation being standard deviation divided by the observed mean [39]. GAMs with and without interactions between age group or time and each independent risk factor on the overall and VT carriage prevalence were fitted and compared using Akaike information criterion (AIC), and results of these tests are presented in S1 Table. Given the model complexities, sensitivity analyses assessed factors that may affect carriage estimates which included the impact on carriage of individual age group or survey, serotyping method, carriage autocorrection, model formulation and spline type. Detailed sensitivity methods and results are presented in Supplementary Material (S1 Text and S2 Text). Analyses were conducted in R v4.1.1 [40], with statistical significance set at $p<0.05$, and the code is publicly shared via GitHub [41].

Ethical approval

Ethical approval for this study was granted by the College of Medicine Research Ethics Committee, Kamuzu University of Health Sciences (P.02/15/1677), the Liverpool School of Tropical Medicine Research Ethics Committee (14.056) and the London School of hygiene and Tropical Medicine (26839). Individual written informed consent, including consent for publication, was obtained from each participant prior to study recruitment.

Results

Descriptive analysis

A total of 2,067 ALWHIV aged 18-40y were enrolled in the study between 29 June 2015 and 9 August 2019. Among adults with non-missing data, 1,427 (69.0%, n=2,067) were females, 413 (23.3%, n=1,770) and 674 (38.1%, n=1,770) were from low and middle SES households, respectively, 1,156 (56.0%, n=2,066) were not living with a child <5y, 1,772 (98.5%, n=1,799) were on one of Malawi's first-line ART regimens, and 2,010 (97.2%, n=2,067) were using prophylactic cotrimoxazole at recruitment. The median age was 33y (IQR: 28-37, n=2,067), median CD4+ count was 252 cells/mm^3 (IQR: 138-443, n=1,117), and median duration on ART at the time of study recruitment was 3.0 years, (range: 0-17, n=1,530) (Fig. 1).

Using survey-aggregated data, serotype 3 comprised 77 (33.2%, n=232) of all VT serotypes identified. Survey-aggregated data showed that carriage prevalence was 784 (37.9%, n=2,067) for overall (VT+NVT) and 232 (11.2%, n=2,067) for VT. It also showed that overall and VT carriage prevalence was 537 (37.7%, n=1,427) and 155 (10.9%, n=1,427) among females, 247 (38.6%, n=640) and 77 (12.0%, = 640) among males, 195 (47.2%, n=413) and 59 (14.3%, n=413) in low SES, 276 (40.9%, n=674) and 85 (12.6%, n=674) in middle SES and 243 (35.6%, n=683), 73 (10.7%, =683) in high SES households, 361 (39.7%,

n=910) and 111 (12.2%, n=910) in adults living with a child <5y, 423 (36.6%, n=1,156) and 121 (10.5%, n=1,156) in adults living without a child <5y, 682 (38.5%, n=1,778) and 199 (11.2%, n=1,778) in adults on a first-line ART regimen, 9 (33.3%, n=27) and 3 (11.1%, n=27) in adults on second-line ART regimen, 767 (38.1%, n=2,010) and 228 (11.3%, n=2,010) in adults taking cotrimoxazole, 17 (29.8%, n=57) and 4 (7.0%, n=57) in adults not taking cotrimoxazole (Fig 1).

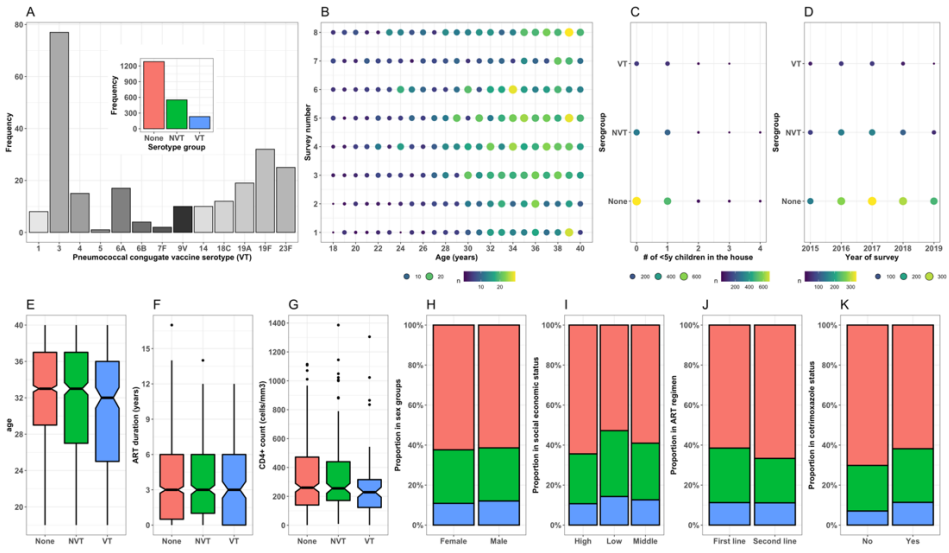

Figure 1. Demographics and clinical characteristics of participants using aggregated data across eight surveys. (A) Frequency of each VT in carriage; insert shows frequency of VT, NVT and no carriage. (B) Number of adults in each annual age per survey with circle size proportional to total sample size. The number of adults with VT, NVT, and no carriage living with (C) varying number of children <5 years or (D) across survey years. Notched box plots by serotype group representing participant distribution by (E) age, (F) duration on ART and (G) CD4+ count. Proportion of serotype group by (H) sex, (I) social economic status, (J) ART regimen and (K) Cotrimoxazole use.

Age- and time-dependent carriage prevalence estimates

Our GAM predicted a significant reduction in overall and VT carriage prevalence with increasing age and time. Among older age categories, overall carriage prevalence was lower than the reference younger adults aged 18-24y, with greatest reduction in adults aged 30-34y (-22.8%, 95%CI -34.1, -10.4). Likewise, VT carriage prevalence was lower in older than younger adults, with highest reduction in adults aged 30-34y (-45.1%, 95%CI -61.8, -25.6). Across time, we estimated lower overall (-38.2%, 95%CI -51.7, -23.6) and VT (-60.6%, 95%CI -79.1, -39.2) carriage prevalence in 2019 compared to 2015. In a sub-analysis, serotype 3 made up 22.6-34.7% (across age groups) and 18.9-38.2% (across time) of VT carriage prevalence (Table 1; Fig. 2).

Table 1. Age- and time-dependent overall and VT carriage prevalence, and relative difference in fitted carriage prevalence among ALWHIV on ART, 2015-2019 in Blantyre, Malawi.

	Observed overall carriage n/N (%)	Modelled‡ overall carriage prevalence (95%CI)	Relative difference† in overall carriage (95%CI)	Observed VT carriage n/N (%)	Modelled‡ VT carriage prevalence (95%CI)	Relative difference† in VT carriage (95%CI)
Age (years)						
18-24	144/310 (46.5)	49.2 (40.9, 58.0)	Reference	50/310 (16.1)	19.5 (13.0, 28.6)	Reference
25-29	120/337 (35.6)	40.0 (33.8, 46.8)	**-18.7 -32.3, -4.1)**	32/337 (9.5)	12.4 (8.7, 17.6)	**-36.4 (-58.0, -11.4)**
30-34	213/585 (36.4)	38.0 (32.1, 44.5)	**-22.8 (-34.1, -10.4)**	63/585 (10.8)	10.7 (7.4, 15.1)	**-45.1 (-61.8, -25.6)**
35-40	307/835 (36.8)	38.0 (31.8, 45.0)	**-22.8 (-33.3, -11.2)**	87/835 (10.4)	11.8 (8.1, 17.1)	**-39.4 (-55.9, -19.9)**
Year						
2015	114/265 (43.0)	45.0 (37.4, 53.3)	Reference	40/265 (15.1)	17.0 (11.4, 24.8)	Reference
2016	218/494 (44.1)	44.7 (38.0, 52.0)	-0.7 (-16.3, 16.8)	67/494 (13.6)	15.3 (10.6, 21.8)	-10.0 (-37.7, 24.4)
2017	226/561 (40.3)	41.6 (35.2, 48.6)	-7.6 (-22.1, 8.7)	69/561 (12.3)	13.1 (9.1, 18.8)	-22.9 (-46.9, 6.8)
2018	156/450 (34.7)	34.8 (29.0, 41.3)	**-22.7 (-36.2, -7.7)**	41/450 (9.1)	8.8 (5.9, 12.9)	**-48.2 (-67.3, -25.3)**
2019	70/297 (23.6)	27.8 (22.0, 34.6)	**-38.2 (-51.7, -23.6)**	15/297 (5.1)	6.7 (4.2, 10.6)	**-60.6 (-79.1, -39.2)**

‡ Carriage prevalence was modelled by fitting a GAM to individual carriage trajectories adjusting for risk factors as described in Methods

† Relative difference was computed by subtracting a GAM carriage prevalence estimate from the reference category and then dividing the difference by the reference category and then multiplying by 100%.

VT: PCV13 vaccine serotype, ALWHIV: adults living with human immunodeficiency virus, ART: Antiretroviral therapy, 95%CI: 95% confidence interval, Values in bold are statistically significant at $p<0.05$.

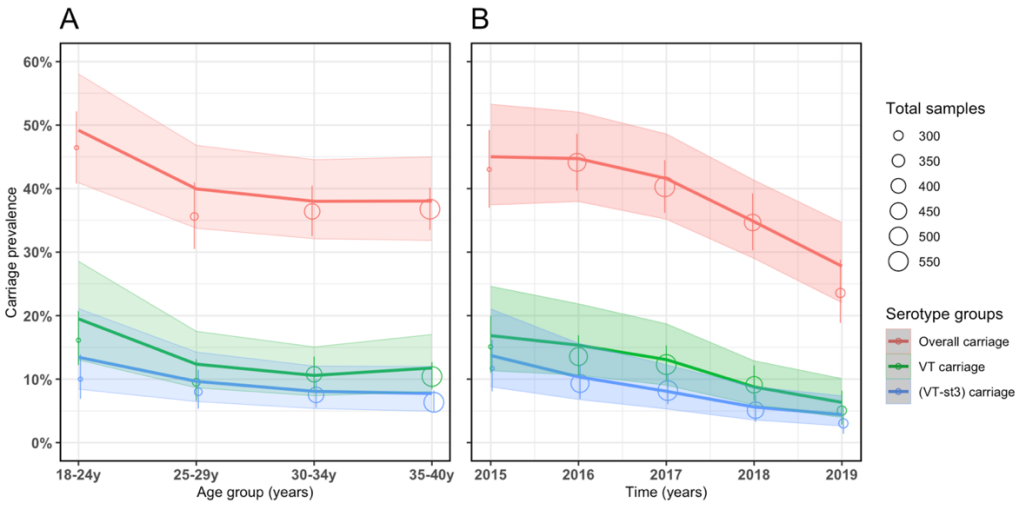

Figure 2. Observed and fitted pneumococcal carriage prevalence curves using data from rolling, prospective cross-sectional surveys in Blantyre, Malawi 2015-19. Number of carriage samples per age group between 18 to 40 years (y) and survey time from 2015 to 2019 represented by open circles radius proportion to total sample size with corresponding confidence intervals (vertical lines). P-spline GAM fitted lines and confidence intervals (ribbons) for the (A) age- and (B) time-dependent carriage prevalence stratified by overall carriage, vaccine serotypes (VT) carriage and VT carriage without serotype 3 (VT-st3).

Factors associated with overall carriage prevalence

Overall carriage prevalence was only independently associated with SES, with adults in low SES having 22% higher overall carriage than those in high SES (21.9, 95%CI 1.6, 43.7). In a sub-analysis with age and time-stratification, our model predicted that being a younger (18-24y) adult in low SES or living with a child aged <5y was significantly associated with higher overall carriage prevalence. Significant associations with low SES and shorter ART duration were also seen with overall carriage. Overall carriage prevalence in younger adults was significantly higher by 42% for those in low vs high SES (41.8, 95%CI 12.5, 74.0) and 27% for those living with vs those living without a child <5y (27.2, 95%CI 0.4, 57.4). Temporally, overall carriage prevalence was persistently higher by 50% in 2018 (49.5,

95%CI 13.4, 89.8) and 84% in 2019 (83.6, 95%CI 20.5, 167.4) in adults in the low vs high SES, and higher by 35% in 2015 (35.4, 95%CI 0.9, 77.2) and 131% in 2019 (130.8, 95%CI 43.2, 255.4) in adults with shorter vs longer duration on ART (Table 2, Fig. 3, S1 Table).

Factors associated with VT carriage prevalence

Sex, SES, ART duration and living with a child <5y were not significantly associated with VT carriage prevalence. However, with age- and time-stratification, our model of VT carriage outcome predicted that being a younger (18-24y) or older (35-40y) adult living without a child <5y or being older male significantly increased VT carriage prevalence. Temporally, living without a child <5y remained a significant predictor of higher carriage prevalence in 2019. Living without vs with a child <5y significantly increased VT carriage prevalence by 67% in younger adults 67.1 (95%CI 10.7, 140.5) and 41.0% in older adults (95%CI 1.5, 88.6). VT carriage prevalence was significantly higher in older males than females (50.0, 95%CI 7.2, 100.7; Table 2, Fig. 3, S1 Table).

Table 2. Risk factors for age- and time-dependent overall and VT with serotype 3 carriage prevalence, and the relative differences in the fitted carriage prevalence between the reference group and comparative groups among ALWHIV on ART, 2015-2019 in Blantyre, Malawi.

Risk factors	Overall % relative difference† (95%CI)	% Relative difference† in age-dependent carriage prevalence (95%CI)				% Relative difference† in time-dependent carriage prevalence (95%CI)				
		18-24y	25-29y	30-34y	35-40y	2015	2016	2017	2018	2019
Overall carriage										
Female vs male	-4.8 (-20.9, 13.5)	-18.1 (-35.7, 1.7)	16.3 (-15.9, 57.2)	19.0 (-8.5, 52.9)	-10.3 (-25.5, 6.8)	-13.5 (-35.5, 12.7)	-6.1 (-23.9, 14.2)	7.1 (-14.5, 32.5)	-12.9 (-33.8, 12.2)	16.8 (-27.4, 79.3)
Low vs High SES	**21.9 (1.6, 43.7)**	**41.8 (12.5, 74.0)**	2.1 (-26.0, 32.9)	22.2 (-2.8, 49.2)	19.9 (-1.8, 42.9)	16.5 (-16.2, 52.2)	19.3 (-5.4, 45.8)	26.7 (-0.1, 55.2)	**49.5 (13.4, 89.8)**	**83.6 (20.5, 167.4)**
ART <3y vs ART ≥3y	11.5 (-6.7, 31.5)	1.9 (-20.8, 28.4)	4.7 (-23.9, 40.6)	4.4 (-15.7, 26.8)	19.9 (-0.4, 41.8)	**35.4 (0.9, 77.2)**	3.9 (-15.7, 25.3)	-0.7 (-19.4, 19.9)	26.2 (-4.1, 61.4)	**130.8 (43.2, 255.4)**
With vs without child <5y	9.7 (-0.8, 29.1)	**27.2 (0.4, 57.4)**	2.6 (-22.9, 31.8)	0.3 (-19.5, 22.1)	8.9 (-9.2, 28.5)	8.7 (-18.4, 39.5)	1.1 (-17.9, 22.2)	7.4 (-12.4, 29.4)	13.8 (-14.3, 44.7)	-7.6 (-41.8, 31.8)
VT carriage										
Female vs male	-18.6 (-64,9, 53.7)	-16.6 (-51.2, 28.6)	26.8 (-42.8, 146.6)	-5.1 (-47.8, 59.1)	**-33.3 (-55.6, -5.8)**	-21.4 (-58.3, 31.3)	-18.0 (-48.9, 22.5)	-13.3 (-47.6, 33.1)	1.1 (-54.4, 92.7)	40.3 (-72.9, 315.6)
Low vs High SES	6.0 (-61.0, 91.2)	-26.5 (-67.6, 19.6)	12.5 (-46.6, 85.4)	23.8 (-32.4, 90.8)	35.8 (-14.5, 93.2)	17.7 (-47.0, 94.6)	-3.2 (-48.7, 47.9)	17.6 (-38.2, 80.9)	37.3 (-39.2, 133.2)	53.1 (-48.0, 229.1)
ART <3y vs ART ≥3y	0.0 (-55.1, 77.4)	-14.5 (-49.6, 32.3)	-15.3 (-63.7, 65.3)	33.7 (-19.3, 102.1)	-2.9 (-36.4, 35.0)	32.7 (-26.2, 114.5)	-6.9 (-42.9, 36.2)	-21.9 (-51.5, 13.6)	1.0 (-49.2, 67.6)	54.4 (-53.7, 255.6)
With vs without child <5y	33.1 (-40.9, 142.5)	**-40.2 (-64.7, -9.9)**	-6.6 (-52.3, 54.3)	8.6 (-36.6, 67.6)	**-29.1 (-52.8, -0.5)**	7.7 (-43.3, 73.9)	26.9 (-21.2, 89.1)	50.4 (-6.0, 125.0)	4.5 (-55.1, 78.6)	**-84.8 (-108.2, -57.9)**

† Relative difference was computed by subtracting a GAM carriage prevalence estimate of the reference category from the comparator category and then dividing the absolute difference by the reference category then multiplied by 100%.

ART: Antiretroviral therapy, ALWHIV: adults living with human immunodeficiency virus, CI: confidence intervals, y: year, SES: Social Economic Status score based a possession index which is calculated as a sum of positive responses for household ownership of each of the fifteen different functioning items such as watch, radio, bank account, iron (charcoal), sewing machine (electric), mobile phone, CD player, fan (electric), bednet, mattress, bed, bicycle, motorcycle, car, and television. Middle and high SES were combined and named as high SES.

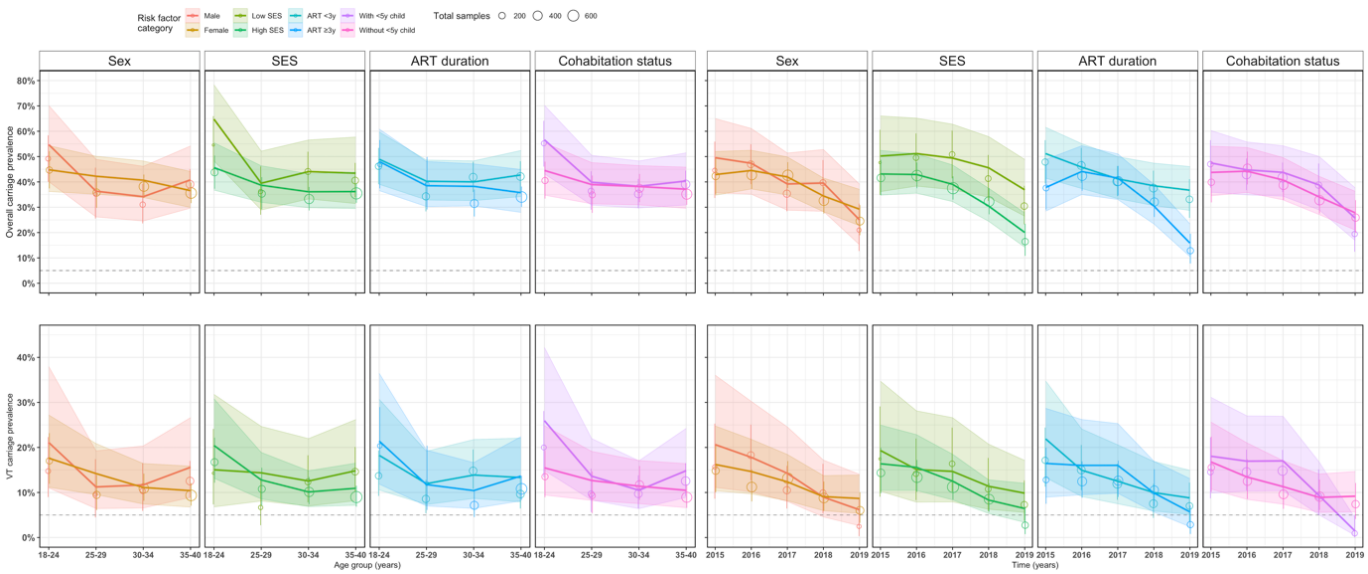

Figure 3. P-spline generalised additive model: Observed and fitted pneumococcal carriage prevalence curves for each potential risk factor category using data from rolling, prospective cross-sectional surveys in Blantyre, Malawi 2015-19. Nasopharyngeal samples across age groups from 18 to 40 years (y) and time represented by open circles. Circle radius is proportional to total sample size with corresponding confidence intervals (vertical lines). The coloured lines show P-spline GAM fitted model and confidence intervals for age- and time-dependent carriage prevalence for overall carriage (plots from first row) and vaccine serotypes (VT) carriage (plots from second row) stratified by risk factor categories.

Discussion

We used GAMs to estimate age- and time-dependent overall (VT+NVT) and VT pneumococcal carriage prevalence and related risk factors in ALWHIV on ART. We analysed overall and VT carriage separately to take into account the effect of a high uptake infant PCV13 programme [42]. Overall and VT carriage declined with increasing age group and time, with VT carriage having a faster decline (faster still if serotype 3 was excluded from VT). Our models predicted higher overall carriage prevalence in younger adults from low SES and living with a child <5y, as well as those with shorter duration on ART. Conversely, VT carriage prevalence was predominantly high in older males, and younger and older adults not living with a child <5y. These findings suggest that the decline in VT carriage prevalence across time in ALWHIV on ART is in part due to VT indirect protection from vaccinated younger children, although it is imperfect in males or adults not living with younger children, who may potentially have different routes of pneumococcal acquisition outside the household. Accelerated temporal reduction in overall pneumococcal carriage suggests a combination of factors including the indirect effect of infant PCV13 vaccination, consequence of demographic change and general improvement in population-level immunity due to suppression of HIV viral load, and improved nutrition and access to healthcare [43–45], on the background of falling rates of pneumococcal disease which were occurring before PCV13 introduction [46].

Our current analysis extends our previous observations that focussed mainly on high residual VT carriage and its determinants in PCV13-vaccinated and unvaccinated children [15,16]. We now show substantially high overall and VT carriage prevalence in ALWHIV during the earlier (45% and 17%) than later (28% and 7%) years post infant-PCV13 introduction. VT carriage declined faster than overall carriage, suggesting cumulative vaccine-induced

community-level indirect protection from infant PCV vaccination [47–49]. The temporal reduction in VT carriage prevalence was even more marked when serotype 3 was excluded (and included as NVT), supporting accumulating evidence of the reduced effectiveness of PCV13 against serotype 3 [36,37].

Higher overall and VT carriage prevalence among younger than older adults reported in this study may suggest distinct high carriage acquisition risk in younger adults, partly supported by recent evidence of higher rates of skin-to-skin contacts between younger adults and with other age groups in urban Blantyre [50]. The shorter median duration on ART amongst the younger adults as shown in S6 Fig may contribute to this residual pneumococcal carriage through incomplete immune reconstitution at both the systemic and mucosal level [27,51,52].

Low SES neighbourhoods in urban Blantyre predominantly comprise high-density informal settlements, relatively larger households and low rates of formal employment [28]. Thus, substantial overall carriage prevalence in younger adults from low SES suggests that factors associated with low SES such as poorly ventilated and overcrowded houses with intense social contacts are reservoirs for pneumococcal carriage in the PCV13 era [16,28,50,53]. On the contrary, non-differential VT carriage prevalence by household SES underlines an important role PCV vaccination plays to outweigh infection risks in poor settings. We uncover a phenomenon where adults living with children <5y, mostly PCV13 recipients given the high (>90%) infant PCV13 vaccination coverage [54], have substantially lower VT but higher overall carriage prevalence suggesting some non-vaccine serotype (NVT) replacement in adults within households, in line with evidence from rural Malawi and South Africa [55,56].

In this setting, VT carriage prevalence was higher in older male than female adults. VT carriage acquisition between mothers and their infants has been demonstrated previously in Malawi and South Africa prior to infant-PCV introduction [20,21]. Thus, our finding aligns with recent evidence in the same setting showing strong intergenerational social mixing patterns between females and their potentially PCV13-vaccinated younger children likely through parental or guardian roles [50]. This suggests that in the infant-PCV13 era, interruption of VT carriage transmission likely favours females than males.

Overall and VT carriage prevalence in ALWHIV on ART are heterogenous by age such that epidemiological models for carriage that incorporate ALWHIV should stratify for age for precise estimations. Our findings have policy implications in sub-Saharan African populations affected by HIV as persistent VT carriage in ALWHIV may imply continued risk of VT-IPD [14]. The indirect impact on VT carriage of alternative infant-PCV13 vaccine strategies, including 2 primary doses with a booster dose or double booster doses (i.e. 2+1 or 2+1+1), currently being tested to improve the control of childhood disease, should also be further evaluated in ALWHIV [18]. Indeed the 2+1 schedule, as implemented in South Africa, has generated indirect protection against IPD in unvaccinated older children and ALWHIV [48,57]. However, simply improving control of carriage in young children to indirectly protect vulnerable immunocompromised adults may be insufficient, particularly in the context of a high local force of infection and a rapid waning of vaccine-induced immunity [16,58]. Furthermore, we provide evidence of heterogeneity in VT carriage prevalence with males or adults living without <5y child in their homes being at highest risk of VT carriage in the PCV era. Together, these data add weight to our viewpoint that as with many people living in high-income countries, targeted-pneumococcal vaccination should be considered in ALWHIV in LMICs.

We used a robust dataset with adequate samples to compute estimates for the overall, VT and risk factor-dependent carriage prevalence. Nonetheless, there were some limitations to our work, including limited data on risk factors such as viral load, use of tobacco, presence of other chronic co-morbidities, adherence to ART and history of antibiotics, which may independently influence pneumococcal carriage dynamics [59]. However, population-level viral suppression has increased from 68% in 2015 to 87% in 2020 suggesting improved ART adherence [43]. In addition, latex agglutination method used in the main analysis for single serotype detection could underestimate our current prevalence estimates as compared to a more sensitive microarray method for multiple serotype detection as show in S2 Fig. Finally, the systematic recruitment of ALWHIV may be prone to bias if a cyclical pattern (unnoticeable here) is present in the important characteristics of the individuals as they attend the ART clinic [60].

In conclusion, despite temporal reductions in overall pneumococcal carriage, the risk of VT carriage and therefore subsequent pneumococcal disease remains high in ALWHIV. Efficient infant PCV schedules that enhance indirect protection together with targeted-vaccination for ALWHIV should be considered, along with other public health measures to further reduce VT carriage and disease. These measures should be supported by robust surveillance to assess effectiveness and identify early evidence of vaccine escape.

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Formal analysis; DT, SF

Funding acquisition; NF, RSH, TDS

Investigation; DT, TM, AK, JM, CB, TDS

Methodology; DT, SF

Project administration; TM, AK, JM, CB, CM, NF, RSH, TDS

Resources; NF, RSH, TDS

Software; DT

Supervision; SF, NF, KCJ, TDS

Validation; DT, TM, KCJ, AK, JM, CB, CM, JO, SF, NF, RSH, TDS

Visualization; DT

Writing – original draft; DT

Writing - review & editing; DT, TM, KCJ, AK, JM, CB, CM, JO, SF, NF, RSH, TDS

All authors read and approved the final manuscript.

Data availability

An R script that was used to analyse the datasets is available in the GitHub repository [41].

Competing interests

The authors declare no competing interests.

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Supplementary or supporting information

Supplementary Text 1

Sensitivity analysis methods

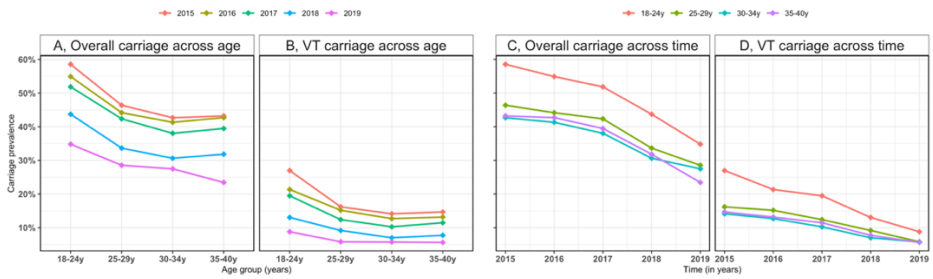
In a sensitivity analysis, we first investigated the overall (VT+NVT) and VT carriage prevalence for separate age groups across time as well as for separate time points across age groups. Second, where microarray showed multiple serotype carriage, we estimated carriage prevalence comparing VT carriage based on latex serotyping (single serotype defined) to microarray serotyping that defined a sample as both VT and NVT if both were detected, irrespective of each serotype's relative abundance. Third, to investigate potential differential smoothing parameters, we refitted the main P-spline model using three alternative types of splines including natural cubic spline, cubic regression spline and thin plate regression spline. Similarly, we evaluated the criteria for GAM selection by refitting the model (all risk factors were retained as before) with i) an age smoother only [$\beta_0 + \sum_k \beta_k G_i + te(a_i)$], and ii) a time smoother only [$\beta_0 + \sum_k \beta_k G_i + te(t_i)$], iii) both age and time smoothers [$\beta_0 + \sum_k \beta_k G_i + te(a_i) + te(t_i)$], and iv) interaction between age and time smoothers [$\beta_0 + \sum_k \beta_k G_i + te(a_i) + te(t_i) + te(a_i, t_i)$]. Finally, diagnostic checks for the P-spline model were conducted by checking residuals of the fitted models for autocorrelation of carriage samples across time.

Supplementary Text 2

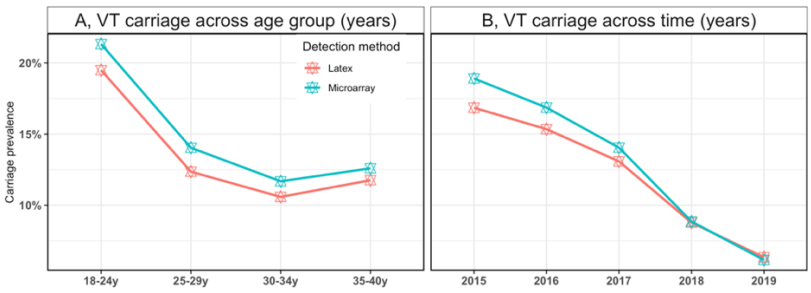
Sensitivity analysis results

Given the model complexities and factors that may affect carriage estimates, sensitivity analyses were implemented to assess the impact on carriage of individual age group or survey, serotyping method, carriage autocorrection, model choice and spline type. Unlike VT carriage, a substantial 15.6-20.6% drop in overall carriage prevalence was seen in the last two surveys (2018-2019) compared to 2015-2017 surveys. Also, younger adults had a higher carriage prevalence (≥18.1% for overall and ≥28.6% for VT) than older adults across time (S1 Fig). Microarray was superior vs latex agglutination at detecting VT carriage, increasing detection by 6.3-11.4% across age groups and 6.4-10.6% across 2015-17 (S2 Fig). Residuals for GAMs fitted to overall and VT carriage for a set of risk factors were mostly random noise, with statistically non-significant autocorrelation in carriage time series (S3 Fig, S4 Fig). The choice of spline for GAMs had no significant influence on fitted carriage prevalence curves whereas the choice of model formulation had, with models that included both age and time splines having similar curves compared to those with only age or only time splines (S5 Fig).

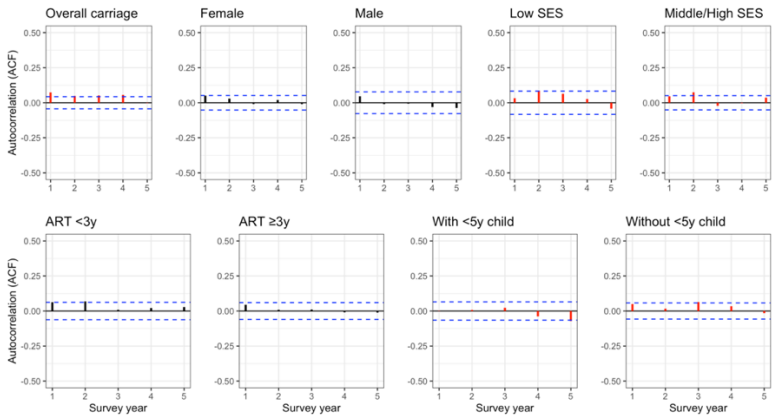
Supplementary Table 1. Test of interaction between age group or time and each independent potential risk factor on pneumococcal carriage prevalence using GAM models with and without interaction terms.					
Outcome (prevalence)	Interaction terms	DF	AIC for model without interaction	DF	AIC for model with interaction
Overall carriage	Age group*sex	10.31861	2683.996	11.09804	2682.404*
Overall carriage	Age group*SES	10.31861	2683.996	11.34193	2685.845
Overall carriage	Age group*ART duration	10.31861	2683.996	11.12247	2684.338
Overall carriage	Age group*cohabitation[1]	10.31861	2683.996	11.26536	2682.175*
Overall carriage	Time*sex	10.31861	2683.996	11.31885	2685.862
Overall carriage	Time*SES	10.31861	2683.996	11.39959	2684.419
Overall carriage	Time*ART duration	10.31861	2683.996	12.72311	2678.682*
Overall carriage	Time*cohabitation	10.31861	2683.996	11.57051	2685.755
VT carriage	Age group*sex	9.609611	1431.703	10.62511	1432.768
VT carriage	Age group*SES	9.609611	1431.703	10.52064	1429.656*
VT carriage	Age group*ART duration	9.609611	1431.703	13.42847	1427.124*
VT carriage	Age group*cohabitation	9.609611	1431.703	10.63943	1431.334*
VT carriage	Time*sex	9.609611	1431.703	10.70135	1431.697*
VT carriage	Time*SES	9.609611	1431.703	10.77890	1432.731
VT carriage	Time*ART duration	9.609611	1431.703	10.84835	1431.816
VT carriage	Time*cohabitation	9.609611	1431.703	12.61655	1428.079*
VT - Vaccine serotype, DF - Degrees of freedom, AIC - Akaike Information Criterion, SES – socio-economic-status, ART – anti-retroviral therapy * Model with interaction terms improves fit to the data Cohabitation refers to participant living with one or more children <5 years old (Yes/No)					



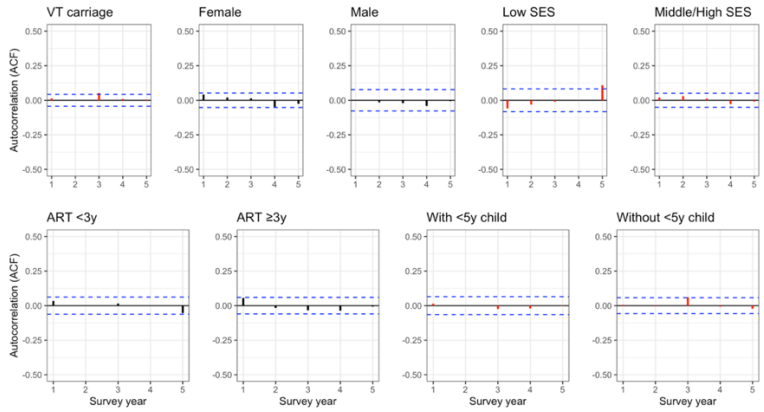
Supplementary Figure 1. Overall and vaccine serotype (VT) carriage prevalence for separate time points and age groups. (A) Overall carriage prevalence estimates for separate time points across age groups; (B) VT carriage prevalence estimates for separate time points across age groups; (C) Overall carriage prevalence estimates for separate age groups across time points; (D) VT carriage prevalence estimates for separate age groups across time points.



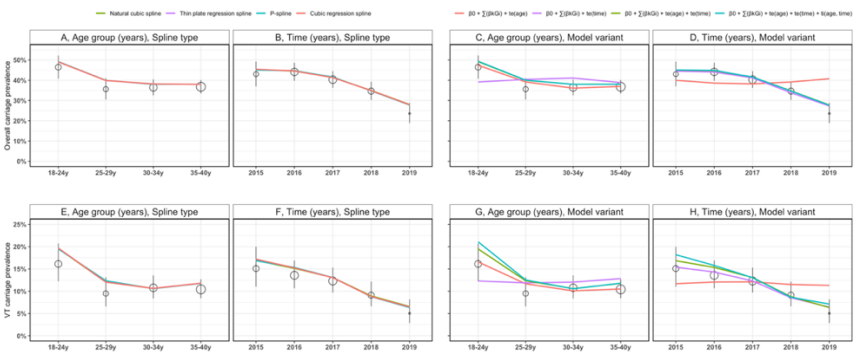
Supplementary Figure 2. Vaccine serotype (VT) carriage prevalence for two unique serotype detection methods across (A) age and (B) time. The latex agglutination method detected a single serotype, usually the one in highest abundance, whereas the microarray method detects all serotypes (VT and non-VT) carried and reports the relative abundance for each pneumococcal serotype in carriage. Assuming that each serotype contributes equally to carriage prevalence, detection by microarray has the advantage of detecting VT in low relative abundance and often not detected using latex agglutination, thus increasing VT carriage prevalence.



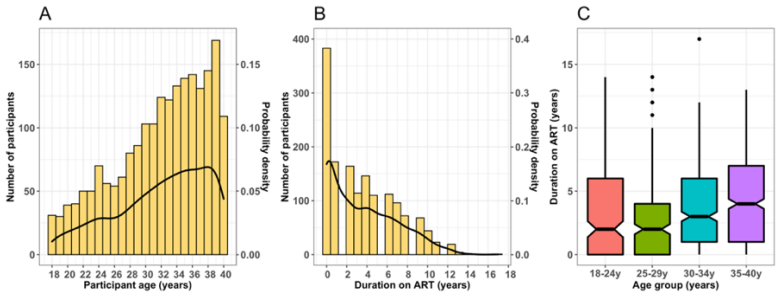
Supplementary Figure 3. Residual autocorrelation (ACF) plot of the main model of the overall carriage and related potential risk factors. No autocorrelation coefficients (values on the y axis) notably surpass the dotted blue region, implying that the autocorrelations across time are statistically zero at 95% confidence level, mostly representing random (white) noise.



Supplementary Figure 4. Residual autocorrelation (ACF) plot of the main model of the vaccine serotype (VT) carriage and related potential risk factors. No autocorrelation coefficients (values on the y axis) notably surpass the dotted blue region, implying that the autocorrelations across time are statistically zero at 95% confidence level, mostly representing random (white) noise.



Supplementary Figure 5. Age- and time-dependent overall and vaccine serotype (VT) carriage prevalence by spline types and variants of model formulation. The left plots compare carriage prevalence curves for models that are fitted using natural splines, thin plate splines, P-splines and cubic regression splines to the overall carriage stratified by (A) age group, (B) time, and to the VT carriage stratified by (E) age group, (F) time. The right plots compare carriage prevalence curves for models that are fitted under different model formulations to the overall carriage stratified by (C) age group, (D) time, and to the VT carriage stratified by (G) age group, (H) time where β_0 is a model intercept, G_i refers to individual risk factor category, β_k is the risk factor coefficient, $te(age)$ and $te(time)$ denote tensor product P-spline of predictor age and time, respectively.



Supplementary Figure 6. Distributions of participant age and their duration on antiretroviral therapy (ART) in years. Histogram and density plots showing frequency (bars) and probability density (black line) of study participants by (A) age and (B) duration on ART, and (C) the stratification of duration on ART by age groups. The notched plots in (C) show median, minimum, maximum, interquartile range and 95% confidence intervals for the median of the duration of ART.

Chapter 6: Research paper 5

Optimal age targeting for pneumococcal vaccination in older adults; a modelling study.

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Candidate's role: I helped to develop the idea that was initially conceived by the World Health Organisation Scientific Advisory Group of Experts. I worked with Dr Samuel Clifford to curate the data, develop analysis methods and generate results. I helped to write the first draft of the manuscript. I reviewed and responded to all comments from co-authors to generate the manuscript that will be submitted to the Journal.

Optimal age targeting for pneumococcal vaccination in older adults; a modelling study.

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Abstract

Background

In adults aged ≥55 years-old (y), invasive pneumococcal disease (IPD) incidence increases with age whereas the population size benefiting from pneumococcal conjugate/polysaccharide vaccines (PCV/PPV) and robustness of immunogenic response to vaccination decline. This poses a conundrum for identifying the optimal age for vaccination. We estimate how demographics, vaccine efficacy/effectiveness (VE), and waning VE impact on optimal age for single-dose pneumococcal vaccination.

Methods

Age- and vaccine-serotype-stratified IPD incidence from routine surveillance of adults ≥55y in Brazil, England, Blantyre (Malawi), and South Africa, ≥4-years after infant-PCV introduction, was used to parameterise exponential growth models of increasing IPD risk with age. A piecewise-constant model estimated VE and waning VE from prior studies. All estimates were then combined in a cohort model to assess the impact of age of vaccination with PCV13/15/20 or PPV23.

Findings

Adults ≥55y totalled 27·7 million, 66,589, and 6·9 million in Brazil, Malawi, and South Africa, of whom 51·3%, 51·0%, and 53·8% were <65y, whereas in England only 39·1% of 16·5 million were <65y. More annual IPD cases but a smaller share among adults <65y old were estimated in England (4,657; 19·9% <65y) compared to Brazil (186; 44·5%), Malawi (4; 62·5%), or South Africa (134, 47·9%). PCV13- and PPV23-serotypes caused the lowest (21·0%) and highest (97·9%) IPD cases in adults aged ≥55y across settings. Vaccination at 55y in Brazil, Malawi, and South Africa, and at 65y in England prevented the greatest

number of all estimated IPD cases, especially cases caused by PCV13 serotypes (30·1%, 22·4%, 18·0%, 10·2%), PCV15 (33·1%, 25·6%, 20·7%, 15·5%), PCV20 (45·0%, %, 52·8%, 37·4%, 30·5%), and PPV23 (23·0%, 24·3%, 16·0%, 15·7%), respectively, under slow waning and age-independent initial VE.

Interpretation

In low/middle-income countries, pneumococcal vaccines prevent more IPD if administered earlier in adulthood than is typical in high-income countries.

Funding

UK National Institute for Health and Care Research.

Research in context

Evidence before this study

Several authors of this work participated in a review on the use of pneumococcal vaccines in older adults as part of the evidence gathering for the World Health Organisation Scientific Advisory Group of Experts Working Group. While this review presented evidence on the efficacy or effectiveness of pneumococcal vaccines in older adults, it identified the absence of evidence on the age of pneumococcal vaccination in older adults that prevents the highest number of invasive pneumococcal disease (IPD) cases. We did an updated search of PubMed, Medline, Embase and Web of Science for studies on age targeting for pneumococcal vaccination in older adults published from Jan 1, 2003 to June 30, 2022, using the search terms "(optimal age targeting OR age targeting OR timeliness) AND (pneumococcal vaccination OR pneumococcal vaccines) AND (adults OR older adults OR elderly)". From this search, we identified only one study on the role of timeliness in the cost-effectiveness of older adult vaccination in Australia, whose results were published in Vaccine journal. This study explored the impact of the timeliness of pneumococcal conjugate vaccination (PCV) in older adults, and found that more hospitalisations and deaths were prevented (along with improved incremental cost-effectiveness ratio estimates) assuming PCV13 was given out in a more realistic average age of 70 years-old (y) than exactly at recommended age of 65y. Nonetheless, pneumococcal vaccines are effective against vaccine-serotype-IPD in older adults aged ≥55y who are at-high-risk of IPD. High-income countries (HICs) typically recommend pneumococcal vaccination at either 60y or 65y. Most low-income countries (LICs) and middle-income countries (MICs) do not have routine older adult pneumococcal vaccination programs, despite often less indirect protection from childhood PCV programs. Due to differences in population size and risk for IPD, the optimal age for older adult vaccination against pneumococci in LICs/MICs is unknown.

Added value of this study

This multicountry study uses data from long-standing older adult pneumococcal surveillance programs at the national/sub-national level, to explore the optimal age-targeting for a single-dose pneumococcal vaccination against vaccine-serotype-IPD in older adults living without human immunodeficiency virus in LIC (Malawi), MICs (Brazil, South Africa), and HIC (England). We provide the first evaluation of optimal age of vaccination with PCV13, PCV15, PCV20 or PPV23 vaccines to prevent the highest number of IPD cases across settings. We show that vaccinating at 55y in considered LICs/MICs is optimal whereas vaccinating at 65y prevents most IPD cases in England. We further show that, if completeness of case ascertainment by age is comparable, the optimal age for vaccinating a smallest number of individuals to prevent a case of vaccine-type IPD (highest vaccination efficiency) may vary by vaccine type and waning VE.

Implications of all available evidence

A sizeable vaccine preventable burden of IPD in older adults persists in many LICs/MICs. Offering pneumococcal vaccines earlier in adulthood than is typical in HICs is likely to maximise the impact in LICs/MICs, albeit cost-effectiveness and affordability will need to be considered when prioritising against other health expenditure. Our findings provide new evidence to enable the design and implementation of age-targeted vaccination policies to maximally reduce the burden of IPD in older adults living without HIV.

Introduction

Streptococcus pneumoniae (pneumococcus) is a major global cause of childhood mortality [1,2], but also causes a high burden of disease among older adults [2,3]. Two vaccines have been used to prevent pneumococcal disease in older adults ≥55 years-old (y): a 13-valent pneumococcal conjugate vaccine (PCV13) and a 23-valent pneumococcal polysaccharide vaccine (PPV23) [4]. Recently, 15- and 20-valent PCVs (PCV15, PCV20) have also been licensed and recommended for older adults in the United States [5,6].

Although routine infant PCV programs have generated indirect protection against vaccine-serotype (VT) pneumococcal disease among older adults [7,8], a substantial disease burden remains, composed of serotypes not targeted by childhood PCV programs and residual circulation of VT [2,9]. Among high-income countries (HICs) with a mature infant-PCV13 program, PCV13- and PPV23-targeted serotypes caused about 15% and 42%, respectively, of invasive pneumococcal disease (IPD) in older adults [2,10]. Routine infant-PCV programs in many low- and middle-income countries (LICs and MICs) have often led to less pronounced herd effects with continued circulation of VTs especially in the unvaccinated adult population [11,12], who happen to have no access to routine pneumococcal vaccination [13].

The recommended age for pneumococcal vaccination in older adults in HICs is typically either at 60y or 65y [4,14]. However, yet only a single study has assessed the age at which the most gain from such program is seen (in the Australian context) [15]. As the risk of severe pneumococcal disease increases with age [10,15], waning of protection from vaccination early in older adulthood risks disease at ages of highest disease incidence, whereas vaccination late in older adulthood cannot address the substantial disease burden among a large pool of susceptible older adults who have not yet been vaccinated.

In this modelling study, we explore the optimal age-targeting for a single-dose pneumococcal vaccination against VT-IPD in older adults living without human immunodeficiency virus (HIV) in Brazil, England, Malawi, and South Africa.

Methods

Study sites

We included England (HIC), Brazil and South Africa (MICs), and Blantyre in Malawi (LIC) in this analysis, to explore the optimal age-targeting for pneumococcal vaccination, as all have long-standing adult pneumococcal surveillance programs at the national or sub-national level [9,16–18]. More details on the respective IPD surveillance systems are in the appendix (Text S1). Infant-PCV13 has been in use since 2011 in South Africa (two primary doses and booster (2+1) schedule) and Malawi (3+0 schedule), with estimated 90-95% vaccination coverage [11,18]. In England, routine PCV13 immunisation program with 92% booster dose coverage has been in place since 2010, initially using a 2+1 schedule, switching to 1+1 schedule in 2020 [19]. In Brazil, a routine infant-PCV10 program was implemented in 2010 with a 3+1 schedule, switched to a 2+1 in 2016, with coverage estimated to be 80-85% [20].

In England, PPV23 has been recommended for risk groups since 1992, and for all adults aged ≥65y since 2003, with single-dose coverage rising to 70% in 2018 [17,21]. In Brazil, PPV23 has been recommended for use since the 1980s, but available free of charge only to institutionalised older adult, and thus coverage of <1% among all older adults [22]. In South Africa, although adult pneumococcal vaccination is recommended, there is no routine program nor nationally accepted guidelines [23]. In Malawi, neither routine adult pneumococcal vaccination program nor national guidelines exist [13].

Population demographics

The population demographics for adults ≥55y were obtained in annual age strata from population censuses conducted in 2010 for Brazil [24], 2011 England (updated in 2017) [25], 2018 Malawi [26], and 2011 South Africa [27]. To align with IPD surveillance timelines in respective countries, annual age population censuses were projected at a constant growth rate of 0·8% during 2010-2016 in Brazil and 1·3% during 2011-2016 in South Africa [28,29]. For England and Malawi, 2017 and 2018 populations already aligned with IPD surveillance time. Annual age population estimates were smoothed to reduce demographic stochasticity in downstream results by applying a 5-year moving average [30].

Invasive pneumococcal disease burden

For each site we used data on IPD burden in older adults in the presence of a mature infant-PCV program, defined as at least 4 years after infant-PCV introduction, to avoid inclusion of ongoing changes in IPD burden attributable to indirect effects from the childhood program [31]. The number of IPD cases caused by all serotypes, and serotypes targeted by PCV13, PCV15, PCV20 and PPV23 in annual age strata (55y to 85y+) were obtained from laboratory-based surveillance in each country (Fig S1). We calculated age and serotype distribution and proportionally inflated estimates by the number of IPD cases without serotyping available to correct for proportion serotyped. In England, where PPV23 has been in use in 65y+ at 70% uptake, we back-inflated the number of IPD cases in order to correct for the fact that in the absence of PPV23 vaccination, IPD incidence would be higher, especially in ages eligible for PPV23 vaccination. Details about back-inflation calculation are in the appendix (Text S2). Age aggregated (55-59y, 60-64y, 65-69y, 70-74y, 75-79y, 80-84y and 85y+) and serotype-specific IPD incidence was calculated by dividing by the age-group

specific population estimates. Due to the small number of reported IPD cases and incomplete serotyping information in Malawi, we only calculated the serotype distribution for all cases and assumed that it was the same in each age group.

The focus of this study was vaccination strategies for older adults living without HIV because adults living with HIV often have independent pneumococcal vaccine recommendations [12]. Thus, for adult HIV prevalence of >10% in South Africa [32], we adjusted IPD incidence estimates for HIV status. For 201 (18·7%) reported IPD cases, HIV status was reported. We took a 30% random subset of IPD cases with known HIV status and estimated a 49.3% proportion of IPD cases without HIV for this subset. We assumed that a similar proportion of IPD cases with unknown HIV status would be without HIV. We further accounted for similar serotype distribution in those with and without HIV. In Malawi, IPD cases could not be stratified by HIV infection status, and thus we used the age-dependent HIV infection rates in the general adult population and applied the relative propensity for IPD in older adults with and without HIV from South Africa to infer the incidence of IPD among older adults without HIV by age.

We modelled the reported age-specific IPD incidence among older adults without HIV per country as a function of age using an exponential growth model. Details about model fitting are in appendix Text S3. The expected incidence at age *a* is:

$$E(I|a) = \gamma e^{\beta a} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (1),$$

where $E(I|a)$ is the expected IPD incidence at age *a*, β is the growth rate, and γ is a constant of proportionality. Uncertainty was obtained by bootstrap sampling 1000 times using the

fitted parameter means and covariance matrix and summarisation of uncertainty via 95% quantiles of samples.

PCV and PPV vaccine efficacy/effectiveness

A previous systematic review identified studies that estimate vaccine efficacy/effectiveness (VE) against IPD from time since vaccination [2]. Four observational studies in HICs estimated VE at two or more time points for PPV23 [17,21,33–35]. One randomised controlled trial estimated VE against IPD and community-acquired pneumonia (CAP) following PCV13 use in older adults and found consistent 75% and 46% respective efficacy for 5 years following vaccination [36,37]. Thus, we assumed that PCVs' efficacy against IPD would continue to stay stable for five years, and thereafter decline in the same way as the scenario for PPV23. We represented the VE as a function of time since vaccination using piecewise constant models. The piecewise constant functions are shown in appendix (Fig S2, Fig S3). The VE was sampled using bootstrap sampling from a normal distribution centred on the mean VE at that time and standard deviation derived from the reported 95% interval.

Little evidence is available on changes in PPV23 or PCV13 VE by age at administration [15,38]. A UK study found no significant difference in VE of PPV23 when administered to 65y, 75y or 85y adults, although point estimates suggested a decline with age [17]. There is also some evidence that immune response to immunisation is partially impaired later in life [2]. Thus, as a base case we assumed that VE for all formulations was independent of the age of administration, but included a sensitivity analysis assuming that VE was 33% less of initial VE if given to adults aged 65-74y and 44% less of initial VE if given to adults aged 75+y using point estimates of VE of PPV23 against IPD in the 5 years following administration in adults <65y of 54%, decreasing to 36% for 65-74y and 30% for 75y+ [17].

PCV and PPV vaccine impact model

We developed a cohort model to simulate the risk for IPD in adults >55y in all four countries. Time steps in the model were set at 1 year. Age-dependent all-cause mortality was set to match observed population demographics of older adults living without HIV in all countries, and age-dependent IPD risks were set to match fitted IPD incidence in respective countries and years. We calculated the vaccine preventable number of IPD cases as the lifetime number of cases averted through vaccinating 100% of adults at the specified age for vaccination under the assumptions of age-dependency on initial VE and waning VE. We estimated the efficiency of the alternative strategies by reporting the number of age cohort individuals needed to vaccinate in order to prevent a case.

Sensitivity analysis assessed the influence of age-dependent initial VE on vaccine impact. All analyses were conducted using R language v4·1·1, with data and code available through GitHub https://github.com/deusthindwa/optimal.age.targeting.pneumo.vaccines.

Ethical approval

In Brazil, no patient consent is required since data are obtained through the National Epidemiological Surveillance approved by the Scientific Committee of the Instituto Adolfo Luiz (CTC 61-M/2020). In England, the UK Health Security Agency (UKHSA) has legal permission, provided by Regulation 3 of The Health Service Regulations 2002, to monitor the safety and effectiveness of vaccines for national surveillance of communicable diseases (http://www.legislation.gov.uk/uksi/2002/1438/regulation/3/made). In Malawi, the study protocol was approved by Malawi's National Health Sciences Research Committee (protocol 867), Kamuzu University of Health Sciences College of Medicine Research Ethics

Committee (COMREC) (P·01/08/609 and P·09/09/826), and the University of Liverpool Research Ethics Committee (RETH490). Individual patient informed consent was not required for the use of publicly available anonymised routine samples as per COMREC guidelines 5·6. In South Africa, ethical approval to conduct laboratory-based and enhanced surveillance was obtained from the Health Research Ethics Committee (Human), University of Witwatersrand (M140159) and individual patient consent was obtained for clinical data collection at enhanced surveillance sites. Ethical approval for this study was granted by the London School of Hygiene and Tropical Medicine (25787).

Results

Population demographics and IPD burden

Of the 27·7 million (m) older adults (≥55y) in Brazil, 16.5m in England, 66,589 in Blantyre Malawi, and 6·9m in South Africa, the proportion of older adults aged 55y to <65y was 51·3%, 51·0% and 53·8% in Brazil, Malawi and South Africa, substantially higher than the 39·1% in England. During the study period, Brazil (2015-2017), England (2016-2019), Malawi (2016-2019) and South Africa (2015-2018) estimated 186, 4,657, 4 and 134 average annual cases of IPD in adults ≥55y of which 44·5%, 19·9%, 62·5%, and 47·9% were in <65y olds. Cases caused by PCV13 serotypes accounted for 61·4%, 21·0%, 41·0%, and 32·8% of all IPD in Brazil, England, Malawi and South Africa, and PPV23 serotypes for 97·9%, 72·5%, 94·8%, and 73·2%, respectively (Fig 1).

The exponential model fitted the increase in IPD incidence with age well. The estimated IPD incidence in 85y was higher than in 55y olds by 2·48-fold (95% CI: 2·13-2·83) in Brazil, 2·19-fold (95% CI: 0·14-4·51) in Malawi, and 2·25-fold (95% CI: 1·88-2·62) in South Africa. In England the incidence increased more steeply to 11·00-fold (95% CI: 10·90-11·40)

higher in 85y than 55y, likely due to large proportion of elderly individuals in whom IPD burden is highest, compared to LIC/MICs, (Fig 1).

While the estimated number of IPD cases declined with age in Brazil, Malawi and South Africa, it increased in England due by a longer life expectancy. On the other hand, age-specific IPD incidence of total IPD incidence (age-scaled IPD incidence) increased with age in all settings irrespective of serotype, and with high uncertainty in Malawi due to small case numbers (Fig S4, Fig S5).

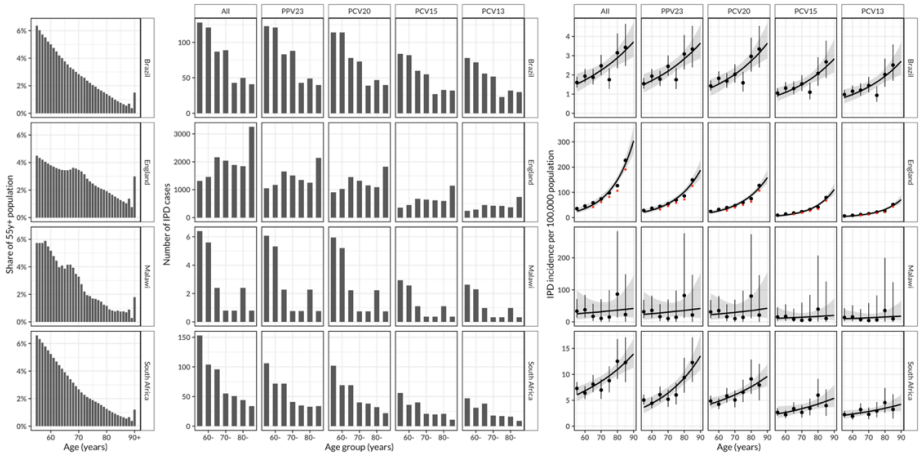

Figure 1. Population demographics and invasive pneumococcal disease (IPD) burden. (Left panel) Among individuals who are aged ≥55y, the proportion in annual age groups in Brazil, England, Malawi and South Africa as estimated from their national censuses, based on five years rolling average smoothed population counts to control for demographic stochasticity; (Middle panel) Number of IPD cases in five year age bands in older adults stratified by serotype in Brazil (2015-2017), England (2016-2019), Blantyre Malawi (2016-2019) and South Africa (2015-2018), reported from at least four years post-infant PCV introduction in each country. (Right panel) Serotype-specific reported and predicted IPD incidence per 100,000 population between 55y and 90y in Brazil, England, Malawi and South Africa. The

black circle represents estimated IPD cases per 100,000 population, the vertical line through the circle represents a 95% uncertainty interval in estimated IPD case number, the line is the exponential model fit and the ribbon represents a bootstrapped 95% confidence interval for the fitted line. The red and black points for England represent estimated IPD cases in the presence and assumed absence of PPV23 vaccination, respectively.

Optimal age for vaccination

The optimal age for vaccination, defined here as the age of a single-dose vaccination that could prevent most IPD cases, is attained when vaccines are given earlier in adulthood in considered LIC/MICs, but not for England (Fig 2). In the scenario of PPV23 use, rapid waning of VE and age-independent VE, we found the highest number of all IPD cases could be prevented if adults aged 55y are vaccinated, resulting in 18·6%, 95% confidence interval [95%CI] (15·3-21·9) of cases averted compared to a scenario without vaccination in Brazil, 19·6%, (16·3-23·1) in Malawi, and 12·8% (10·6-15·1) in South Africa, and if adults aged 65y are vaccinated in England, with 12·0% (9·7-15·1) prevented cases (Table S1). Higher proportion of all averted cases are estimated for using PCV20 vs PPV23 under fast waning VE among adults aged 65y compared to a scenario without vaccination in Brazil 27·4% (25·2-29·7) vs 13·3% (11·1-15·7), Malawi 28·5 % (26·0-31·3) vs 13·2% (11·1-15·4), South Africa 20·3% (18·6-22·1) vs 9·8% (8·2-11·5) and England 24·4% (22·5-26·2) vs 12·0% (9·7-14·3), respectively (Table S2). Additionally, more IPD cases are prevented under slow vs rapid waning VE scenario when PPV23 is given to adults aged 65y in Brazil 16·3% (14·6-18·0) vs 13·3% (11·1-15·7), Malawi 15·5 % (13·7-17·2) vs 13·2% (11·1-15·4), South Africa 12·0% (10·8-13·3) vs 9·8% (8·2-11·5), and England 15·7% (14·1-17·3) vs 12·0% (9·7-14·3), respectively (Table S3).

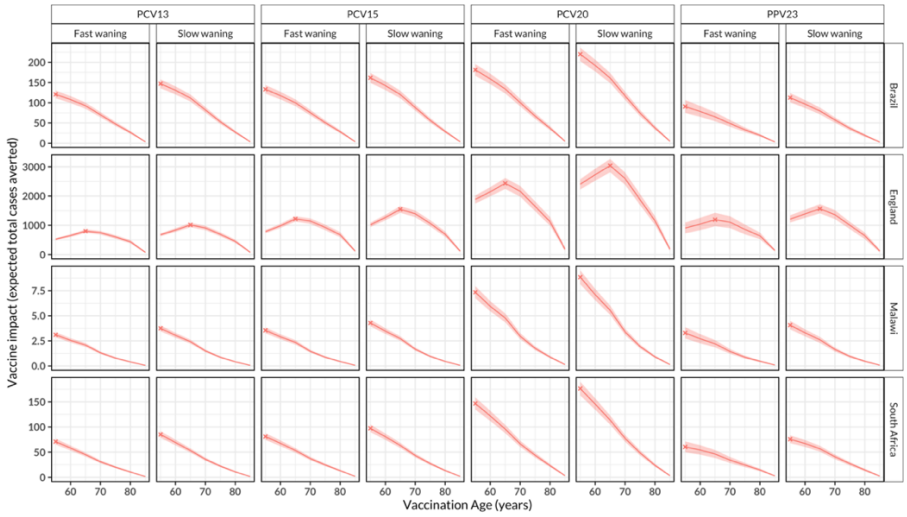

Figure 2. The impact of routine pneumococcal vaccination in older adults aged ≥55 years old (y). The expected absolute number of total IPD cases averted for the rest of age cohort lifetime by vaccinating every older adult in the age cohort stratified by country and vaccine product, under assumptions of age-independent initial vaccine efficacy/effectiveness (VE) and waning VE in Brazil, England, Malawi and South Africa. The lines represent cohort model mean estimates and the shaded ribbon represents 95% bootstrap confidence intervals for the mean estimates. The X corresponds to the optimal age for pneumococcal vaccination. In Brazil, Malawi and South Africa, most cases are prevented at age 55y whereas in England this is achieved at age 65y.

The lowest number of individuals needed to vaccinate with single pneumococcal vaccine dose to prevent a case of IPD (vaccination efficiency) is estimated in different age cohorts depending on the setting, vaccine product or waning VE scenario (Fig 3). In a scenario of PPV23 use under rapid waning of VE, vaccination efficiency is achieved in 65y in Brazil 16,129 (13,741-19,346), 55y in Malawi 1,159 (987-1,395), and 75y in South Africa 5,402 (4,583-6,510) and England 477 (400-592) (Table S4).

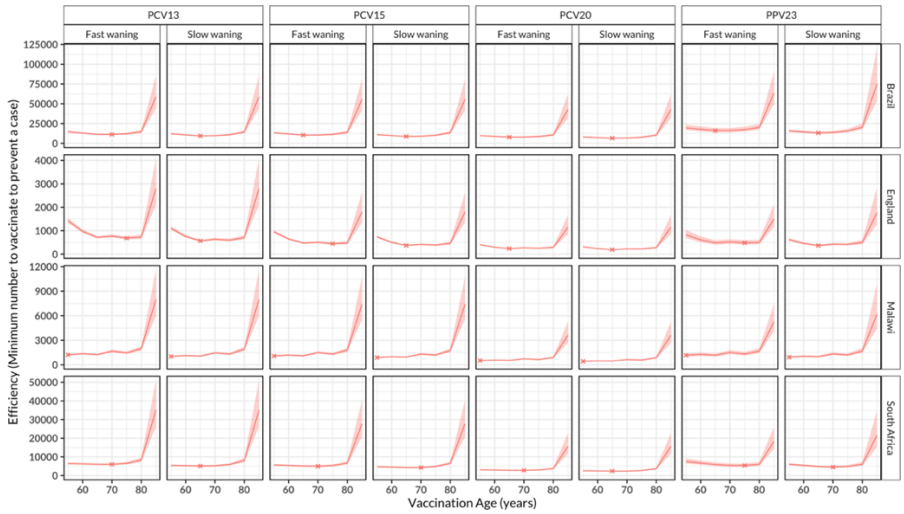

Figure 3. The efficiency of routine pneumococcal vaccination in older adults aged ≥55 years old (y). The number of individuals needed to vaccinate to prevent a case in each age of vaccination, stratified by country and vaccine product, under assumptions of age-independent initial vaccine efficacy/effectiveness (VE) and waning VE in Brazil, England, Malawi and South Africa. The lines represent cohort model mean estimates and the shaded ribbon represents 95% bootstrap confidence intervals for the mean estimates. The X represents the optimal age for efficiency of pneumococcal vaccination.

Sensitivity analyses

If age-dependent initial VE is assumed, vaccine impact (total cases averted) remains maximum at 55y in Brazil, Malawi, and South Africa for all vaccine types, like with age-independent initial VE assumption. In contrast, optimal age for vaccination drops to 60y in England across all vaccine types and waning VE scenarios (Fig S6). On the other hand, under the age-dependent initial VE assumption, vaccination efficiency is achieved in 60y age cohort in Brazil, England and South Africa, and in 55y age cohort in Malawi, irrespective of vaccine product or waning VE scenarios (Fig S7).

Discussion

We have assessed the optimal age-targeting for a single-dose PCV/PPV vaccination against VT-IPD in older adults ≥55y in Brazil, England, Malawi, and South Africa under different scenarios of waning VE and assumptions of age-dependency on initial VE. We find that vaccinating earlier at 55y in adulthood in the considered LIC/MICs maximises prevented burden of IPD while vaccination at 65y is optimal in England. These findings suggest that the optimal age for vaccination may be distinct between countries, and is driven by population age demographic, age-dependent IPD incidence and initial VE, allowing for projection to other settings.

Despite the lower incidence of IPD in early rather than late older adulthood, this is outweighed by the larger number of at-risk individuals in this age group than in the late older age group in LIC/MICs. The different age population structure in England, with a higher proportion of ≥55y in the middle to older adult age groups, results in the optimal age for vaccination peaking later at 65y, and is lower than the observed average age for vaccination of 70y in Australia [15].

The lowest number of individuals needed to vaccinate to prevent a case was found to be in different age cohorts across settings, reflecting on complex interactions between vaccine product, initial VE, waning VE, IPD risk and population demographics in different countries. Although this finding accounts for life expectancy, it does not consider quality-adjusted life years which would likely shift our estimates for efficiency of vaccination.

Our cohort model prediction of higher prevented cases in all settings with the use of PCV20 vs PPV23 under similar conditions reflects on higher efficacy/effectiveness of PCV20 than

PPV23 over a comparable IPD burden [2]. Moreover, a larger number of IPD cases prevented by PCV20 than lesser-valent PCVs underlines the importance of additional serotypes in PCV20 (8, 10A, 11A, 12F and 15B and/or 22F, 33F) in tackling the remaining IPD burden in the mature infant-PCV era [10]. Generally, other disease endpoints may also be important for vaccine choice such as effectiveness against non-bacteraemic pneumonia to which PPV23 is shown substantial effects even though it remains to be fully proven whether PCV or PPV is more effective [40]. Moreover, if non-invasive pneumococcal pneumonia cases were included in our analysis, then vaccine impact would be higher than estimated. However, with the likely upcoming use of PCV15 and PCV20 in infants in the near future [41], the preventable fraction of adult disease is likely to shift correspondingly because of the indirect effects of such infant program, and thus reducing the benefit of adult programs that target the same serotypes as those targeted in infants.

Of note, IPD cases estimated in this analysis are in older adults without HIV. We excluded older adults with HIV not because they should not be vaccinated, but because they typically are considered separately before they reach ≥55y. However, any inclusion of remaining older adult HIV IPD cases is likely to shift estimates of older adult disease burden and prevention, particularly in Malawi and South Africa where adult HIV prevalence is relatively high [29]. In this analysis, the contribution of PCVs' indirect protection from older adults to overall vaccine impact is ignored on the assumption that aging adults are less likely to make intense contacts [42], and therefore unlikely to generate substantial herd immunity. Sequential dosing with the same or different vaccine regimen was not modelled, although PCV15 followed by PPV23 is now recommended by the advisory committee on immunisation practices in the United States [39]. This sequential regimen would likely generate slightly higher impact than a single dose of PCV20 or PPV23, albeit with cost-effectiveness implications that need

further research, particularly in LICs [2]. On the other hand, PCV21 (investigational vaccine) targets most serotypes not targeted by PPV23 or PCV20 [43], which could likely improve tackling the remaining burden of pneumococcal disease in older adults, in long absence of vaccines that target surface proteins common to all serotypes [44].

IPD data included cases caused by serotype 3 to which PCVs and PPV23 have poor effectiveness [45], suggesting that our vaccine impact estimates are likely biased upwards. On the other hand, PPV23 is already in use in ≥65y in England [17], and we show in this analysis that the effects of PPV23 use have reduced the original IPD burden (Fig 1), and without adjusting for the current PPV23 vaccination program, our optimal age for vaccination in this country may be overestimated. Reported IPD case data in LMICs are usually incomplete or under-ascertained due to limited resources e.g. only 19 IPD cases were reported in Malawi and even less so when stratified by age and serotype [3]. Thus, our results should be cautiously interpreted. Despite potential biases of case underreporting, it seems reasonable to assume that underreporting is consistent across adult age groups, such that a relative change in IPD incidence by age to identify optimal age-targeting vaccination is less likely affected.

In conclusion, the optimal age-targeting for vaccination is largely driven by population age demographic, age-dependent IPD incidence and initial VE. In contrast to the typical use in adults ≥65y in many HICs, we find that pneumococcal vaccination in 55y older adults in LIC/MICs may be most effective in reducing the IPD burden among older adults without HIV.

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Author contributions

Conceptualization; DT, SC, SF, EM, PM, NA, World Health Organization Scientific Advisory Group of Experts.

Data curation; DT, JK, SM, TDS, ZAC, NFY, SCGA, MCdCB.

Formal analysis; DT, SC, SF.

Funding acquisition; DT, NF, SL, RSH, CC, MCdCB, SF.

Investigation; DT, SC, JK, AvG, SW, SM, TDS, EM, PM, NA, ZAC, NFY, KJ, NF, SCGA, SL, RSH, CC, MCdCB, SF.

Methodology; DT, SC, NF, SL, RSH, CC, MCdCB, SF

Project administration; JK, AvG, SW, SM, TDS, ZAC, NFY, KJ, NF, SCGA, SL, RSH, CC, MCdCB.

Resources; DT, NF, SL, RSH, CC, MCdCB, SF.

Software; DT, SC.

Supervision; SF, NF

Validation; SC, JK, AvG, SW, SM, TDS, EM, PM, NA, ZAC, NFY, KJ, NF, SCGA, SL, RSH, CC, MCdCB, SF.

Visualization; DT, SC.

Writing - original draft; DT, SC, SF.

Writing - review & editing; DT, SC, JK, AvG, SW, SM, TDS, EM, PM, NA, ZAC, NFY, KJ, NF, SCGA, SL, RSH, CC, MCdCB, SF.

All authors read and approved the final manuscript.

Data availability

An R script that was used to analyse the datasets and aggregated data are available in the GitHub repository https://github.com/deusthindwa/optimal.age.targeting.pneumo.vaccines.

Declaration of interests

The authors declare no competing interests.

Role of the funding source

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Supplementary or supporting information

Table of Contents

Text S1: Invasive pneumococcal disease surveillance

IPD in adults is notifiable in Brazil, England, Malawi and South Africa, and hence part of their national or subnational disease surveillance. In Brazil, IPD isolates are routinely sent to the Centre of Bacteriology at Adolfo Lutz Institute (IAL), the Brazilian National Reference Laboratory for Meningitis and IPD, for serotyping. IAL receives IPD isolates collected from private hospitals and laboratories, and from the national network of 25 laboratories coordinated by Brazilian Ministry of Health, with each laboratory covering each Brazilian state [1]. In England, the National Health Service (NHS) hospital laboratories routinely submit IPD isolates to the UK Health Security Agency (UKHSA) for confirmation and serotyping with corresponding electronic reports sent via second generation surveillance system (SGSS) [2]. Reports without isolates are followed-up by UKHSA to request isolate referral to ensure consistently high serotyping rates. In Malawi, an ongoing sentinel surveillance for the laboratory confirmed IPD at a government referral hospital, Queen Elizabeth Central Hospital (QECH), in Blantyre has been in place since 1998, serving now 1.3 million residents of Blantyre district. IPD isolates are submitted to the Malawi Liverpool Wellcome Clinical Research Programme laboratory sitting next to QECH through surveillance programme of IN-patients and Epidemiology system where confirmation and serotyping are conducted [3,4]. In South Africa, the Group for Enteric, Respiratory and Meningeal disease Surveillance in South Africa (GERMS-SA) conducts national, active laboratory-based surveillance across South Africa in a network consisting of nearly 130 public and private microbiology laboratories. Each laboratory submits pneumococcal isolates a long with patient demographics to the Centre for Respiratory Diseases and Meningitis (CRDM) at the National Institute for Communicable Diseases where confirmation and serotyping are performed [5,6].

Text S2: Back-inflation method to correct for IPD cases in England due to the presence of PPV23 vaccination

To estimate the number of English IPD cases assuming absence of PPV23 vaccination in the population, we combined data on PPV23 vaccination coverage (70%), observed number of IPD cases in the presence of PPV23 vaccination program, and age-adjusted vaccine effectiveness of PPV23 of 41% from 0 to <2 years, 34% 2 to <5 years, and 23% from 5+ years as estimated by Djennad et al. The formula below was used to estimate the new number of IPD cases (inflated) assuming the absence of PPV23 vaccination in the older English adult population.

$$C_I = \frac{C_o}{\nu * (1 - VE_a) + (1 - \nu)} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (1)$$

Where C_I is the total IPD cases assuming no PPV23 vaccination in the older English population, C_o is the observed total IPD cases in the presence of PPV23 vaccination program, ν is the PPV23 coverage, and VE_a is the age (a) adjusted PPV23 vaccine effectiveness from time since vaccination as estimated by Djennad et al.

Text S3: Exponential growth model

To interpolate and extrapolate IPD incidence to annual ages from 55 to 90 years old adults, a nonlinear model (NLS) was fitted to the reported age-specific IPD incidences, minimising the least-squares difference between the model and data using Gauss-Newton algorithm (NLS) as depicted in the main analysis [7]. Initial values of the intercept (α) and gradient (β) for the NLS model were obtained from a fitted linear model, as shown in equation 1.

$$Log(I|\alpha) = Log(\gamma) + \beta * \alpha \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (2)$$

Where I is the IPD incidence for each age group α, γ is the model intercept, and β is the model gradient (growth rate) needed as initial values for equation 2.

Table S1. A scenario of PPV23 use under fast waning efficacy/effectiveness (VE) and age independent initial VE. Reduction in vaccine-type IPD cases between different vaccination age cohorts (e.g., 55 vs 65 years cohorts) relative to no vaccination scenario.

Country	Serotype group	Vaccination age	2.50%	50%	97.50%
Brazil	PPV23	55	15.3	18.6	21.9
Brazil	PPV23	60	13.3	16.1	18.9
Brazil	PPV23	65	11.1	13.3	15.7
Brazil	PPV23	70	8.3	10.0	11.8
Brazil	PPV23	75	5.6	6.8	7.9
Brazil	PPV23	80	3.3	4.0	4.6
Brazil	PPV23	85	0.5	0.7	0.9
England	PPV23	55	7.3	9.1	11.0
England	PPV23	60	8.4	10.4	12.6
England	PPV23	65	9.7	12.0	14.3
England	PPV23	70	9.1	11.1	13.2
England	PPV23	75	7.0	8.6	10.3
England	PPV23	80	5.3	6.4	7.6
England	PPV23	85	1.0	1.4	1.8
Malawi	PPV23	55	16.3	19.6	23.1
Malawi	PPV23	60	13.5	16.2	19.0
Malawi	PPV23	65	11.1	13.2	15.4
Malawi	PPV23	70	7.3	8.6	10.1
Malawi	PPV23	75	4.3	5.2	6.1
Malawi	PPV23	80	2.3	2.8	3.2
Malawi	PPV23	85	0.4	0.6	0.7
South Africa	PPV23	55	10.6	12.8	15.1
South Africa	PPV23	60	9.6	11.5	13.5
South Africa	PPV23	65	8.2	9.8	11.5
South Africa	PPV23	70	6.0	7.3	8.6
South Africa	PPV23	75	4.3	5.2	6.1
South Africa	PPV23	80	2.6	3.1	3.6
South Africa	PPV23	85	0.4	0.6	0.7

Table S2. A scenario of vaccinating 65- and 55-years old cohort under fast waning efficacy/effectiveness (VE) and age independent initial VE. Reduction in vaccine-type IPD cases between use of different vaccines (e.g., PCV20 vs PPV23) relative to no vaccination scenario.

Country	Vaccination age	Serotype group	2.50%	50%	97.50%
Brazil	55	PCV13	22.8	24.7	26.7
Brazil	55	PCV15	25.1	27.3	29.5
Brazil	55	PCV20	34.2	37.1	40.1
Brazil	55	PPV23	15.3	18.6	21.9
England	55	PCV13	4.9	5.3	5.6
England	55	PCV15	7.3	7.9	8.4
England	55	PCV20	17.5	18.9	20.3
England	55	PPV23	7.3	9.1	11.0
Malawi	55	PCV13	17.0	18.5	20.1
Malawi	55	PCV15	19.5	21.2	23.0
Malawi	55	PCV20	40.3	43.9	47.5
Malawi	55	PPV23	16.3	19.6	23.1
South Africa	55	PCV13	13.8	15.0	16.3
South Africa	55	PCV15	15.8	17.2	18.6
South Africa	55	PCV20	28.6	31.1	33.7
South Africa	55	PPV23	10.6	12.8	15.1
Brazil	65	PCV13	17.4	19.0	20.5
Brazil	65	PCV15	18.8	20.5	22.2
Brazil	65	PCV20	25.2	27.4	29.7
Brazil	65	PPV23	11.1	13.3	15.7
England	65	PCV13	7.4	8.0	8.6
England	65	PCV15	11.3	12.2	13.1
England	65	PCV20	22.5	24.4	26.2
England	65	PPV23	9.7	12.0	14.3
Malawi	65	PCV13	11.3	12.4	13.6
Malawi	65	PCV15	12.8	14.0	15.4
Malawi	65	PCV20	26.0	28.5	31.3
Malawi	65	PPV23	11.1	13.2	15.4
South Africa	65	PCV13	8.7	9.5	10.4
South Africa	65	PCV15	10.4	11.3	12.3
South Africa	65	PCV20	18.6	20.3	22.1
South Africa	65	PPV23	8.2	9.8	11.5

Table S3. A scenario of PPV23 use in 65 years old cohort and age independent initial efficacy/effectiveness (VE). Reduction in vaccine-type IPD cases between fast and slow waning VE relative to no vaccination scenario.

Country	Serotype group	Waning VE	2.50%	50%	97.50%
Brazil	PCV13	Fast waning	17.4	19.0	20.5
Brazil	PCV13	Slow waning	21.1	22.9	24.6
Brazil	PCV15	Fast waning	18.8	20.5	22.2
Brazil	PCV15	Slow waning	22.7	24.6	26.5
Brazil	PCV20	Fast waning	25.2	27.4	29.7
Brazil	PCV20	Slow waning	30.4	33.0	35.5
Brazil	PPV23	Fast waning	11.1	13.3	15.7
Brazil	PPV23	Slow waning	14.6	16.3	18.0
England	PCV13	Fast waning	7.4	8.0	8.6
England	PCV13	Slow waning	9.4	10.2	10.9
England	PCV15	Fast waning	11.3	12.2	13.1
England	PCV15	Slow waning	14.3	15.5	16.6
England	PCV20	Fast waning	22.5	24.4	26.2
England	PCV20	Slow waning	28.2	30.5	32.8
England	PPV23	Fast waning	9.7	12.0	14.3
England	PPV23	Slow waning	14.1	15.7	17.3
Malawi	PCV13	Fast waning	11.3	12.4	13.6
Malawi	PCV13	Slow waning	13.3	14.4	15.7
Malawi	PCV15	Fast waning	12.8	14.0	15.4
Malawi	PCV15	Slow waning	15.0	16.3	17.7
Malawi	PCV20	Fast waning	26.0	28.5	31.3
Malawi	PCV20	Slow waning	30.4	33.1	35.9
Malawi	PPV23	Fast waning	11.1	13.2	15.4
Malawi	PPV23	Slow waning	13.7	15.5	17.2
South Africa	PCV13	Fast waning	8.7	9.5	10.4
South Africa	PCV13	Slow waning	10.4	11.3	12.2
South Africa	PCV15	Fast waning	10.4	11.3	12.3
South Africa	PCV15	Slow waning	12.4	13.4	14.5
South Africa	PCV20	Fast waning	18.6	20.3	22.1
South Africa	PCV20	Slow waning	22.2	24.1	26.1
South Africa	PPV23	Fast waning	8.2	9.8	11.5
South Africa	PPV23	Slow waning	10.8	12.0	13.3

Table S4. A scenario of PPV23 use under fast waning efficacy/effectiveness (VE) and age independent initial VE. Number of individuals needed to vaccinate to prevent a case (e.g., individual aged 55 vs 65 years old).

Country	Vaccination age	2.50%	50%	97.50%
Brazil	55	16621	19565	23707
Brazil	60	15139	17776	21392
Brazil	65	13741	16129	19346
Brazil	70	13804	16243	19483
Brazil	75	14801	17376	20986
Brazil	80	17248	20165	24380
Brazil	85	49647	63554	90133
England	55	682	822	1028
England	60	502	606	756
England	65	400	478	589
England	70	438	519	634
England	75	400	477	592
England	80	423	497	606
England	85	1170	1498	2125
Malawi	55	987	1159	1395
Malawi	60	1083	1269	1521
Malawi	65	1002	1169	1394
Malawi	70	1296	1514	1800
Malawi	75	1121	1315	1580
Malawi	80	1433	1682	2045
Malawi	85	4100	5248	7443
South Africa	55	6402	7560	9150
South Africa	60	5686	6682	8050
South Africa	65	5006	5866	7057
South Africa	70	4582	5410	6504
South Africa	75	4582	5402	6510
South Africa	80	5125	6001	7286
South Africa	85	14300	18305	25961

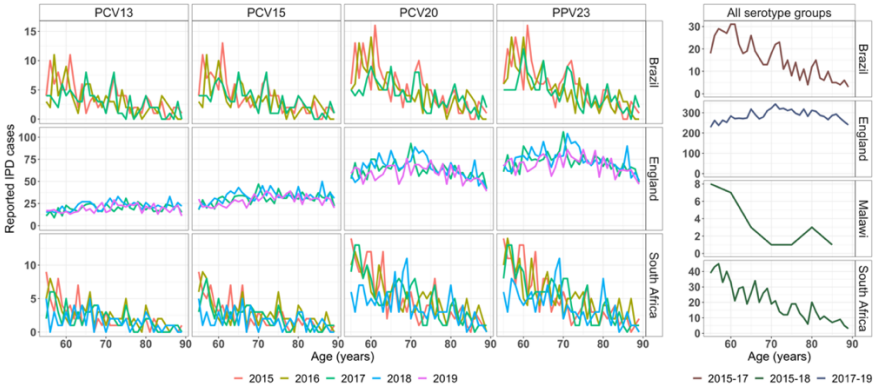

Figure S1. Distribution of invasive pneumococcal disease (IPD) cases in annual age stratified by serotype group (serogroup), year of surveillance and country. Serogroup-specific IPD cases in Brazil (from 2015-2017), England (from 2017-2019) and South Africa (from 2015-2018) in annual age in older adults. Serogroup-specific IPD cases in each setting were average for all reported years and used to compute serogroup- and age-specific IPD incidence. Due to small sample size of IPD cases reported and incomplete serotyping data for age-group specific serotype distributions in Malawi, we calculated all-age serotype distribution and assumed that it was the same in each age group.

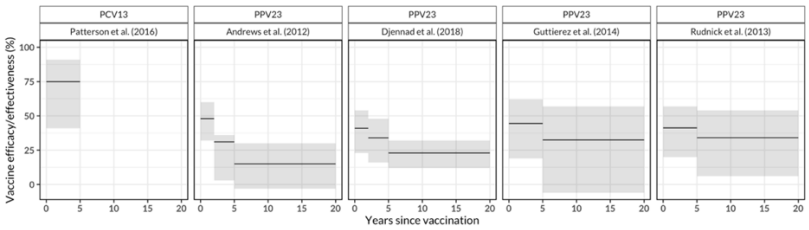

Figure S2. Reported initial vaccine efficacy/effectiveness (VE) and waning VE of pneumococcal polysaccharide vaccine (PPV23) and pneumococcal conjugate vaccine (PCV13), with bootstrapped 95% confidence intervals (line and ribbon) estimated from a piecewise constant model, with time since vaccination and stratification by study's first author name. Initial VE and waning VE from Andrews et al. and Djennad et al. are used for the PPV23 in the vaccination impact cohort model as they provide the highest and lowest initial VE levels as well as fast and slow waning VE, respectively, whereas the initial VE from Patterson at al. (stable for 5 years) and fast waning VE from Andrews et al. and slow waning VE from Djennad et al. are used for all the PCVs (PCV13, PCV15, and PCV20).

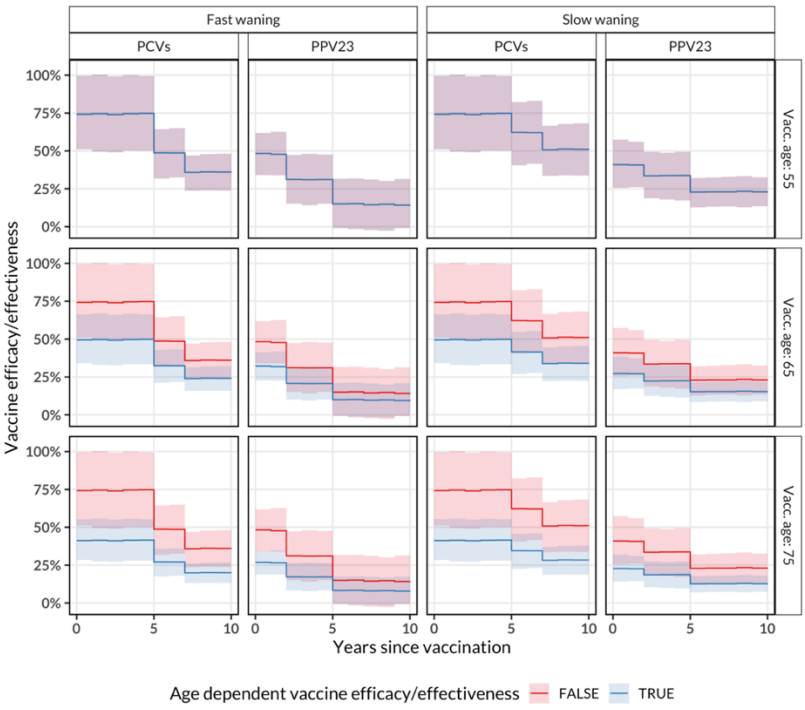

Figure S3. Reported initial vaccine efficacy/effectiveness (VE) and estimated waning VE of pneumococcal polysaccharide vaccine (PPV23) and pneumococcal conjugate vaccine (PCV13) with bootstrapped 95% confidence intervals (line and ribbon), estimated from a piecewise constant model, with time since vaccination and stratification by study's first author name and *a priori* age of 55, 65 and 75 years old at which waning vaccine protection decreases.

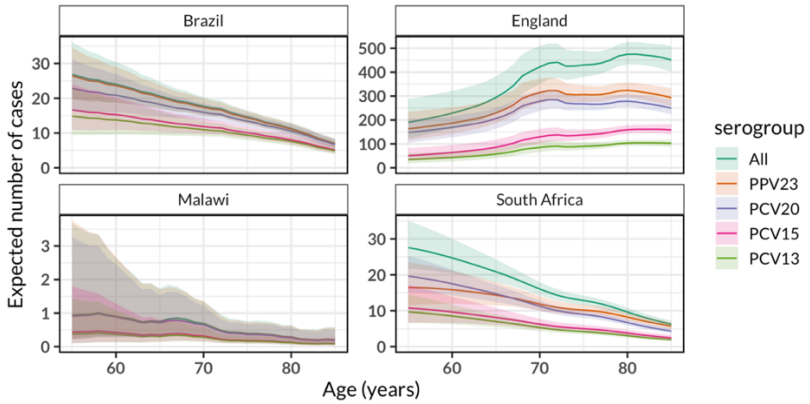

Figure S4. The expected burden of invasive pneumococcal disease (IPD) cases across age stratified by serotype group (serogroup) in Brazil (from 2015-2017), England (from 2017-2019) and South Africa (from 2015-2018) in annual age in older adults. Serogroup-specific expected number of IPD cases in each setting was obtained by computing the product of observed IPD cases aggregated for all reported years and the fitted IPD incidence. Uncertainty in the expected number of cases was based on uncertainty in the fitted incidence obtained by bootstrap sampling 1000 times using the fitted parameter means and covariance matrix of a fitted exponential model.

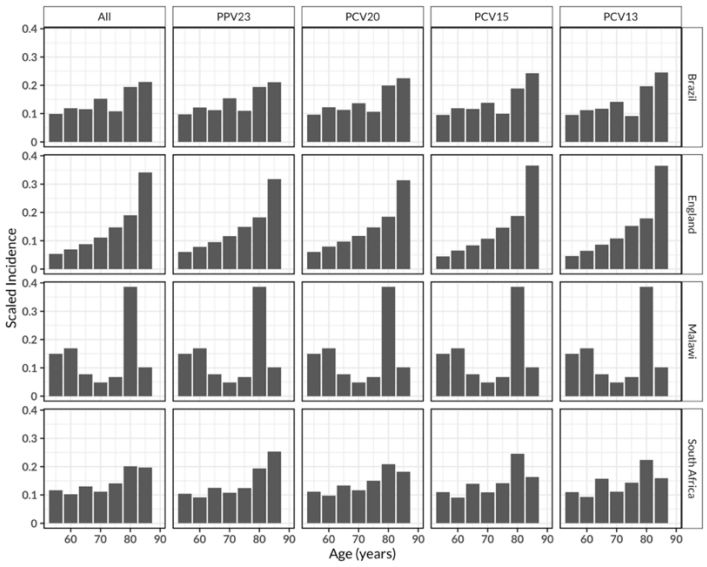

Figure S5. Age-scaled invasive pneumococcal disease (IPD) incidence in age groups stratified by serotype group and country for all years of IPD surveillance in a mature infant PCV era (at least four years post-introduction). Age-scaled IPD incidence is estimated by dividing age group-specific IPD incidence by total incidence across all age groups within that serotype group. Age-scaled IPD incidence increases monotonically with increasing age irrespective of serogroup or country except for Malawi where the unstable signal in age-scaled IPD incidence reflects small numbers of reported IPD cases.

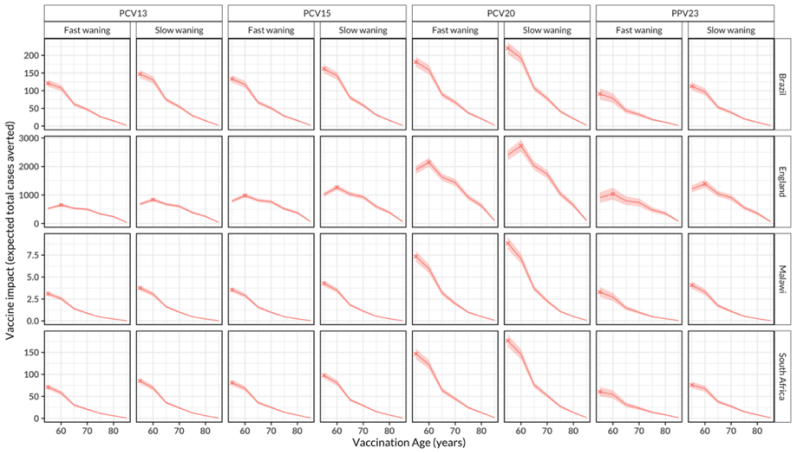

Figure S6. The impact of routine pneumococcal vaccination in older adults aged ≥55 years old (y). The expected absolute number of total IPD cases averted for the rest of age cohort lifetime by vaccinating every older adult in the age cohort stratified by country and vaccine product, under assumptions of age-dependent initial vaccine efficacy/effectiveness (VE) and waning VE in Brazil, England, Malawi and South Africa. The lines represent cohort model mean estimates and the shaded ribbon represents 95% bootstrap confidence intervals for the mean estimates. The X represents the optimal age for pneumococcal vaccination. In Brazil, Malawi and South Africa, most cases are prevented at age 55y whereas in England this is achieved at age 60y.

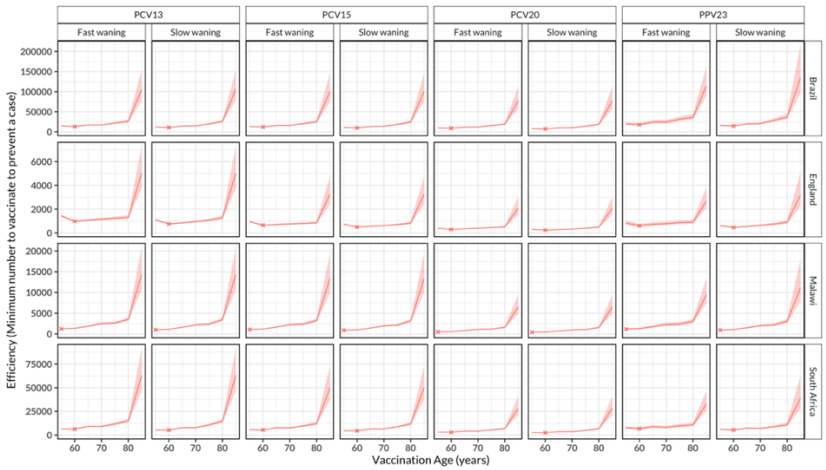

Figure S7. The efficiency of routine pneumococcal vaccination in older adults aged ≥55 years old (y). The number of individuals who are needed to vaccinate in each age of vaccination to prevent a case, stratified by country and vaccine product, under assumptions of age-dependent initial vaccine efficacy/effectiveness (VE) and waning VE in Brazil, England, Malawi and South Africa. The lines represent cohort model mean estimates and the shaded ribbon represents 95% bootstrap confidence intervals for the mean estimates. The X represents the optimal age for efficiency of pneumococcal vaccination program. In Brazil, England and South Africa, vaccination efficiency is achieved in 60y age cohort irrespective of vaccine product whereas in Malawi, efficiency is achieved in 55y age cohort.

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Chapter 7: Research paper 6

Use of seasonal influenza and pneumococcal polysaccharide vaccines in older adults to reduce COVID-19 mortality.

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Use of seasonal influenza and pneumococcal polysaccharide vaccines in older adults to reduce COVID-19 mortality

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Background and aim

SARS-CoV-2 that causes COVID-19 has emerged as a pandemic with all continents now reporting cases, most of them community acquired [1]. Many COVID-19 infections cause pneumonia and some are fatal, predominantly among older adults [2]. Co-infection with other viruses or bacteria, particularly those that similarly cause inflammation of the respiratory tract would likely enhance the risk for severe COVID-19 disease. Such disease enhancing co-infections have been frequently reported for respiratory pathogens [3–5], most notably so for the 1918 influenza pandemic [6,7]. Vaccinating older adults at elevated risk of severe COVID-19 disease against vaccine preventable diseases may therefore not only help to reduce the strain on the healthcare system from those diseases during a pandemic, but also alleviate some of the potential COVID-19 mortality due to co-infecting pathogens [8].

Vaccines that can prevent respiratory tract infections in adults and particularly in older adults, either through direct protection or indirectly through high coverage childhood immunisation programmes, include vaccines against seasonal influenza, *Streptococcus pneumoniae*, measles, *Bordetella pertussis* and *Haemophilus influenzae* type b (Hib). Measles, pertussis and Hib vaccines are already included in almost all routine infant immunisation programmes globally and have largely eliminated the targeted pathogens as a risk to the older adult population through indirect protection [9]. Hence, they have limited scope for use in older adults in order to limit COVID-19 morbidity and mortality. Pneumococcal conjugate vaccine (PCV), either 10- or 13-valent, is used in three-quarters of routine infant immunisation programs globally; in countries that use PCV, the burden of adult pneumococcal disease due to PCV serotypes has also substantially decreased [10]. These considerations mean there is a relatively small preventable disease burden in countries routinely using PCV in children. As vaccine costs are relatively high and there is no current World Health Organisation

recommendation regarding PCV use in adults, PCVs are not considered further here. Two vaccines that target a large burden of the remaining respiratory disease in older adults are seasonal influenza vaccines and 23-valent pneumococcal polysaccharide vaccine (PPV23). These vaccines are only included in routine adult immunisation in some countries and even there with only moderate coverage [11]. We conducted a non-systematic review of the published, pre-print and grey literature to evaluate whether vaccination of older adults with seasonal influenza vaccine or PPV23 could help reduce COVID-19 mortality.

Seasonal influenza vaccines

The World Health Organization recommends seasonal influenza vaccine use for pregnant women as well as older adults (>65yrs), health care workers and persons with specific chronic illnesses (particularly HIV) [12]. In 2014, 45% of countries globally had established a seasonal influenza vaccine programme that targets older adults, hardly any of them are in low or middle income countries [13].

Seasonal influenza as a risk factor for COVID-19 could be an important consideration in tropical climates and the southern hemisphere, and potentially during future waves of COVID-19 in the northern hemisphere [14–16]. Inactivated influenza vaccine effectiveness varies markedly by season from about 20% in seasons with a poor match to the circulating strains to up to 60% for closer matched seasons [17,18]. Hence, influenza vaccination could prevent 20% to 60% of influenza infections and thereby potentially a similar percentage of influenza-attributable COVID-19 morbidity and mortality (Table 1).

Several studies to date have tried to assess the percentage of influenza-attributable COVID-19 morbidity and mortality. Some reported the occurrence of co-infection of COVID-19

inpatients with influenza viruses, although the proportion of co-infections varies by study, from no influenza coinfection identified to more than 60% of PCR positive COVID-19 patients being currently or having been recently infected with influenza [19–25]. Whether this co-occurrence is co-incidental, or indeed influenza contributes to the clinical severity of COVID-19 presentation is not yet clear. However, to date there is no evidence that would suggest clinical manifestations in COVID-19 patients with influenza co-infection differ from those without co-infection [19].

Pneumococcal polysaccharide vaccine

PPV23 targets 23 of the over 90 serotypes that are responsible for most adult pneumococcal disease. In countries with an infant PCV program, about 48-66% of invasive pneumococcal disease (IPD) in older adults is caused by serotypes that PPV23 is effective against [26]; in countries without an infant PCV programme this percentage is likely about 20% higher (details see Appendix). PPV23 is recommended for routine use in older adults in most high-income countries, but rarely in low and middle-income countries [27]. It provides short-term protection against IPD caused by vaccine serotypes in healthy older adults with a pooled efficacy across targeted serotypes of about 60% [28–30]. However, PPV23's effectiveness is much lower among high risk groups including the immunocompromised [31–33], who may be at particular risk for severe COVID-19. Consequently, PPV23 use in older adults could prevent up to 33-40% of pneumococcal disease and thereby potentially pneumococcal-attributable COVID-19 morbidity and mortality (Table 1).

The extent of pneumococcal-attributable COVID-19 morbidity and mortality is largely unknown. Pneumococci have been identified as a major source for often fatal secondary bacterial infections during pandemic and seasonal influenza infections. Estimates for the

proportion of pneumococcal co-infections among pandemic influenza deaths range from about 7% during the 2009 H1N1 pandemic to more than 50% during the 1918 pandemic [6,34–37]. Few studies so far have tried to identify bacterial co-infections among COVID-19 cases, and those that did found very few bacteria and only a limited number of cases with pneumococci [23,38,39]. This may be due to the empirical treatment with antimicrobials for the majority of severely ill suspected COVID-19 patients, or because bacterial infection plays little role in the severity of COVID-19 disease [23,40]. However, elevated procalcitonin levels, a sensitive but not very specific biomarker for bacterial infections, have been reported in 13% of severe and 25% of fatal COVID-19 infections, but largely absent in COVID-19 infected persons with less severe outcomes, which may suggest some role for bacterial coinfection [41,42].

COVID-19 associated risk of attending clinics to receive PPV23 or influenza vaccination

Attending a vaccination clinic during the COVID-19 pandemic will likely come with an excess risk of SARS-CoV-2 infection. This risk may be small, particularly if physical contact reducing interventions are implemented. To illustrate the potential magnitude of such excess risk, we assume a reasonably high COVID-19 burden scenario: contact reducing interventions can be implemented and upheld to substantially slow COVID-19 spread but not contain it, so that after 6 months and in the absence of a COVID-19 vaccine herd immunity will end the outbreak [43]. Assuming a basic secondary attack rate of R_0=2.5 and that contact-reducing interventions spread the COVID-19 infection risk equally across that 6-month time period, the increase in risk for COVID-19 acquisition attributable to the vaccination clinic visit would be roughly 0.3-1.3%, depending on the effectiveness of transmission-reducing measures during the vaccination visits (details see Appendix) [44]. This implies, that if either seasonal influenza vaccine or PPV23 reduces COVID-19

morbidity and mortality by a similar amount or more, their benefit on COVID-19 alone would outweigh the risk associated with the vaccination visit in this scenario, while also preventing morbidity from influenza and pneumococcal disease.

Conclusion

Both seasonal influenza vaccine and PPV23 can prevent a substantial burden of targeted disease and mortality among older adults and adults at-risk. Despite a potential collateral reduction in influenza and pneumococcal circulation due to contact reducing interventions, in countries where the COVID-19 pandemic coincides with the season of high risk for pneumococcal and/or influenza disease, vaccination at high coverage will have added benefits: minimising the number of pneumococcal and influenza hospital admission reduces the resources needed to care non-COVID-19 patients and minimises the risk of health-care acquired COVID-19 infection. For influenza, the similarity of symptoms with COVID-19 cases also suggests that vaccination will increase the specificity of syndromic COVID-19 surveillance and interventions. Similarly, maintaining high vaccine coverage of existing PCV and live attenuated influenza vaccine programmes in children reduces the associated disease burden in older adults through herd effects, and will further enhance benefits for limiting COVID-19 risks.

The magnitude of COVID-19 morbidity and mortality prevented by influenza vaccine and PPV23 is probably relatively small, although at present we cannot exclude the possibility of either preventing a considerable amount of COVID-19 related mortality (Table 1). This uncertainty highlights the importance for detailed monitoring and additional studies where possible, in both high- and low-income settings. The proportion of vaccine preventable

COVID-19 morbidity and mortality could be assessed, for example, by post mortem examinations or test-negative case-control studies [45].

In summary, where already in routine use among older adults and/or adults at-risk, maintaining both seasonal influenza and PPV23 at high coverage have the potential to not only reduce the burden of the targeted diseases but also prevent a proportion of COVID-19 morbidity and mortality, if they can be delivered while minimising the risk for SARS-CoV-2 transmission. However, for countries who previously decided that seasonal influenza vaccine or PPV23 programmes for older adults are not a priority, there is currently little evidence to encourage implementation of either during the COVID-19 pandemic solely for the purpose of reducing COVID-19 mortality.

Supporting information

Proportion of PPV23 serotypes among older adults

The PSERENADE project aims to understand the impact of PCV10/13 on invasive pneumococcal disease (IPD) incidence and serotype distribution using IPD data contributed by surveillance sites across the world. In settings with mature PCV10/13 infant immunization programmes, the estimated proportion of IPD in older adults (≥65 years of age) attributable to PPV23 serotypes is 67-79% for countries using PCV10 in infants and 68-71% for countries using PCV13. Excluding ST3 (PPV23-minus-ST3), these proportions drop to 48-66% and 51-57% respectively. Because effectiveness against ST3 has not been observed in all countries, the proportion of IPD in older adults attributable to PPV23-minus-ST3 is used here as a more conservative estimate of preventable disease. In the time period prior to PCV use in children, the estimated proportion of IPD in older adults attributable to PPV23-minus-ST3 serotypes was about 20% higher; this can be a proxy for countries without an infant PCV programme. However, most of the data included comes from high-income countries and may not be entirely representative of the serotype distribution in countries without a PCV programme, which are mostly low and middle income.

Risk of SARS-CoV-2 infection during a vaccination clinic visit

Assume that contact reducing interventions spread the risk of COVID-19 out roughly equally over a 6-month period. This scenario is in line with model predictions for SARS-CoV-2 spread in the presence of a 50% reduction in contacts for the duration of 6 months. Assuming an R_0 of 2.5 and a duration of infectiousness of 1 week means that about 60% of the population will have been infected at the end of the pandemic and that at any one time about 2% of the population is infectious. Further, assume that an adult attends a vaccination clinic and makes a total of 2-10 contacts (hereby 2 may reflect a scenario of effective measures to

avoid contacts) related to that visit and that the probability of infection per potentially infectious contact is about 10% (R_0 attributed over the number of contacts during the infectious period e.g., 2.5 transmissions during the two days before symptom onset and self-isolation, with 12 contacts per day before isolation). Then the probability for SARS-CoV-2 infection during that vaccine clinic visit is $P = 1 - (1 - 10\%)^{\#contats * 2\%} = 0.4$ to 2%. Hence, the excess absolute risk for SARS-CoV-2 infection over the pandemic baseline risk is P*(1-60%) and corresponds to a relative risk increase over the pandemic baseline risk of 0.3 to 1.3%.

Table 1. Estimating COVID-19 death attributable to influenza and pneumococcal coinfection

Parameter description	Minimum value	Maximum value	Reference
Seasonal influenza vaccine efficacy	20%	60%	[17,18]
COVID-19 deaths attributable to influenza coinfection (assuming it is similar to COVID-19 cases attributable to influenza co-infection)	0%	60%	[19–24] †
Preventable COVID-19 deaths due to influenza co-infection	0*0.2=0%	0.6*0.6=36%	
PPV23 vaccine efficacy	20%	60%	[28–30]
PPV23 preventable serotypes in older adults	48%	66%	[26]
COVID-19 deaths attributable to pneumococcal co-infection (assuming it is similar to influenza A (H1N1) deaths attributable to pneumococcal co-infection)	0%	25%	[6] ‡
Preventable COVID-19 deaths due to pneumococcal co-infection	0.2*0.48*0=0%	0.6*0.66*0.25=10%	

† In five studies, co-infection occurred in 41/68, 0/20, 11/127, 0/99 and 5/115 cases
‡ In seven studies, co-infection occurred in 0/100, 2/182, 2/45, 13/585, 20/199, 2/585 and 5/21 cases

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Author contribution

Conceptualization: SF; Writing-Original Draft: DT, SF; Writing-Review and Editing: DT, MGQ, YL, JB, CC, MDK, AvG, KH, SF. All authors read and approved the final manuscript

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the discussions in this paper.

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Chapter 8: Discussion

Childhood PCV is widely used globally in LICs or MICs [1], commonly under a third-dose vaccination coverage of more than 90%, similar to many HICs [2,3]. The use of PCV in infants has greatly reduced the burden of pneumococcal carriage, disease and subsequent mortality caused by the targeted serotypes among vaccinated children and, through herd protection, in unvaccinated adults [4–7]. Despite that impact, VT are still in substantial circulation in LICs or MICs, particularly in African countries that implemented a 3+0 PCV dosing schedule [7–9], suggesting less herd immunity against pneumococcal carriage than has been reported in HICs [7,10], as well as pneumococcal disease [6]. Potential reasons for suboptimal herd immunity may include lack of booster pneumococcal vaccine doses or higher local force of pneumococcal infection [11]. Thus, VT circulation may or may not be addressed by optimising the infant PCV program alone. Overall, this implies that vulnerable adults remain at high risk of pneumococcal disease from both residual VT carriage and vaccine-preventable serotypes not targeted by infant PCV.

1.1 Summary of findings

My PhD research outlines pneumococcal vaccination strategies to further reduce VT carriage and disease among HIV-infected adults either through (a) indirect effects by changing the 3+0 infant PCV dosing schedule to use a 2+1 dose schedule or a 2+1+1 dose schedule e.g., (with an additional booster dose at school entry), or (b) direct effects by directly vaccinating HIV-infected adults or only HIV-infected pregnant women for direct protection, with added indirect protection to the high-risk neonates. My findings suitably show that children remain a major reservoir for VT pneumococcal carriage transmission, having higher pneumococcal carriage duration, acquisition, and prevalence rates than adults as also reported elsewhere [12,13]. However, despite HIV-infected adults carrying pneumococci for longer than HIV-

uninfected adults in the infant PCV era, their transmission risk to the rest of the household members are similar, suggesting no greater herd protection than would be induced by other groups if offered pneumococcal vaccination in surplus to their direct protection against pneumococcal disease. My findings are based on a densely sampled pneumococcal carriage cohort study conducted in a mature infant PCV era (at least six years after infant PCV7 introduction in 2009, before switching to PCV13 in 2011), and extend the scope of previous studies during pre-PCV era to look at pneumococcal carriage dynamics from every HIV-infected adult in the household [12–14]. Previously, studies investigated carriage acquisition limited to HIV-infected mother and child pairs, reporting more frequent pneumococcal carriage transmission from HIV-infected than HIV-uninfected mothers to their children as well as non-differential pneumococcal carriage acquisition in infants by maternal HIV status [12–14].

My results on homogeneous pneumococcal carriage transmission risk to younger children by adult HIV-infection status are further supported by the first evaluation of the role of adult HIV infection status in social contacts behaviour showing similar social mixing patterns between HIV-infected adults on ART and HIV-uninfected adults with the rest of the population despite the high, age-assortative, localised, more intense, and mostly physical social contacts in the population. Together, these findings suggest that in the mature infant PCV and adult ART eras, HIV-infected adults on ART and HIV-uninfected adults in LICs or MICs indeed have similar contact behaviour relevant for pneumococcal transmission as well as onward pneumococcal carriage transmission risk to their household members, implying that their vaccination is most relevant for protection against pneumococcal disease and less important for generating substantial herd immunity above what is already generated by the infant PCV vaccination.

As vaccination of HIV-infected adults on ART may be less important for VT herd immunity generation and most relevant for protection against VT disease, whose precursor is pneumococcal carriage [15], the risk of pneumococcal carriage among groups of HIV-infected adults on ART may be different. Thus, further investigation of my PhD research into residual VT carriage and their reservoirs among groups of HIV-infected adults on ART show that while VT carriage prevalence has declined across time in the infant PCV era [7,11], partly due to cumulative vaccine-induced community-level indirect protection from infant PCV vaccination, male sex and not living with children <5 years old are associated with persistent VT carriage. My results suggest that the risk of pneumococcal disease among HIV-infected adults on ART remains, partly due to residual VT carriage. Moreover, there may be distinct routes of VT carriage exposure or durations of VT carriage among groups of HIV-infected adults on ART. Overall, in LICs or MICs with high local force of pneumococcal infection and rapid waning of vaccine-induced immunity from the infant PCV vaccination [11,16], improving carriage control in younger children to indirectly protect vulnerable adults against pneumococcal carriage and subsequent disease may not be enough. Thus, in addition to efficient infant PCV schedules that may enhance indirect protection [17], targeted vaccination for HIV-infected adults could be considered along with other public health measures including well-ventilated housing structures [18].

While one part of my PhD research focussed on HIV-infected adults, the other considered adults older than 55 years who also have a high risk of IPD, which increases with age in the course of declining robustness of immunogenic response to pneumococcal vaccination [19]. While older adult pneumococcal vaccine programs already exist in most HICs countries [20], under heterogeneous policies on age of vaccination and vaccine products, LICs or most MICs

do not have routine older adult pneumococcal vaccine programs [21], in large part due to constrained resources and competing public health priorities, under the uncertainty of age of vaccination to prevent maximum number of pneumococcal cases.

Thus, my findings to guide older adult pneumococcal vaccination strategy in LICs or MICs show that total IPD cases are maximally prevented when age of vaccination is early in older adulthood at 55 years old in LICs or MICs than is typical in HICs [22,23], whereas the highest efficiency of a single dose pneumococcal vaccination program is achieved when vaccination is offered at 85 years old, irrespective of country. Generally, this implies that the age at which to offer pneumococcal vaccination in older adults for maximum preventable IPD cases is distinct by countries, and driven by population demography, age-specific IPD incidence, and initial vaccine efficacy or effectiveness, providing a utility for projection to many countries, globally. Moreover, my findings are insensitive to the pneumococcal vaccine product, suggesting that this could also be used for projecting the impact of any potential future high-valent pneumococcal vaccine product for use in older adults. My further assessment, in the early phases of COVID-19 pandemic, on the additional benefits of using pneumococcal vaccines in older adults (who are at high risk of severe COVID-19) to prevent serious clinical outcomes of COVID-19 due to coinfection with pneumococcus revealed little evidence of coinfection to support implementation of adult pneumococcal vaccination programs in settings that did not have, but to maintain high vaccination coverage in settings where such programs already existed to prevent worst consequences of COVID-19 outcomes due to potential coinfections. My findings align with the evidence that emerged later during the pandemic which showed rare SARS-CoV-2 and pneumococci coinfections but with devastating clinical outcomes when it occurred [24], partly due to impaired antiviral immune responses facilitated by pneumococcus [25]. However, further consideration in this area may

need to investigate the impact of SARS-CoV-2 infections when individuals are already colonised with pneumococci.

1.2 Evidence in the global context and limitations

My PhD research finds homogeneous social mixing patterns between HIV-uninfected and HIV-infected adults on ART with the rest of the population, and similar role of HIV-infected adults to household pneumococcal transmission compared to HIV-uninfected adults in the PCV era. These findings suggest that in the era of effective ART, HIV infection has mostly become a chronic disease with HIV-infected adults on ART socially behaving like HIV-uninfected adults due to their controlled illnesses against opportunistic infections that would potentially prevent them from working, doing businesses or other social interactions with the rest of the population in the community [26]. However, social contacts relevant for pneumococcal transmission from within and outside households are usually setting-specific due to differential socio-economic and cultural factors hence limiting my findings' generalisation to other African settings with generalised HIV epidemic [27]. Even though I hypothesised greater contribution to pneumococcal carriage transmission from HIV-infected than HIV-uninfected adults due to their slightly higher pneumococcal carriage prevalence and density, my findings align with what was reported in rural Malawi during the pre-PCV era [13], where infant pneumococcal acquisitions did not differ by maternal HIV infection status. Potential reasons for this finding may include use of antibiotics and ART among HIV-infected adults which may have cumulatively lowered their pneumococcal carriage duration and density, even though contrasting reports in other African settings indicate that the use of ART increases pneumococcal carriage prevalence [28], and cotrimoxazole increases antimicrobial resistant pneumococci [29].

Data on pneumococcal serotypes are usually not available in the LICs or MICs due to high costs of serotyping. Unavailability of serotyping impacted parts of my PhD research with predictions on the contribution of HIV-infected adults to pneumococcal transmission limited to pneumococcal carriage as whole bacterium rather than serotypes. This may have consequences on transmission inferences such as attributing community vs family as source of transmission [30,31]. Thus, further analysis may be needed to provide a better understanding of serotype-specific pneumococcal carriage, and links between serotypes and transmission by HIV infection status [30]. Also, in identifying the optimal age to offer pneumococcal vaccines to HIV-uninfected older adults, pneumococcal serotyping data was incomplete in LIC, and I made simplified assumptions by calculating all-age serotype distribution and considered it was the same in each age group, which may not hold. Moreover, the frequency of reported IPD cases in LICs is usually low suggesting lack of capacity for IPD surveillance coverage [32]. This implies that without effective investment in pneumococcal surveillances as well as serotyping of pneumococcal isolates in LICs or MICs, unmasking pneumococcal carriage and disease dynamics is increasingly difficult.

Despite investigating the optimal age-targeting for pneumococcal vaccination among HIV-uninfected older adults using maximum prevented IPD cases as outcome end point, most LICs or MICs are resources-constrained, and may also be interested in the economic value of investing in adult pneumococcal vaccination programs. The cost-effectiveness analysis, of prevented IPD burden presented in this PhD thesis, was not conducted, and thus remains to be addressed to align with recommendations from the World Health Organisation's Scientific Advisory Group of Experts, who previously synthesised available evidence on cost-effectiveness of pneumococcal vaccination among older adults, and reported inconclusive evidence due to conflicting reports [33].

Social mixing patterns are widely studied in HICs to understand the spread of infectious diseases [34], and were extensively explored to inform the impact of COVID-19 control strategies [35,36]. Despite my PhD research generating an important dataset on social contacts behaviour in a high-density urban setting to inform models of transmission dynamics and control strategies of respiratory pathogens, extrapolation of these social contacts data may not be valid to rural African settings [37], and even less so to different African urban areas where previous studies have reported unique social contact patterns compared to my PhD research findings [38]. Potential reasons for varying social contacts results may include (a) a reflection that social contacts are indeed setting-specific due to unique socio-economic activities and cultural norms, or (b) use of different levels of control of selection and/or information/reporting biases.

In LICs, resources to conduct pneumococcal carriage studies are usually unavailable [39], and data on important factors that shape pneumococcal transmission and disease risks in vulnerable adults are poorly completed or not at all collected. For instance, data on smoking, history of antibiotic use, chronic comorbidities, viral load, CD4 count and ART adherence are poorly documented. Subsequently, it becomes challenging to unmask the contribution of different factors to pneumococcal carriage risk in vulnerable adults. Nearly every part of this work investigating pneumococcal carriage and disease risk in vulnerable adults included serotype 3 as part of VT carriage and disease yet PCV is reported to be less effective against serotype 3, globally [40]. Thus, my PhD findings should be interpreted in the context of global persistence of serotype 3 in VT carriage e.g., sizable residual VT is caused by serotype 3 whose burden may partly not be vaccine preventable, despite fully unproven reports of

PCV13 efficacy against serotype 3 pneumonia in adults, and with no such data for PPV23 use.

Furthermore, to understand the risk factors for persistent carriage, we used automatic flexible statistical methods (P spline GAM) to identify and characterize nonlinear regression effects on the changes in pneumococcal carriage over time. Despite having only 5 years of distinct pneumococcal surveys (observed changes in pneumococcal carriage at population level) from 2015 to 2019, P spline fitting by its properties ensured flexible use of less parameters without need to choose the number and position of knots (hence, the degrees of freedom) due to penalisation compared to other regression splines. Nonetheless, the effective degrees of freedom in a P-spline model with a smoothness parameter equal to 0 is equivalent to the number of regression coefficients, unlike a P spline model with a larger value of smoothness parameter which may lead to a few degrees of freedom. Our calculation of the confidence intervals for the relative difference between categories of each covariate in the fitted P spline GAM was based on the formulae that assumes independence between those categories. However, this formulation may not account for the standard errors, and hence variability, in the P spline GAM predictions, and therefore result in narrower confidence intervals since it is mostly applicable to raw data than predicted values. This may have an effect on the identified risk factors and not on nonlinear age and time trends in pneumococcal carriage prevalence largely determined by the fitted P spline GAM.

Even though my research addresses the optimal age-targeting for a single dose pneumococcal vaccination in HIV-uninfected older adults in LICs/MICs where its likely applicable due to resource constraints, it does not explicitly address sequential dosing of pneumococcal vaccines in older adults in some European countries including Austria, Belgium, Greece,

Czech Republic, Hungary and Luxembourg where the current recommendation is PCV13 followed by PPV23 [20], nor in the United States of America where the advisory committee on immunisation practices (ACIP) currently recommends an option of PCV15 followed by PPV23 [41].

1.3 Future work

In most LICs or MICs in Africa, circulation of VT still persists in a mature infant PCV era and results in a continued high and potential vaccine preventable burden of pneumococcal disease in vulnerable adults [6,7,9,42]. Routine pneumococcal vaccination programs for vulnerable adults, both HIV-infected adults and older adults ≥55y, are not implemented in LICs or some MICs [21]. Mitigation of pneumococcal disease in HIV-infected adults in LICs may be achieved by either added direct protection or increased indirect protection from infant immunisation programs at high coverage and improved vaccine schedules [17]. For added direct protection, PCV is preferred because it is more immunogenic than PPV23 in HIV-infected adults, despite being more expensive and with lower serotype coverage than PPV23 [17]. Thus, it will be vital to use modelling to evaluate the impact on IPD of changing the infant PCV schedules vs direct PCV vaccination of HIV-infected adults. On the other hand, with the new licensing of high-valent PCVs in adults [43,44], expanded serotype coverage implies prevention of additional disease burden caused by preventable serotypes outside the current childhood PCV e.g., PCV20 targets all PCV13 serotypes and additional 8, 10A, 11A, 12F, 15B, 22F and 33F that cause 39.2% of IPD across age groups [45].

Among older adults ≥55y in LICs, added direct protection could likely be preferred since they are less likely to be impacted by indirect protection from infant PCV due to their relatively low social mixing behaviour in the community as presented in this work. Despite

the superiority of PCV with 75% vaccine efficacy compared to 60% pooled effectiveness of PPV23 against IPD in older adults [22,33], the higher cost of PCV from Pfizer than PPV23 implies that LICs may have to either choose PPV23 even though it shows less impact than PCV20 against IPD as reported in this thesis, or resolve to using the upcoming low cost PCV10 (Pneumosil) from Serum Institute of India [46], though will lower serotype coverage. Nonetheless, the cost-effectiveness evaluation of pneumococcal vaccination strategies in older adults in LICs or MICs needs further investigation given the inconclusive evidence [33]. Expanding the current work on optimal age-targeting for pneumococcal vaccination in older adults in this thesis to explore the cost-effectiveness of offering pneumococcal vaccine at different ages would help to better inform LICs or MICs. While I explored a likely scenario for LICs or MICs, due to their resource constraints, of the impact of using a single dose of pneumococcal vaccine in older adults to prevent maximum IPD cases, future analysis could inform the use of sequential dosing schedules especially in HICs.

High-valent PCVs currently licensed for use in adults (PCV15 and PCV20) may likely be used in infants in the near future which will potentially lead to reduced direct benefit in older adults due to similarity of targeted serotypes [47]. Thus, focusing on exploring the potential effects of using new high-valent PCVs in infants on pneumococcal disease under the existing or improved vaccine schedules will be important for understanding future disease-causing serotype landscape. It is essential to mention that the recent development of investigational PCV21 by Merck [48], to undergo phase 3 trials later this year, is a step forward in tackling the remaining burden of pneumococcal disease in vulnerable adults since most of its targeted serotypes are not targeted by PPV23. On the contrary, vaccines that target surface proteins common to all serotypes rather than polysaccharides that are present in some serotypes is

ideal for vulnerable adults but would likely face high regulatory scrutiny compared new conjugate vaccines targeting specific serotypes [47].

Due to high costs of conducting pneumococcal carriage studies, poor IPD surveillances, and substantial funding cuts by some major global health funders to LICs [39], monitoring serotype replacement in carriage and disease under the current infant PCV use remains an important gap, and so will be when future higher-valent PCV are used in infants. Statistical and/or mathematical modelling techniques could be used to help evaluate serotypes that are most likely to increase in disease if a higher-valent PCV replaces a lower-valent PCV. Serotype-specific data on pneumococcal carriage prevalence, and the proportion of new carriage acquisitions resulting in disease invasiveness based on estimates of validated invasiveness of many serotypes in various settings, could be used to compute disease incidence [47,49–51], and this may subsequently help inform potential additional benefits of introducing higher-valent infant PCV to reduce pneumococcal disease in vulnerable adults. Nonetheless, there is a great need for improved pneumococcal disease surveillance coverage as well as the accuracy of data capture in adults in LICs or MICs to better understand disease time trends.

Since a major route of pneumococcal carriage transmission is through close social contacts [52], further exploration of contact patterns in the absence of pandemic associated risk will still be necessary to inform the baseline contact rates in many LICs in the era of high urbanisation [53]. In addition, understanding rural as well as temporal changes in social contact patterns may need to be assessed to inform policy on countrywide epidemic preparedness and mitigation measures. Exploring other options of capturing social contacts data to reduce recall and information biases, and generate a connected social contact network

using wearable sensors [54,55], could help gain in-depth understanding of interactions among individuals, and inform or validate disease contact tracing during epidemics, especially in LICs where resources are very limited. However, acceptability of such technology may need to be established beforehand [56].

1.4 Conclusion

Despite the indirect protection against VT pneumococcal disease from widespread use of infant PCV in LMICs, a substantial disease burden remains among vulnerable adults, those living with HIV or aged ≥55y, composed of serotypes not targeted by childhood PCV and substantial residual VT circulation. Thus, vulnerable adults remain at high risk of preventable pneumococcal disease. My PhD research provides evidence of (a) continued circulation of substantial preventable VT in vulnerable adults, with PCV13 residual carriage being associated with HIV-infected adult males and those not living with potentially vaccinated younger children, (b) high risk of pneumococcal carriage acquisitions in HIV-infected adults but with similar close social contact patterns and onward carriage transmission risk to household members as HIV-uninfected adults, and (c) maximise prevented IPD cases when pneumococcal vaccines are offered earlier in older adulthood in LICs or MICs than are typically given in HICs.

In conclusion, efficient infant PCV schedules that enhance indirect protection together with targeted-vaccination for vulnerable adults should be considered in LICs or MICs, along with other public health measures to further reduce VT carriage and disease in vulnerable adults. With the upcoming high-valent PCVs and cheaper infant PCV options from the Serum Institute of India, future opportunities exist for LICs or MICs to tackle a huge gap of expanded serotype coverage and introduction of adult pneumococcal vaccine programs,

potentially optimised by age-targeting as demonstrated in this PhD research. With these opportunities, robust surveillance systems for pneumococcal carriage and disease surveillance to assess vaccine effectiveness and identify early evidence of vaccine escape could be implemented and supported.

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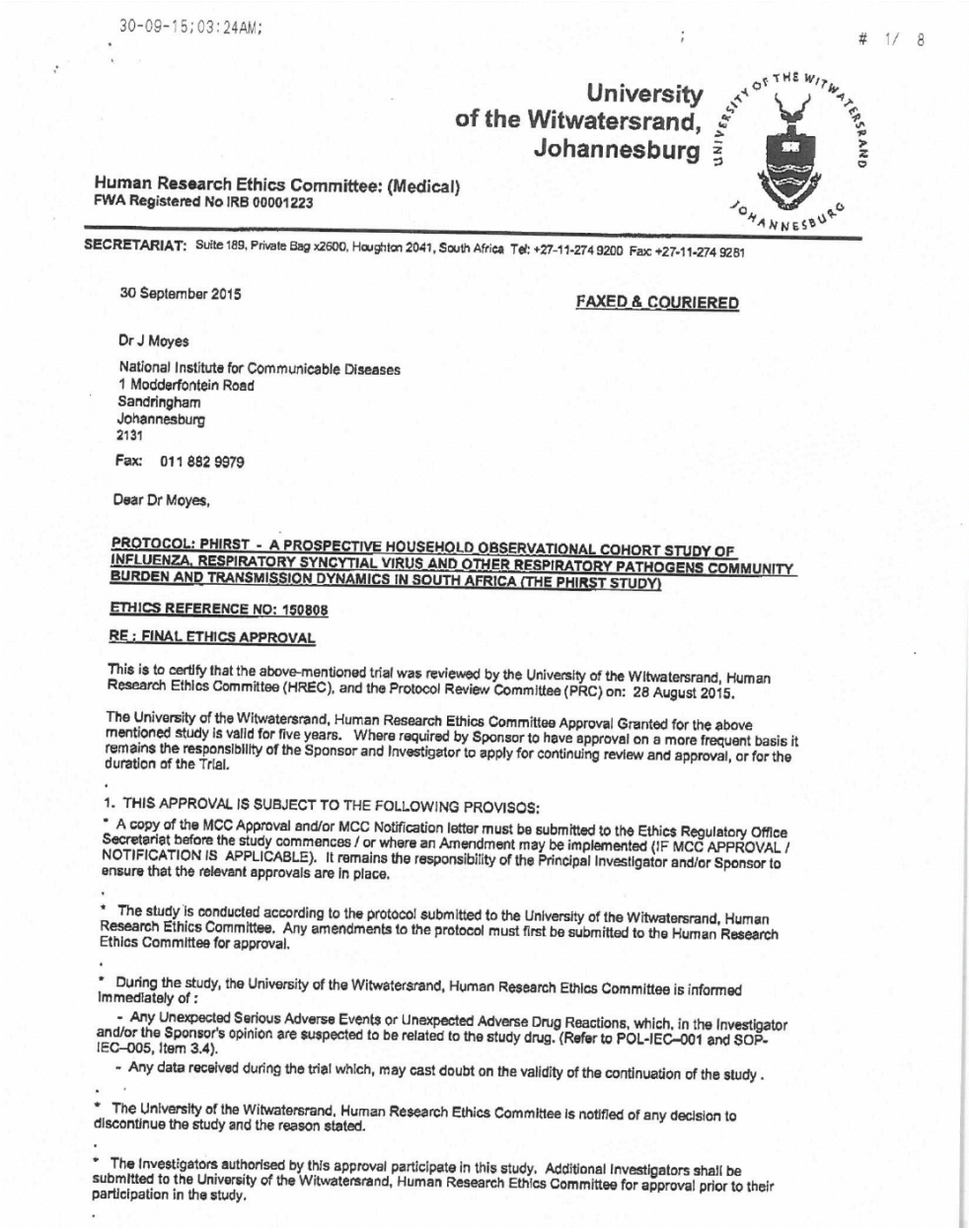
Appendix 1: Ethical approvals for all analyses

A. Study: Estimating the contribution of HIV-infected adults to household pneumococcal transmission in South Africa, 2016-2018: A hidden Markov modelling study.



30-09-15;03:24AM; # 1/ 8

University of the Witwatersrand, Johannesburg

Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

SECRETARIAT: Suite 189, Private Bag x2600, Houghton 2041, South Africa Tel: +27-11-274 9200 Fax +27-11-274 9281

30 September 2015

FAXED & COURIERED

Dr J Moyes

National Institute for Communicable Diseases
1 Modderfontein Road
Sandringham
Johannesburg
2131

Fax: 011 882 9979

Dear Dr Moyes,

PROTOCOL: PHIRST - A PROSPECTIVE HOUSEHOLD OBSERVATIONAL COHORT STUDY OF INFLUENZA, RESPIRATORY SYNCYTIAL VIRUS AND OTHER RESPIRATORY PATHOGENS COMMUNITY BURDEN AND TRANSMISSION DYNAMICS IN SOUTH AFRICA (THE PHIRST STUDY)

ETHICS REFERENCE NO: 150808

RE : FINAL ETHICS APPROVAL

This is to certify that the above-mentioned trial was reviewed by the University of the Witwatersrand, Human Research Ethics Committee (HREC), and the Protocol Review Committee (PRC) on: 28 August 2015.

The University of the Witwatersrand, Human Research Ethics Committee Approval Granted for the above mentioned study is valid for five years. Where required by Sponsor to have approval on a more frequent basis it remains the responsibility of the Sponsor and Investigator to apply for continuing review and approval, or for the duration of the Trial.

1. THIS APPROVAL IS SUBJECT TO THE FOLLOWING PROVISOS:

* A copy of the MCC Approval and/or MCC Notification letter must be submitted to the Ethics Regulatory Office Secretariat before the study commences / or where an Amendment may be implemented (IF MCC APPROVAL / NOTIFICATION IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.

* The study is conducted according to the protocol submitted to the University of the Witwatersrand, Human Research Ethics Committee. Any amendments to the protocol must first be submitted to the Human Research Ethics Committee for approval.

* During the study, the University of the Witwatersrand, Human Research Ethics Committee is informed immediately of :
  - Any Unexpected Serious Adverse Events or Unexpected Adverse Drug Reactions, which, in the Investigator and/or the Sponsor's opinion are suspected to be related to the study drug. (Refer to POL-IEC–001 and SOP-IEC–005, Item 3.4).
  - Any data received during the trial which, may cast doubt on the validity of the continuation of the study .

* The University of the Witwatersrand, Human Research Ethics Committee is notified of any decision to discontinue the study and the reason stated.

* The Investigators authorised by this approval participate in this study. Additional Investigators shall be submitted to the University of the Witwatersrand, Human Research Ethics Committee for approval prior to their participation in the study.

* In the event of an authorised investigator ceasing to participate in the study, the University of the Witwatersrand Human Research Ethics Committee must be informed and the reason for such cessation given.

2. PRINCIPLES OF INFORMED CONSENT:

* The University of the Witwatersrand, Human Research Ethics Committee requires that in all studies, the Principles of Informed Consent are adhered to. This applies to volunteers as well as patients.

3. PROGRESS REPORTS:

* The University of the Witwatersrand, Human Research Ethics Committee requests that the MCC Progress Reports be submitted twice a year either in March and September or six monthly from start of study to the HREC Secretariat Office - 011 274 9281 and a report of the final results, at the conclusion of the study. (IF APPLICABLE)

4. REIMBURSEMENT TO PATIENTS FOR TRANSPORT:

* The Human Research Ethics Committee: (Medical) is in agreement that reimbursement per visit is according to the Medicines Control Council of SA and that reimbursement should be appropriate according to the situation.

5. TRANSPORT AND STORAGE OF BLOOD AND TISSUE SAMPLES IN SOUTH AFRICA:

* If blood specimens are to be stored for future analysis and is planned that such analysis will be done outside Wits, then the blood must be stored at a facility in South Africa agreed with the relevant IRB, with release of sub-samples only once projects have been approved by the local Research Ethics Committee applicable to where the analysis will be done as well as by the Wits Human Research Ethics Committee: (Medical).

6. GENETIC TESTING

* The Human Research Ethics Committee: Medical; will not approve open-ended genetic testing as this does not fit the Human Research Ethics Committee criteria.

7. GOOD CLINICAL PRACTICE

The South African Department of Health, Medicines Control Council requires Good Clinical Practice (GCP) Training for all Investigators in Clinical Trials, and that GCP training be renewed every three (3) years.

As yet, there are no National Guidelines for the content of GCP courses. Until these are available the Wits Human Research Ethics Committee (Medical) will note courses completed by Investigators without approval of the content of the individual courses.

8. THE SUPPORTING APPROVAL DOCUMENTS ARE ATTACHED:

8.1 Ethics Approval Form signed by the Chairperson of the HREC - Kindly return the copy of the Approval Form signed by the Principal Investigator /(s) per fax: 011 274 9281 for our records (this is applicable with the initial Approval).

8.2 Protocol Review Committee Approval Signature page signed by the Acting Chairperson of the PRC.

8.3 List of members present at the HREC meeting held as per INDEPENDENT ETHICS COMMITTEE APPROVAL FORM

9. WE AWAIT YOUR RESPONSES AS REQUESTED: Ensure to have these documents forwarded at the earliest for the HREC records.

* MCC Approval letter and/or letter of Notification before the above study may commence / or where an Amendment may be implemented (IF MCC APPROVAL / NOTIFICATION IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.
* Copy of Independent Ethics Declaration Approval Form signed by the Principal Investigator. (this is applicable with the initial Approval).
* Kindly forward the above to the undersigned at fax: 011 274 9281 at your earliest convenience.

Please ensure that all Investigators have valid GCP training before participating in the above-mentioned study.

Noted: The study will not be conducted in any health care facilities and does not require PRC clearance. The site will apply for provincial ethics clearance on receipt of Wits HREC clearance.

The above has been noted for the Ethics Committee information and records.

KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA / SPONSOR / STUDY CO-ORDINATORS - WHERE APPLICABLE

Regards,
DR MERRYLL VORSTER
For and on behalf of the Human Research Ethics Committee: (Medical)

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Mr Deus Thindwa
LSHTM

31 October 2019

Dear Deus

Submission Title: Household adult HIV prevalence and risk of pneumococcal carriage acquisition in children

LSHTM Ethics Ref: 17902

Thank you for responding to the Observational Committee Chair's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Local Approval	PHIRST Ethics Aproval Sep2015	30/09/2015	Sep2015
Consent form	PHIRST_assentinformation sheet enrol2018clean	10/11/2017	enrol2018
Consent form	PHIRST_Information sheet adults2018enrolclean	10/11/2017	enrol2018
Consent form	PHIRST_Informed consent adultsenrol2018clean	10/11/2017	enrol2018
Consent form	PHIRST_informed consent minor and assent enrol2018clean	10/11/2017	enrol2018
Protocol / Proposal	Community Burden RSV and Influenza - protocol version ammend 13 July 201...	13/07/2018	ammendment13 July201
Investigator CV	DEUS THINDWA CV v0.8	30/07/2019	0.8
Protocol / Proposal	Pneumococcal acquisition and HIV proposal v0.6	19/09/2019	0.6
Covering Letter	Response to LSHTM Ethics Committee v0.1	21/10/2019	0.1
Covering Letter	data sharing agreement	21/10/2019	DataSharingAgreement

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

Professor Jimmy Whitworth
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

B. Study: Social mixing patterns relevant to infectious diseases spread by close contact in urban Blantyre, Malawi.

CERTIFICATE OF ETHICS APPROVAL

This is to certify that the College of Medicine Research and Ethics Committee (COMREC) has reviewed and approved a study entitled:

P.01/21/3244 - DETERMINANTS OF SOCIAL MIXING PATTERNS RELEVANT FOR PNEUMOCOCCAL TRANSMISSION IN BLANTYRE, MALAWI by Deus Thindwa

On 04-Mar-21

As you proceed with the implementation of your study, we would like you to adhere to international ethical guidelines, national guidelines and all requirements by COMREC some of which are indicated on the next page for your study

04-Mar-21

Prof. E. Umar -Chairperson (COMREC)

Date

Approved by College of Medicine 04-Mar-2021 (COMREC) Research and Ethics Committee

REQUIREMENTS FOR YOUR COMREC APPROVED RESEARCH PROTOCOL

1. Pay the research overhead fees to College of Medicine or Kamuzu College Of Nursing (depending on your affiliation) as required for all approved studies (except undergraduate studies).
2. You should note that the COMREC Sub-Committee on Research Participants' Safety will monitor the conduct of the approved protocol and any deviation from the approved protocol may result in your study being stopped.
3. You will provide an end of study (close-out) report.
4. All COMREC approvals of new applications and progress reports are valid for one year only. Therefore all approved studies running for more than one year are subject to continuing review annually. You are required to submit a progress report to COMREC within 90-30 days before the expiration date. Your current expiration date is 04-Mar-22. Studies shall be considered lapsed and inactive if continuing review application is not received one month after the expiry of the previous approval. In that case, all study related operations should cease immediately except those that are necessary for the welfare of subjects.
5. All investigators who are Medical Practitioners must be fully registered with the Medical Council of Malawi.

Approved by College of Medicine 04-Mar-2021 (COMREC) Research and Ethics Committee

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Observational / Interventions Research Ethics Committee

Mr Deus Thindwa
LSHTM

30 March 2021

Dear Mr Deus Thindwa

Study Title: Determinants of social mixing patterns in urban Blantyre, Malawi: A study of age-specific contact rates to inform studies of pneumococcal transmission and vaccine evaluation.

LSHTM Ethics Ref: 22913

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Information Sheet	SCALE_PIS_ICF	04/04/2019	4.0
Local Approval	RSG feedback Letter - LOI628 Deus Thindwa2	29/10/2020	2
Investigator CV	DEUS THINDWA CV 2020-12-05	05/12/2020	6.1
Advertisements	SOMIPA Study Procedure v1.0	19/12/2020	1.0
Local Approval	Thindwa COMREC 3244 approval	04/03/2021	2
Other	Research_Ethics_online_training_certificate v1	19/03/2021	1
Covering Letter	SOMIPA_Cover_Letter_v3	24/03/2021	3
Protocol / Proposal	SOMIPA_01 Protocol_English v3	24/03/2021	3
Information Sheet	SOMIPA_02_PIL_ICF_English v3	24/03/2021	3
Information Sheet	SOMIPA_02_PIL_ICF_Chichewa v3	24/03/2021	3
Local Approval	20210326_Liz_Corbett_support_letter_SOMIPA_study	26/03/2021	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

Professor Jimmy Whitworth
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

C. Study: Risk factors for pneumococcal carriage in adults living with HIV on antiretroviral therapy in the infant pneumococcal vaccine era in Malawi.

CERTIFICATE OF ETHICS APPROVAL

This is to certify that the College of Medicine Research and Ethics Committee (COMREC) has reviewed and approved a study entitled:

P.02/15/1677- Herd immunity and reservoirs of vaccine escape following implementation of pneumococcal protein conjugate vaccines in Malawi by Dr. Thandie Mwalukomo

On 19 May 2015

As you proceed with the implementation of your study, we would like you to adhere to international ethical guidelines, national guidelines and all requirements by COMREC as indicated on the next page

Dr. C. Dzamalala- Vice-Chairperson (COMREC)

Approved by
College of Medicine
19 MAY 2015
(COMREC)
Research and Ethics Committee

19/05/15
Date

REQUIREMENTS FOR ALL COMREC APPROVED RESEARCH PROTOCOLS

1. Pay the research overhead fees as required by the College of Medicine for all approved studies.
2. You should note that the COMREC Sub-Committee on Research Participants' Safety will monitor the conduct of the approved protocol and any deviation from the approved protocol may result in your study being stopped.
3. You will provide an interim report in the course of the study and an end of study report.
4. You are required to obtain a continuation approval after 12 months from the date of approval.
5. All investigators who are Medical Practitioners must be fully registered with the Medical Council of Malawi.

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Observational / Interventions Research Ethics Committee

Mr Deus Thindwa
LSHTM

24 January 2022

Dear Mr Deus Thindwa

Study Title: Age- and time-dependent risk factors for pneumococcal carriage in HIV-infected adults on ART in infant PCV era in Blantyre, Malawi.

LSHTM Ethics Ref: 26839

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Protocol / Proposal	pcvpa_icf_adult_ Eng_v3_160315_clean	16/03/2015	3
Protocol / Proposal	pcvpa_information_adult_Eng_v1_160315	16/03/2015	1
Protocol / Proposal	PCVPA_P.02151677_Protocol_Clean_v10_160315	16/03/2015	10
Protocol / Proposal	PCVPA_CRF_Adult_v02_20150613	13/06/2015	2
Other	Research_Ethics_online_training_certificate v1	19/03/2021	1
Investigator CV	DEUS THINDWA CV 2021-12-08	08/12/2021	6.4

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

Professor Jimmy Whitworth
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

D. Study: Optimal age targeting for pneumococcal vaccination in older adults; a modelling study.

SECRETARIA DE ESTADO DA SAÚDE
COORDENADORIA DE CONTROLE DE DOENÇAS
INSTITUTO ADOLFO LUTZ
CONSELHO TÉCNICO CIENTÍFICO – CTC / IAL

São Paulo, 10 de Fevereiro de 2021

Projeto: **CTC 61-M / 2020**

"Idade alvo para vacinas pneumocócicas em adultos mais velhos imunocompetentes"

Coordenação: Maria Cristina de Cunto Brandileone

Prezado(s) Coordenador(es),

Comunicamos que o projeto foi **aprovado quanto ao Mérito Científico** pelo Conselho Técnico Científico do IAL com **Ciência da Direção Geral** e cadastro **CTC-IAL 61-M/2020.**

Por tratar-se de projeto que *não envolve, direta ou indiretamente, a pesquisa com seres humanos*, e que *não envolve a utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (não humano) segundo a Lei nº 11794/2008*, ***não exige*** a avaliação quanto aos aspectos éticos pelo Comitê de Ética em Pesquisa do Instituto Adolfo Lutz (CEPIAL) e pela Comissão de Ética no Uso de Animais de Experimentação do Instituto Adolfo Lutz (CEUA/IAL).

Atenciosamente,

ADRIANA BUGNO
Presidente do CTC/IAL

1ª Via: Coordenador
2ª Via: Diretor de Núcleo
3ª Via: Diretor de Centro
4ª Via: CTC

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

02 October 2017

Dr Vanessa Quan
Division of Public Health Surveillance and Response
National Institute for Communicable Diseases
1 Modderfontein Road
Sandringham
2031
Sent by email to: vanessaq@nicd.ac.za

Dear Dr Quan

Re: **Protocol Ref no: M140159 (Previously M081117)**
Protocol Title: GERMS-SA: Laboratory-based Surveillance for Pathogens of Public Health Importance in South Africa
Principal Investigator: Dr Vanessa Quan et al
Protocol Amendments

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (Medical) has approved the protocol amendments for the abovementioned protocol, as detailed in your letter dated 20 September 2017.

The following documents were received:

- Cover Letter dated 20 September 2017.
- Study Proposal version 1.4 for 2018.
- Appendix C-1 version 1.4 for 2018.
- GERMS-SA: CRF for version 1.4 for 2018 dated 18 September 2017.
- GERMS-SA: Instruction Sheet for Case Report Form 2018.
- GERMS-SA: Questionnaire version 1.4 for 2018.
- Appendix D-4 Instruction Sheet version 1.4 for 2018.
- GERMS-SA: Case Report Form 2018 version 1.4 for 2018.
- GERMS-SA: Clinical based Surveillance version 1.4 for 2018.
- Candida Case Report Form for NICD/GERMS Lab-based Surveys.

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Thank you for keeping us informed and updated.

Yours Sincerely,

.....

Mr Lebohang Moeng
Administrative Assistant
Human Research Ethics Committee (Medical)

UNIVERSITY OF THE WITWATERSRAND
OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH
02 OCT 2017
RESEARCH OFFICE HREC (Medical)
JOHANNESBURG

UNIVERSITY OF MALAWI
COLLEGE OF MEDICINE

GENERAL GUIDELINES ON HEALTH RESEARCH

COLLEGE OF MEDICINE RESEARCH AND ETHICS COMMITTEE (COMREC)

College of Medicine Research and Ethics Committee
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29th September, 2010.

5.6 Exemption from Review

COMREC will decide whether a proposal can be exempted from review by the full committee. Exemption from review may be considered under the following conditions:

- Research involving collection of existing data, documents, records, programme evaluation, pathological specimens, or diagnostic specimens, only if the sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified directly or through identifiers linked to subjects.

The Chairperson shall review the application for exemption and determine whether to grant the exemption or defer to a full committee seating. Where the Chairperson has granted an exemption at his/her discretion, a full report shall be made at the next full committee meeting.

5.7 Review of Studies of 'National Interest'[7]

Most health research being done in Malawi is generally of national interest. However, there are some studies that deserve particular attention because of their sensitive, political, and safety implications. Studies covering the following areas are to be regarded as examples of "National Interest Studies":

- All vaccine trials
- All drug and medical device trials where patent issues are involved and where safety issues remain fully unknown
- All stem cell research
- All cloning research
- All genetic studies
- All national health surveys

All studies of "national interest" regardless of the origin of the protocol should be referred to the NHSRC who may form a standing committee for that specific project composed of members to be drawn on the basis of their expertise rather than which committee they come from. This ad hoc committee will monitor the project through to its conclusion. The project may be carried out in any geographical location as the committee sees fit. This ad hoc committee shall include a representative each from MOH, NCST and COMREC.

COMREC shall define, based on national guidelines, criteria to be used by COMREC secretariat to assess and refer such protocols to the NHSRC.

5.8 Decision-Making

In making decisions on the applications for ethical review, the committee shall take the following into consideration:

- A member shall withdraw from the meeting for the decision procedure concerning an application where there arises a conflict of interest;
- The conflict of interest should be indicated to the chairperson prior to the review of the application and recorded in the minutes;
- A decision shall only be taken when sufficient time has been allowed for review and discussion of an application in the absence of non-members (e.g., the investigator, representatives of the sponsor, independent consultants) from the meeting, with the exception of COMREC staff;

[7] National Research Council, 2005

The Health Service (Control of Patient Information) Regulations 2002

Status: This is the original version (as it was originally made).

Communicable disease and other risks to public health

3.—(1) Subject to paragraphs (2) and (3) and regulation 7, confidential patient information may be processed with a view to—

(a) diagnosing communicable diseases and other risks to public health;

(b) recognising trends in such diseases and risks;

(c) controlling and preventing the spread of such diseases and risks;

(d) monitoring and managing—

(i) outbreaks of communicable disease;

(ii) incidents of exposure to communicable disease;

(iii) the delivery, efficacy and safety of immunisation programmes;

(iv) adverse reactions to vaccines and medicines;

(v) risks of infection acquired from food or the environment (including water supplies);

(vi) the giving of information to persons about the diagnosis of communicable disease and risks of acquiring such disease.

(2) For the purposes of this regulation, "processing" includes any operations, or set of operations set out in regulation 2(2) which are undertaken for the purposes set out in paragraph (1).

(3) The processing of confidential patient information for the purposes specified in paragraph (1) may be undertaken by—

(a) the Public Health Laboratory Service;

(b) persons employed or engaged for the purposes of the health service;

(c) other persons employed or engaged by a Government Department or other public authority in communicable disease surveillance.

(4) Where the Secretary of State considers that it is necessary to process patient information for a purpose specified in paragraph (1), he may give notice to any body or person specified in paragraph (3) to require that body or person to process that information for that purpose and any such notice may require that the information is processed forthwith or within such period as is specified in the notice.

(5) Where confidential information is processed under this regulation, the bodies and persons specified in paragraph (3) shall make available to the Secretary of State such information as he may require to assist him in the investigation and audit of that processing and in his annual consideration of the provisions of these Regulations which is required by section 60(4) of the Act.

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Observational / Interventions Research Ethics Committee

Mr Deus Thindwa
LSHTM

20 July 2021

Dear Deus

Submission Title: Optimal age targeting for pneumococcal vaccination in older adults

LSHTM Ethics Ref: 25787

Thank you for responding to the Observational Committee Chair's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Local Approval	comrec_guidelines	29/09/2010	1.0
Local Approval	WHREC v1.4 for 2018	17/10/2017	1.4
Investigator CV	CV Deus Thindwa	02/02/2018	6.1
Investigator CV	CV_Neil_French_2pagerpubs_sep 2020-2	02/09/2020	2
Local Approval	South Africa Data Sharing Agreement v1	09/12/2020	1
Local Approval	61M_2020 Cadastro definitivo sem CEP (1)-1	10/02/2021	1.0
Local Approval	Brazil Data Sharing Agreement v1	18/02/2021	1
Other	Research_Ethics_online_training_certificate v1	19/03/2021	1
Investigator CV	CV Stefan Flasche	26/03/2021	1
Investigator CV	CV John Ojal	26/03/2021	1
Protocol / Proposal	Study protocol v2	12/07/2021	2
Covering Letter	LSHTM_ethics_response_letter_v2	19/07/2021	2

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

Professor Jimmy Whitworth
Chair

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Research Ethics Committee

Mr Deus Thindwa
12 July 2022

Dear Mr Deus Thindwa,

Study Title: Optimal age targeting for pneumococcal vaccination in older adults

LSHTM Ethics ref: 25787 - 1

Thank you for submitting your amendment for the above research project.

Your amendment has been assessed by the Research Governance & Integrity Office and has been approved as a non-substantial change. The amendment does not require further ethical approval from the observational ethics committee.

List of documents reviewed:

Any subsequent changes to the application must be submitted to the Committee via an Amendment form on the ethics online applications website: http://leo.lshtm.ac.uk .

Best of luck with your project.

Yours sincerely,

Rebecca Carter

Ethics Facilitator

Ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/