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Systematic Review

Pneumococcal Colonization and Disease Burden in Malawi from 1995 to 2020, A Systematic Review

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Abstract

Background: *Streptococcus pneumoniae* (SPN*)* is one of the leading causes of mobility and mortality in children, particularly in low- and lower-middle-income nations. This review aims to describe the SPN colonization and the effectiveness of the 13-valent pneumococcal conjugate vaccine (PCV13) immunization in Malawi, from 1995 - 2020 as well as an estimate if Sustainable Development Goal 3 of eliminating SPN will be achieved by 2030. We examine pneumococcal carriage in Malawi before and after the 2011 introduction of the PCV13 vaccine.

Methods: The research is based on a thorough review of the literature. Relevant articles were systematically evaluated for information on the prevalence of SPN carriage in children (0 - 15 years), adults (>18 years), and HIV-infected individuals residing in Malawi using PubMed, MEDLINE, Scopus, and the African Index Medicus. Seven of the 31 publications found were included in the review.

Results: This study contained seven papers, the bulk of which 4(57.1%) were from Blantyre.

Carriage rates varied greatly between trials. Children under the age of five had the highest rate of SPN carriage, which gradually decreased as they grew older. Individuals over the age of 18 years on ART had more pneumococcal colonization than those not on ART (25.9% vs. 19.8%, P 14 0.03). The five most prevalent isolates were 1,6A, 6B, 19F, and 5.

Conclusion: Despite the introduction of PCV13, the burden of pneumococcal infection remains high in Malawi. With the introduction of PCV13, there is a reduction of Vaccine-type (VT) carriage while Non-Vaccine-type (NVT) carriage has increased. The top seven serotypes that cause invasive pneumococcal disease (IPD) in children worldwide include the five most prevalent serotypes in Malawi. PCV13 vaccination changes the distribution of serotypes detected in the nasopharynx. To further assess the impact of PCV13 introduction, ongoing carriage surveillance is required.

Keywords: *Pneumococcal Colonization; Disease Burden; Streptococcus pneumoniae*

Introduction

Streptococcus pneumoniae (SPN) is the most common cause of morbidity and mortality in the world due to community-acquired pneumonia, meningitis, and bacteremia. SPN is thought to be responsible for over 318,000 (uncertainty ratio: 207,000 - 395,000) mortalities in children between the ages 1 - 59 months every year around the world, with the highest mortality burden falling on developing countries with a combination of factors favoring high and persistent pneumococcal carriage and transmission, such as poor living conditions, economic hardship, and high human immunodeficiency virus (HIV) prevalence [1-3].

Pneumococcus enters the body through the nose and is transmitted through the nasopharynx. Even though pneumococci colonization is usually asymptomatic, nasopharyngeal carriage is regarded to be a prerequisite for invasive disease [423F]. Furthermore, asymptomatic carriers are the primary source of pneumococcal infection, with person-to-person transmission happening among people close by [423F]. Colonization of mucosal membranes in the human respiratory tract is a continuing phenomenon in which microbes are acquired, expelled, and reacquired numerous times throughout a person's life. Colonization is a need for disease occurrence, and because it is far more prevalent than a disease outcome, it might be a useful indicator of novel pneumococcal vaccination effectiveness [5]. Pneumococcal colonization is usually harmless to the host, although it can rarely disseminate to the vertically or horizontally respiratory tract, as well as the circulatory and meninges, resulting in pneumonia, septicemia, or meningitis [6].

In Africa, it has proven challenging to implement treatment regimens that focus on early identification and antibiotic therapy for suspected pneumonia infections [5]. As a result, in this region, the provision of an efficient vaccination against pneumococcal colonization for children is critical. Between 2009 and 2015, 34 African nations used Gavi to add PCV13 into their extended vaccination programs, following WHO recommendations [7]. These vaccinations have been found to reduce the occurrence of pneumococcal illness as well as the frequency of carriage by some of the highly virulent of the 97 pneumococcal serogroups. Additionally, the vaccination prevents the unvaccinated populace indirectly from pneumococcal carriage and illness by lowering the transmission of pneumococcal from PCV13 vaccinated children, who are at higher risk of carrying and hence transmission sources [8,9we enrolled HIV-infected children age <5 years presenting for routine care at seven HIV clinics in 3 sites, including Maputo (urban-south].

Numerous researchers have found a decrease in invasive pneumococcal disease (IPD) since the initiation of the PCV13 vaccination. Nevertheless, this is typically accompanied by a shift in circulating serotypes. In South Africa and Tanzania, there has been a decline in (VT) IPD as well as a spike in (NVT) IPD [10]. Pneumococcus is the most common cause of meningitis in Malawi, as well as the second most common cause of bacteremia and community-acquired pneumonia [11].

It's still unclear if the introduction of PCV13 in Malawi in 2011 has the long-term direct or indirect protection needed to lower pneumococcal colonization to levels low enough to stop disease transmission. Pneumococcal infections and carriage in under-five children and people living with HIV in Malawi remain high despite the introduction of the PCV13 vaccine. Based on the information mentioned above, this review aims to summarize data available on pneumococcal colonization and disease in Malawi from 1995 to 2020, explain the variations in carriage prevalence, describe the distribution of serotypes, and Pneumococcal pneumonia incidence and/or prevalence patterns in Malawi before and after the introduction of PCV13 to determine whether the 2030 sustainable development goals (SDG) 3 of reducing mobility and mortality from pneumococcal infections will be met. These research questions adopted the Population Intervention Comparators outcome (PICO) acronym.

Population	children (0 - 15 years), adults (>15 years), and HIV-infected persons living in Malawi
Intervention	PCV13 vaccine
Comparators	PRE and POST PCV13 period
outcome	Pneumococcal Prevalence/Incidence/Serotype distribution
Question	1. Explain the variations in carriage prevalence
Question	2. Describe the distribution of serotypes
Question	3. What is Pneumococcal pneumonia incidence and/or prevalence patterns in Malawi before and after the introduction of PCV13?

Table A

Methods

Published, PubMed, MEDLINE, Scopus, and the African Index Medicus listed studies on pneumococcal carriage and disease in Malawi were reviewed. The literature search technique was used to find all papers published between1995 and 2020 that met the eligibility and exclusion requirements. The search was conducted by investigating and merging medical subject headings and free search phrases linked to carriage OR colonization, pharyngeal OR nasopharyngeal, *Streptococcus pneumoniae*, Serotypes, pneumococcal vaccination, and particular names from Malawi to assure the extraction of relevant publications. Duplicates, non-relevant publications, and those involving streptococcal diseases apart from *S. pneumoniae* were eliminated from the study (Figure 1). Then, the entire texts of the proposed articles were evaluated to see if they were eligible. To gather data on the following factors, a standardized data extraction form from Microsoft Excel spreadsheet 2016 was utilized, which was built particularly for each result of interest. Identification of the study: primary author's name, year of publication, research region, the aim of the study, prevalence/incidence, serotype distribution and Critical Appraisal Skills Program (CASP). The Population Intervention Comparators outcome (PICO), which included children (0 - 15 years), adults (> 15 years), and HIV-infected persons living in Malawi, served as the eligibility criteria for relevant research with PCV13 as the intervention. The periods before PCV13 introduction (1995 - 2010) and after PCV13 introduction (2011 - 2020) were used as comparisons, and the outcomes were the percentage difference in the aggregated prevalence of pneumococcal colonization after PCV13 initiation against the period before PCV13 initiation; prevalence percentages in the aggregated prevalence of pneumococcal pneumonia between post-PCV introduction and pre-PCV initiation; and serogroup distribution. The studies' exclusion criteria were as follows: Letters, opinions, narratives, and editorials were omitted because they are likely to contain skewed estimations, which might alter estimates. Studies that had not been published in English were also excluded. CASP, (2020), checklist tool was used to analyze all the eligible studies. The CASP technique allows for a systematic assessment of the reliability, applicability, and results of published articles [12].

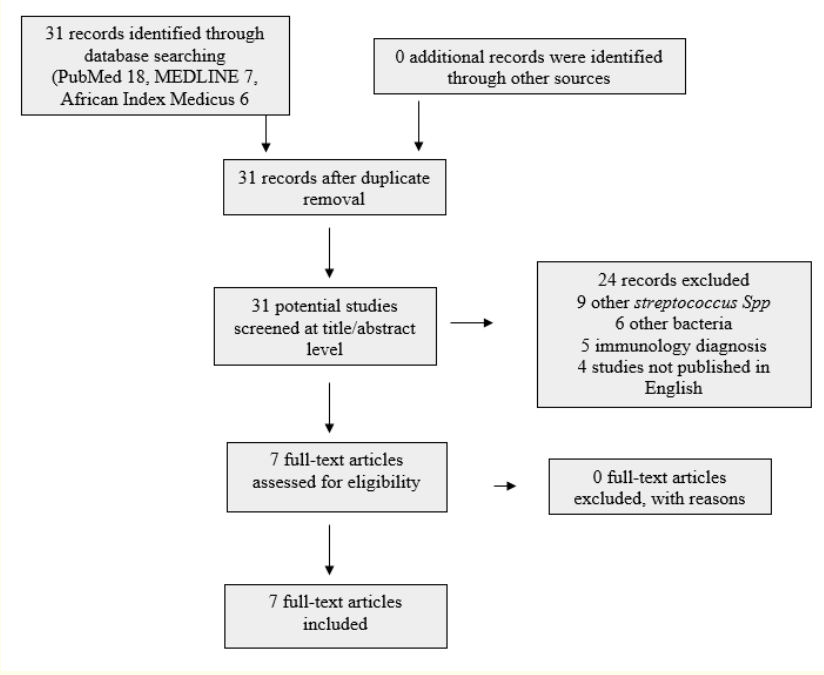

Figure 1: *Flow chart for eligible articles.*

Results

Characteristics of the studies

A total of 7 studies are included in this review (Table 1). Blantyre, in the Southern part of Malawi, contributed 4 studies (57.1%) while 3 studies (42.9%) were from Karonga in the Northern part of Malawi. One study among the 7 studies was conducted in both Blantyre and Karonga 14.3% and no other studies were found from other regions of Malawi. The majority of the studies used prospective study design 4 (57.1%), 1 (14.3%) was an observational cohort study, 1 (14.3%) had a combination of cross-sectional and longitudinal, and the other was prospective observational and case-control 1 (14.3%). The majority of the studies 6 (85.7%) were conducted in children, 1 (14.3%) involved both children and adults and only 1 (14.3%) study exclusively recruited adults. Most studies 6(85.7%) investigated the prevalence/incidence of SPN and only 1 (14.3%) did not investigate. 4 (57.1%) investigated serotype distributions and the remaining 3 (42.9%) did not.

First author	Location	Aim	SPN Prevalence / Incidence	Serotype Distribution	CASP, (2020)
Marianne Koenraads 2021	Blantyre	Investigate the burden of IPD in infants <90 days	**Before PCV-13**(VT+NVT) IPD 319 (95% CI 264-385) per 100,000 **Post PCV-13.** 72 (49-106) per 100,000 (P<0.01).	5 (27.8%) 1 (15.6%)	The findings of the study provide a distinct collection of data on the prevalence of IPD in newborns under 90 days of age across 14 years. The report was based on lengthy strong ongoing prospective, systematic, and repeatable monitoring in one of Africa's only major datasets. However, the researchers were unable to analyze clinical, follow-up, and outcome data, as well as individual immunization information, making a definitive conclusion on the findings difficult.
Arox W. Kamng'ona 2015	Blantyre and Karonga	Investigated prevalence of multiple carriage	0-2y (71 %, 40/56), 3-13 (50 %, 30/60)	6B (47 %, 16/34)	The use of the microarray was appropriate to analyze multiple serotypes. A pneumococcal serotyping approach that is acceptable for use in reliable carriage and surveillance investigations must, at the very least, be precise in its serotype assignment, especially in regard to VT and NVT. The essential to identify numerous serotypes in carriage (particularly in high-burden settings) and detection of most or all serotypes are important attributes of microarray (22).

Ellen Heinsbroek 2018	Karonga	Compared SPN carriage before and after PCV-13	**(Before PCV-13)**.6-week old infants11.4%, 18-week old infants 45.1%, children 1–4 years 28.2%, children 5–15 years 21.2% mothers 6.6%	**(Post PCV-13).**19F (14), 6B (13) and 6A (10), 19A (7), 9 V (5), 14 (5), 3 (4), 18C (2) 5(1).	All the vaccine type serotypes were reported appropriately, however, because the study was not designed to examine changes in individual serotypes and laboratory techniques used could not distinguish individual NVT, the researchers were unable to determine whether specific serotypes had risen or dropped after the initiation of PCV13. The researchers would have deployed the use of microarray like in the a study by Kamng'ona, *et al.*,(13)despite the reported high rates of pneumococcal carriage in Malawi, no data on carriage of multiple serotypes has been reported previously. Our study provides the first description of the prevalence of multiple pneumococcal carriage in Malawi. METHODS: The study was conducted in Blantyre and Karonga districts in Malawi, from 2008 to 2012. We recruited 116 children aged 0-13 years. These children were either HIV-infected (N = 44.
Ellen Heinsbroek 2015	Karonga	Impact of ART on pneumococcal carriage	**ART vs NOT on ART** (25.9 vs. 19.8%, P 1/4 0.03) **Serotypes not in PCV-13** (16.1 vs. 9.6% P 1/4 0.003).		To investigate the impact of ART on pneumococcal carriage, the researchers used an observational cohort study design, which was appropriate to address the research questions. Despite two years of antiretroviral therapy, pneumococcal carriage in HIV-infected people in Malawi remained high, with indications of increasing carriage of non-PCV13 serotypes. Simultaneous colonization with various serotypes was not detectable using the laboratory techniques utilized in this investigation. Though ART status has no direct impact on the pneumococcal carriage, it may have influenced the results of serotype diversity. The researchers used a self-reported definition to poor adherence to ART, this might have led to misclassification of patients recruited, and hence the comparison might have been under or overestimated.
A. YOMO 1997	Blantyre	Determine the prevalence of SPN carriage in children	95 (47.5%)		The methods used by the researchers were appropriate and compared carriage rates from two different sample sites using swabs from the nasopharyngeal and throat. Nasopharyngeal swabs are highly sensitive, and studies that use only one method for collecting sample to detect carriage may underestimate pneumococcal carriage rates, so use of two samples method is suggested.

Jennifer E. Cornick 2011	Blantyre	Investigate serotypes of SPN isolates from febrile children		1 (23%), 6A/B (18%), 14 (6%), and 23F (6%).	The research design used in this study was appropriate to address the aim of the study which was to investigate the incidence of disease in this area. However, the study was not a formal epidemiologic study because it did not comprise a truly random selection of isolates. Randomization is important for improving the quality of evidence-based investigations by reducing selection bias, which can alter the results (23)
Naor Bar-Zeev 2021	Blantyre	Assess impact of PCV13 on the incidence of VTs/NVTs IPD	**infants (<1-year-old)** 19% (IRR 0·81, 95% CI 0·74 to 0·88, p<0·0001)		The researchers' study design was acceptable for addressing the research goal, which was to investigate the influence of VT and NVT invasive IPD in children and adults of vaccine-eligible and vaccine-ineligible ages. However, the use of case-control study design was underpowered due to the sample size. The statistical strength of the matched case-control study, which requires coverage discordance, was hampered by the reduced sample size.
			1–4 years 14% (0·86, 0·80 to 0·93, p<0·0001)		
			5–14 years 2%up (1·02, 0·93 to 1·11, p=0·72).		
			≥15 years old 8% (0·92, 0·83 to 1·01, p=0·084)		

Table 1: *Shows the characteristics of the studies that were included in the review.*

Pneumococcal carriage by age and geographic region

Carriage rates differed significantly between studies. The carriage was highest in children under the age of five and dropped as they grew older in all the studies that investigated carriage (Table 1). In a study by Kamng'ona, *et al.*,(13)despite the reported high rates of pneumococcal carriage in Malawi, no data on carriage of multiple serotypes has been reported previously. Our study provides the first description of the prevalence of multiple pneumococcal carriage in Malawi. METHODS: The study was conducted in Blantyre and Karonga districts in Malawi, from 2008 to 2012. We recruited 116 children aged 0-13 years. These children were either HIV-infected (N = 44, multiple serotypes were found in 39.7% (46/116) of the children. Younger (0 - 2 years) children (71%, 40/56) carried more vaccination

type (VT) strains (p = 0.028) than older (3–13 years) children (50%, 30/60). Pneumococcal colonization was found in 47.5% of children under the age of five in another investigation by [14]. The carriage rate was greatest in children aged 3 to 12 months and did not differ according to household size or if they had previously been admitted to the hospital. According to Heinsbroek *et al.*, [1512, 18 and 24 months. We compared pneumococcal carriage by ART status using generalized estimated equation models adjusted for CD4 cell count, sex, seasonality, and other potential confounders. RESULTS: In total, 336 individuals were included, of which 223 individuals started ART during follow-up. Individuals receiving ART had higher pneumococcal carriage than individuals not receiving ART (25.9 vs. 19.8%, P=0.03], adults who received ART had greater pneumococcal colonization than those not on ART (25.9% vs. 19.8%, P 14 0.03), especially for serotypes not included in PCV13 (16.1 vs. 9.6%, P 14 0.003).

PCV and pneumococcal carriage and infections

Two studies from Blantyre by Koenraads *et al.*, [16] ,Bar-Zeev *et al.*, [17], and one from Karonga by Heinsbroek *et al.*, [18], looked at the link between PCV and infection and carriage. Before the introduction of PCV13, VT carriage ranged from 6.6 - 45.1% in a research by Heinsbroek *et al.*, [18], with 18-week-old newborns having the greatest rate and children 5 - 15 years and mothers having the lowest rate. VT carriage reduced in immunized 18-week-old newborns (adjusted prevalence ratio 0.24 (95% confidence interval 0.08 - 0.75), immunized children 1 - 4 years (0.54 (0.33 - 0.88), unimmunized children 5 - 15 years (0.37 (0.17 - 0.78), and mothers (0.34 (0.15 - 0.79) following immunization launch. For 6-week-old babies who were too young to be vaccinated (1.07 (0.38 - 3.02) and PCV-13-ineligible children aged 1 - 4 years (0.84 (0.53 - 1.33), no reduction in VT carriage was found. Only among vaccinated children aged 1 - 4 years did NVT carriage rise (1.58 (1.21 - 2.06). In a study by Bar-Zeev *et al.*, [17], there was a reduction in total VT and NVT for IPD incidence before the introduction of PCV: 19% (IRR 081; 95% CI 074 to 088; p00001) among newborns (less than 1 year), 14% (086, 080 to 093; p00001) among children between the aged of 1 - 4 years, and 8% (092, 083 to 101; There was a 2% rise in total IPD among children aged 5 - 14 years (102, 093 to 111, p = 072). Koenraads *et al.*, [16], reported 130 verified incidences of IPD in infants less than 90 days of which there were a total of 104 cases of IPD, 25 (24.0%) had the early-onset disease, whereas 79 (76.0%) had the late-onset illness before the adoption of PCV13 in 2011. After the introduction of PCV13, 11 (42.3%) of the 26 IPD cases were early-onset, while 15 (57.7%) were late-onset.

Pneumococcal carriage serotypes distribution in Malawi

Four (57.1%) of the studies had collected data on serotypes distribution. Cornick *et al.*, [19], serotyped a total of 176 isolates and serotypes 1 and 6A/6B were the most common, accounting for 23% and 18% of all isolates, respectively. PCV7, PCV10, and PCV13 serotypes were found in 69 (39%), 116 (66%), and 154 (88%) of the 176 samples, correspondingly. Koenraads *et al.*, [16], managed to isolate 90 serotypes from a total of 130 cases and serotypes 5 (27.8%) and 1 (15.6 %) were the most common. Heinsbroek *et al.*, (2018), reported serotyping 61 isolates following post-vaccination with PCV13 and 19f (23.0%) was the common serotype followed by 6B (21.3%) and the least was 5(1.6%). Kamng'ona, *et al.*, [13], identified 179 pneumococcal strains among the 116 children that participated in this research. VT serotypes accounted for 60% of all serotypes discovered. The NVT serotypes constituted 39% of the total serotypes found. Other NT strains made up the final 1% of the total variants. Serotype 6B was found in 47% of the isolates (16/34). Overall serotype 6B was among the most prevalent serotypes in 3/4 studies (2 Blantyre and 1 Karonga), serotype 1 in 2/4 (Blantyre), serotype 5 in 2/4 (Blantyre and Karonga) and serotype 19F in 1/4 (Karonga) studies.

Discussion

This systematic review of pneumococcal carriage in Malawi summarizes the prevalence of carriage, distribution of serotypes and the effect of PCV on the carriage. The 4 of the studies were from Southern and 3 from Northern Malawi, particularly Blantyre and Karonga. Published research considered in this analysis were sparsely spread over a nearly two-decade span among those available. At the time of data retrieval, there were no published pneumococcal carriage investigations from other parts of Malawi.

Findings from studies highlighted in this review show that the rate of colonization in children less than 5 years is higher than in adults especially for serotypes not included in PCV13. This is consistent with other studies outside Malawi which found Pneumococcal carriage being prevalent throughout the African continent, especially in young children [24-2663.2% (95% CI: 55.6–70.8]. The large range of carriage rates identified in this article could be due to several factors, including the age groupings of the people involved, ethnicity, low vaccine uptake or the vaccines not being effective, poverty, poor nutrition and living in buildings with crumbling infrastructure and seasonal variation. This review brings to light that it is likely that pneumococcal infections and death will not be eradicated in Malawi by 2030. If Malawi is to eradicate pneumococcal infection by 2030, and achieve SDG 3, the impact of PCVs on pneumococcal VT carriage must be increased further. This is critical for Malawi, as well as other supporting partners like Gavi. Malawi is a high-burden country where post-PCV VT carriage data indicates that local epidemiological factors may influence a lower vaccine impact on carriage than elsewhere [27Malawi introduced the 13-valent pneumococcal conjugate vaccine (PCV13]. Enhanced immunization schedules and catch-up initiatives tailored to Malawi population and the sub-Saharan Africa region could help reduce VT carriage, improve herd protection, and maximize cost-effectiveness [28]. To do so, we must first have a deeper understanding of local transmission patterns throughout ages, which are likely influenced by socio-demographic variables, as well as the short- and long-term effects of PCV.

This review also analyzed the distribution of pneumococcal serotypes. It was found that serotypes 1, 6A, 6B, 19F and 5 which are included in the current PCV13 were the most common serotypes identified in Malawi. It's worth mentioning that few investigations on SPN serotype distribution have been undertaken in Malawi. Importantly, the serotyping findings in this review are similar to findings in several other nations throughout Africa [25,29,30with more than 900,000 deaths annually in children under five years of age. Streptococcus pneumoniae causes most deaths, most often in the form of community acquired pneumonia. Pneumococcal conjugate vaccines (PCVs]. The 5 most prevalent serotypes in this study are among the 7 that causes the most widespread IPD in infants; PCV 10 and PCV13 will cover nearly 70% of IPD infections caused by these serotypes [7,31]. Although serotypes 1 and 5 are closely correlated with pneumococcal illness epidemics, they are infrequently isolated from carriage investigations [6,32,33one of the five regions in the Northern Territory. Carriage data were also collected in 2003 and 2005 from four regions in the Northern Territory. Twenty-six cases of serotype 1 IPD were reported from 1994 to 2007 in the Northern Territory. Forty-four isolates were analyzed by BOX typing and 11 by multilocus sequence typing. In the Darwin region, 26 children were reported carrying serotype 1 (ST227]. The ability of different serotypes to cause IPD varies according to the geographical region as well [34although the majority of pneumococcal infections occur in this setting. The aim of the study was to apply MLST to investigate the population biology of S. pneumoniae in West Africa. Methods Seventy three invasive and carriage S. pneumoniae isolates from three West African countries including The Gambia, Nigeria and Ghana were investigated. The isolates covered seven serotypes (1, 3, 5, 6A, 11, 14, 23F]. The serotypes found in this review have also been discovered from other surveillance study conducted in sub-Saharan Africa that found 6A/B, 19F and 23F were the most common circulating serotypes [35,36mainly in countries with no pneumococcal conjugate vaccines (PCVs]. Furthermore, a study conducted in numerous nations discovered that serotypes 6A, 6B, 19F, and 23F were the most commonly isolated serotypes in Malaysian children, as well as in African and Chinese children [37-3995% confidence interval (95% CI]. It is sad to note that only four out of 7 studies included in this review investigated serotype distributions. The significant prevalence of pneumococcal illness necessitates research and assessment of *S. pneumoniae* serotypes to provide evidence and guidelines for the use of pneumococcal vaccinations and medicines and this will help in the fight of pneumococcal infections. Researchers must investigate the epidemiological consequences of conjugate vaccines in Malawi and sub-Sharan Africa, by looking into the serotype distribution related to pneumococcal illnesses and why there are many NVT ever since the introduction of PCV13. Because non-PCV13 serotypes play such a large role in pediatric IPD in Malawi, next-generation PCVs with good coverage would be required to minimize the residual pneumococcal disease burden thus eradicating the infection by 2030.

Because pneumococcal illness is caused by newly acquired serotypes, it has been suggested that pneumococcal colonization studies can be used to detect the influence of PCV on disease [40Malawi introduced the 13-valent pneumococcal conjugate vaccine (PCV13]. In this review, studies that looked at the effect of PCV on VT carriage found a decrease in VT carriage. A rise in the incidence of NVT IPD complemented the decrease in VT IPD. This is in line with the findings of other surveillance studies conducted in Germany, Norway, and

the United States, which showed a decrease in VT carriage rates after PCV13 was introduced [41-43samples were cultured for SP and isolates were serotyped. Clinical and immunization records were reviewed. Findings during 6 sequential 6-month study periods were compared. Surveillance isolates of invasive disease isolates were reviewed. RESULTS: A total of 2048 children were enrolled, and 656 (32%]. Following the introduction of PCV13 in Nigeria, another study found a significant decrease in VT carriage and an increase in NVT [44Kano]. Usuf *et al.*, [24], also showed a reduction of VT after the introduction of PCV13 and an increase in NVT in sub-Saharan Africa. A reduction in VT following the introduction of PCV13 might not be the definite picture of Malawi in terms of winning in the fight against pneumococcal infections but rather a few studies have investigated the effect of the vaccine in children. As countries implement PCV, continuous observation of circulating serotypes will be critical. In all post-vaccination investigations, the rise in NVT may have influenced the effect of PCV13 initiation. If the NVTs that are replacing the VTs are also the reason for IPD, the reduction in IPD-related child fatalities may not be as significant as projected. Although it appears that the novel serotypes substituting the VT's are less intrusive, more research into serotype substitutions is needed to assess PCV13's impact [45].

The results from this review indicate that PCV immunization alone may not be enough to protect vulnerable populations from IPD, stressing the need for further research into alternative strategies to address the IPD burden in Malawi and Sub-Saharan Africa. According to changing epidemiological data, Malawi and the majority of Low- and Middle-Income Countries in Sub-Saharan Africa are less likely to eradicate Pneumococcal infection and death by 2030, hence failing to meet SDG #3. The poor progress in eliminating the pneumococcal disease is partly due to a failure to prioritize addressing inequality as a key component of reaching the SDGs. The findings of this systematic review, which consider both the direct and indirect effects of the vaccines, provide more data to the research world and policymakers about the use of PCV and its significance in reducing the incidence of pneumococcal illness in Africa and at the same time indicating the need for increased effort from donors, government and non-governmental organizations to help combat the disease. The persistent disease load in newborns and adults should be investigated further. Future research should concentrate on developing effective vaccines to protect infants, the elderly, and other susceptible populations. Future research should investigate the safety and efficacy of PCV prenatal immunization in mothers to minimize the prevalence of newborn pneumococcal disease in regions where the pneumococcal disease is acquired relatively early in life, as well as the active and passive benefits of PCV booster dosages in newborns. The advent of NVT diseases should inspire more lengthy disease monitoring to track changes and provide additional data for future vaccine modeling.

For Malawi, globalization can also be seen as a remedy in the fight against pneumococcal disease, as the world's interconnectivity makes it simpler for political figures and multi-governmental organizations (MGOs) to collaborate to eradicate this contagious illness. For example, if world leaders and international organizations banded together to make pneumococcal vaccination mandatory for all vulnerable populations, the disease could be eradicated in Malawi and the rest of the world by 2030. According to Bonten *et al.*, [46], adult and newborn immunization have been demonstrated to be advantageous due to the persistence of vaccine serotype carriage and IPD in vulnerable populations.

In Malawi, there are a number of obstacles in managing pneumococcal infections, including a lack of medications, a scarcity of community health professionals, insufficient diagnostic and treatment equipment, and ineffective referral procedures for children who require a high degree of care. It's worth noting that UNICEF is one of the organizations assisting Malawi's government in achieving the SDGs by training health workers in rural areas and acquiring vaccinations and pharmaceuticals to keep village clinics operational. The determination to combat pneumococcal infection and death by 2030 in Malawi, is a test of that commitment since it necessitates global collaboration, resource transfers, and a readiness to prioritize the needs of the poorest and most vulnerable and if more organizations just like UNICEF would join hands , pneumococcal would be history in Malawi. Setting high health objectives is worthless unless health services in Malawi are established and maintained to fulfill the requirements of the needy. There are several reasons why pneumonia is still known as the "Princess disease" of the world: curing it necessitates long-term investments in healthcare systems that are tilted toward low-income populations. Action at all levels is required, including increased health funding in poor countries like Malawi, specialized action programs to combat pneumonia, and international measures to improve supplies of low-cost medications such as penicillin. Measures

are necessary to produce next-generation vaccines having longer-lasting protection and greater serotype diversity that are effective in vulnerable populations. Changes in the distribution of pneumococcal disease-causing serotypes among children and adults should inform the development of future higher-valent conjugate vaccines [47].

The study was limited by the nature of the topic which was looking at pneumococcal infections in Malawi with few articles being at disposal for the analysis. An important thing worth noting is the listed studies' sample sizes vary from 116 to 10 281 476 person-years. If all of the investigations had a bigger sample size, the results might have been more indicative of each region's carrier condition and hence better for analyzing the PCV's effect. In one of the studies the researchers were unable to analyze clinical, follow-up, and outcome data, as well as individual immunization information, making a definitive conclusion on the findings difficult. Only 4 from a total of 7 managed to investigate serotype distribution of participants which made the carriage results and presentation of results incomplete. Transmission of pneumococcal depends on establishment of carriage and the serotypes involved.

Most notable thing that this article has shown is the benefit that came with the introduction of PCV13 in Malawi that lead to a decrease in VT that are included in PCV 13 and also the techniques that were used in one of the articles that included examining changes in serotypes and is a core thing in the modeling of effective and next generation vaccine that will help us understand serotype replacement and how antimicrobial resistant comes about.

Conclusion

This review summarizes data available on pneumococcal colonization and disease in Malawi from 1995 to 2020. SPN carriage varies significantly in different parts of Malawi, according to this study. SPN carriage was greatest in children under the age of five, and it steadily reduced as they grew older. Pneumococcal colonization was higher in ART-treated adults over the age of 18 than in non-ART-treated adults. It was also noted that there was a surge in NVT carriage and a reduction of VT after the introduction of PCV13. Despite significant variations in carrier state and vaccine coverage, it is obvious that SPN carriage, including carriage of VTs and pneumococcal infections, would not be eradicated in Malawi by 2030, hence not meeting SDG 3. More effort is required towards the fight against pneumococcal infections and this includes world leaders joining hands to make vaccination mandatory for all vulnerable groups, increasing health funding and investing in new vaccine research. Constant monitoring of carrier frequencies and serotype distribution in Malawi and L-MICs is required to assess the effect of the vaccine's subsequent introduction.

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