Pneumonia

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# Radiographically confirmed pneumonia in Malawian children and associated pneumococcal carriage after introduction of the 13-valent pneumococcal conjugate vaccine

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## Abstract

**Background** The 13-valent pneumococcal conjugate vaccine (PCV-13) was introduced in Malawi in 2011 with an expected impact of reducing pneumococcal pneumonia in children. We aimed to describe clinical characteristics and nasopharyngeal (NP) carriage of pneumococcus by serotype in children hospitalized with primary end-point pneumonia (PEP) between 2013 and 19 after the introduction of PCV-13.

**Methods** We conducted a secondary analysis of children aged under-5-years hospitalized with acute respiratory illness (ARI) in Malawi. Chest radiographs conducted at admission were read by two independent clinicians according to WHO criteria for PEP, and a third reviewer resolved discordant diagnoses. NP swab specimens were processed and *Streptococcus pneumoniae* growth was serotyped. Multivariable regression analysis was conducted to assess the association between clinical characteristics, NP serotypes, and PEP.

**Results** We had complete radiographic and NP serotype data for 500 children, of which 54 isolates were vaccine-type (VT) (10.8%), 165 were non-VT (NVT; 33.0%), and 281 had no pneumococcal growth (56.2%). Among these, 176 (35.2%) had PEP on chest x-ray. Among those with PEP, pneumococcal carriage was documented in 43.8% of cases, and VT serotypes accounted for 10.8%. For children with PEP, we found no association between clinical characteristics and carrying either VT, NVT, or no pneumococcus.

**Conclusion** Carriage of *S. pneumoniae* remains high among children hospitalized with ARI in Malawi, but children with VT carriage were no more likely to have PEP than children carrying no pneumococcus or those with NVT carriage. There were no differences in clinical characteristics between those carrying VT, NVT, or no pneumococcus.

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## Introduction

Pneumonia is the leading cause of mortality globally among children older than one month [1, 2] with *Streptococcus pneumoniae* being the leading causative pathogen. While the clinical diagnosis of pneumonia is insensitive and nonspecific [3, 4], chest radiography has been shown to be reliable in identifying lobar pneumonia [1, 5].

In low- and middle-income country settings, there were reductions in pneumococcal pneumonia severity and mortality after introduction of pneumococcal conjugate vaccines (PCV) [6–11], as well as childhood primary end-point pneumonia (PEP) [11, 12]. The World Health Organization defines PEP as 'the presence of end point consolidation or pleural effusion in the lateral pleural space' [13]. End point consolidation is defined as 'a dense or fluffy opacity that occupies a portion or whole of a lobe or entire lung that may or may not contain an air bronchogram' [13].

In Malawi, after the 13-valent pneumococcal conjugate vaccine (PCV-13) was introduced into the infant vaccination programme in November 2011 [14, 15], surveillance studies demonstrated high residual nasopharyngeal (NP) carriage of vaccine serotypes (VTs) in PCV-13-vaccinated children [16, 17], and a predominance of non-vaccine serotypes (NVTs) [16–18]. Furthermore, pneumococcal serotypes vary in NP carriage prevalence, invasiveness, and disease incidence [19, 20]. The more invasive serotypes causing more severe disease were therefore selected for inclusion in the conjugate vaccines.

There is lack of data in sub-Saharan Africa on the pneumococcal serotypes seen in children with radiographic PEP, on whether radiographic PEP is seen more commonly among VT or NVT, and whether clinical characteristics of radiographic PEP differ between VT and NVT. The objective of this study was to determine the odds of PEP in children with VT compared with NVT carriage, and to evaluate whether clinical characteristics differ between children with radiographic PEP due to VT v. NVT. We hypothesized that radiographic PEP would be more common in VT than NVT carriers, consistent with the greater invasiveness of these serotypes, and that clinical characteristics in radiographic PEP may differ between VT and NVT.

## Methods

### Study design

This study is a secondary analysis of data collected from two studies on acute respiratory illness (ARI) in Blantyre, Malawi between 2013 and 2019. ARI was defined as having a fever of over 38 °C and cough with onset of less than 10 days.

The first study, VacSurv, was a case-control study of children ≤ 5 years hospitalized with clinical diagnosis of severe ARI at Queen Elizabeth Central Hospital carried out between 2013 and 2016 [18]. Clinical and demographic data, chest x-rays (CXRs), and NP swabs were collected. For every case enrolled at hospitalization, there were four otherwise healthy controls enrolled from the community, matched by age and neighbourhood [18].

The second study, a series of rolling pneumococcal carriage surveys (PCVPA), was a surveillance study carried out between 2015 and 2019, that investigated the impact of PCV-13 on pneumococcal carriage and disease in children and adults in the community after vaccine introduction [17]. Concomitantly with the community cohort, PCVPA enrolled a hospital cohort among children 1–4 years of age who were clinically diagnosed with severe ARI on presentation. Clinical and sociodemographic data, CXRs, blood, and NP swabs were collected [17]. NP swabs were collected for all children at admission to hospital with respiratory signs, and were also collected for healthy community controls [17, 18].

All NP samples were processed at the Malawi-Liverpool Wellcome Programme laboratory following WHO recommendations and as described elsewhere [18]. Presence of *S. pneumoniae* was determined by culture growth on NP swab, and isolates were serotyped and categorized as VT or NVT.

### Chest radiography

Eight clinicians (NBZ, PH, MJ, AK, GM, VM, LN, OO) read CXRs, following the methodology and training provided by the WHO Chest Radiography in Epidemiological Studies (CRES, https://who-cres.mcri.edu.au/) [13]. CXRs from both VacSurv and PCVPA were each read in duplicate, and any disagreements were resolved by a third read. In addition, 10% of CXRs were randomly selected for quality control reads. CXRs were read as either PEP, other infiltrate, or no pathology. We defined no PEP as a CXR with other infiltrate or no pathology.

### Statistical analysis

We conducted multivariable regression analysis to assess the association between PEP and VT v. NVT. Stata v.18 (College Station, TX: Statacorp LLC) was used for data analysis. P-values of $<0.05$ were considered statistically significant.

## Ethics

This study was approved by the College of Medicine Research Ethics Committee (P.02/15/1677) and the Liverpool School of Tropical Medicine Research Ethics Committee (14.056). Ethical approval for the primary studies PCVPA and VacSurv was obtained by the National Health Sciences Research Committee (protocol 867), the College of Medicine Research Ethics Committee (P.01/08/609 and P.09/09/826), and the University of Liverpool Research Ethics Committee (RETH490). Written informed consent was obtained from the parents/guardians of participants.

## Results

There were a total of 1,088 children enrolled in the VacSurv case-control study, and 1,224 children enrolled in the PCVPA hospital cohort (Fig. 1). CXRs were collected for 873 children in VacSurv and 654 children in PCVPA. A total of 358 CXRs scored as PEP, 120 (13.7%) in VacSurv and 238 (36.4%) in PCVPA. After merging and aligning variables across both datasets, we had complete CXR and NP serotype data for 500 children. Only one death was recorded.

Of the 500 NP swabs, *S. pneumoniae* was detected in 219 cases (43.8%). Of those, 54 were VT and 165 were NVT. The most common VT serotypes were 19 F with 21 cases (38.9%), 23 F with 9 cases (16.7%), 3 with 6 cases (11.1%), and 19 A with 5 cases (9.3%). There were three

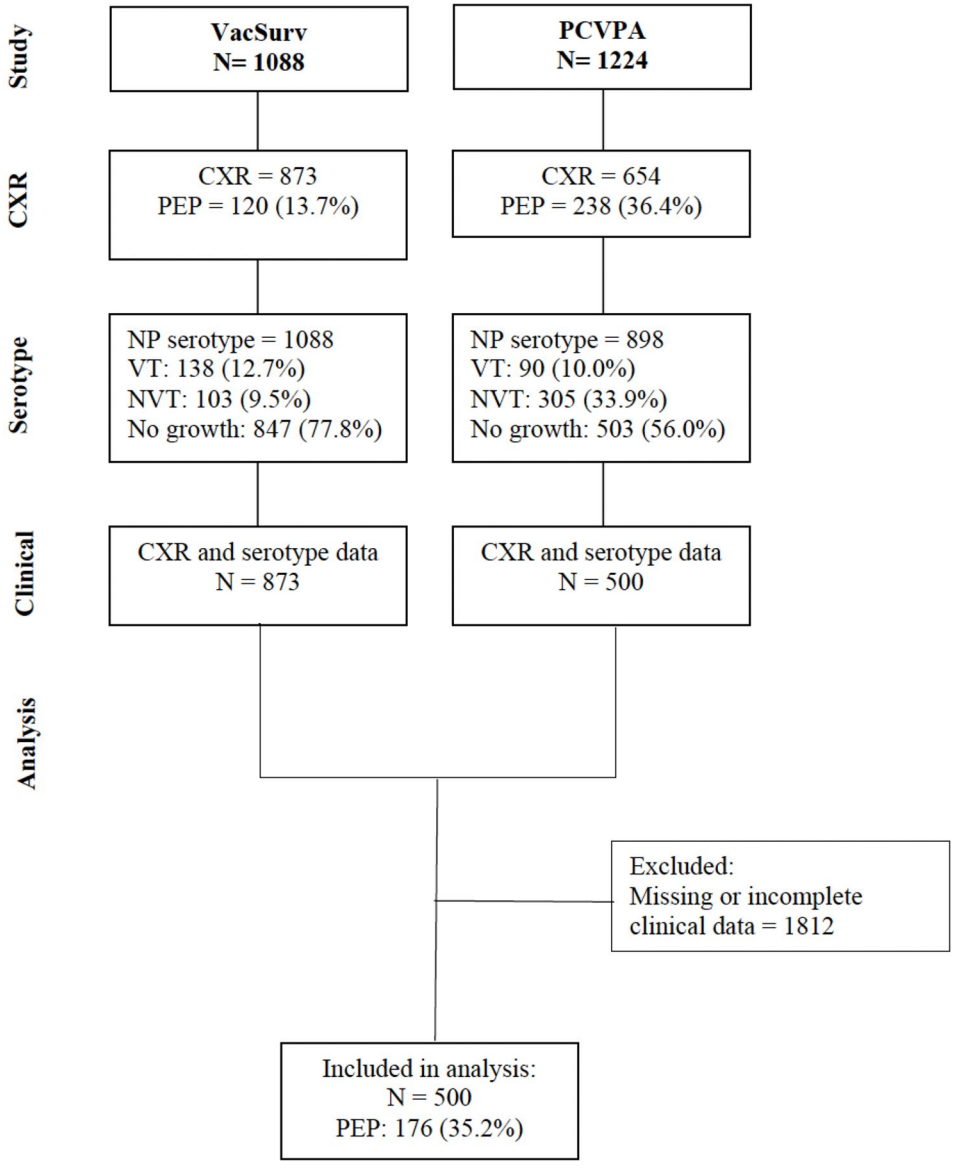


**Fig. 1** Flow diagram of data included in the analysis

**Table 1** Primary end-point pneumonia in children with VT v. NVT v. no pneumococcus

| Nasopharyngeal carriage (%) | Non-primary endpoint pneumonia (*n* = 324) | Primary endpoint pneumonia (*n* = 176) | Odds ratio (95% CI) | *P* value |
|---|---|---|---|---|
| No pneumococcus | 175 (54.0%) | 106 (60.2%) | Reference | |
| VT serotypes | 35 (10.8%) | 19 (10.8%) | 0.89 (0.46–1.64) | 0.72 |
| NVT serotypes | 114 (35.2%) | 51 (29.0%) | 0.73 (0.49–1.11) | 0.15 |

CI, confidence interval; NVT, non-vaccine type; VT, vaccine type

**Table 2** Clinical characteristics of children with PEP due to VT v. NVT v. no pneumococcus

| | Primary endpoint pneumonia (*n* = 176) | | | |
|---|---|---|---|---|
| | Nasopharyngeal carriage | | | P value |
| | No pneumococcus (*n* = 106) | VT (*n* = 19) | NVT (*n* = 51) | |
| Age in months, median (25th -75th IQR)[a] | 28 Months (16.9–36.2) | 22 Months (15.5–32.5) | 20 Months (15.2–28.4) | 0.16 |
| Prior antibiotic use (*n* = 70) | 44/106 (41.5%) | 7/19 (36.8%) | 19/51(37.2%) | 0.61 |
| Mother HIV positive (*n* = 26) | 16/106 (15.1%) | 4/19 (21.1%) | 6/51 (11.8%) | 0.31 |
| Child HIV positive (*n* = 13) | 8/106 (7,5%) | 2/19 (10.5%) | 3/51 (5.9%) | 0.64 |
| Fever (*n* = 125) | 79/106 (74.5%) | 12/19 (63.2%) | 34/51 (66.7%) | 0.43 |
| Cough (*n* = 175) | 105/106 (99.1%) | 19/19 (100%) | 51/51 (100%) | 1.00 |
| Apnoea (*n* = 3) | 3/106 (2.8%) | 0 (0%) | 0 (0%) | 0.68 |
| Nasal flaring (*n* = 155) | 94/106 (88.7%) | 17/19 (89.5%) | 44/51 (86.3%) | 0.94 |
| Chest indrawing (*n* = 152) | 92/106 (86.8%) | 16/19 (84.2%) | 44/51 (86.3%) | 0.95 |
| Stridor (*n* = 2) | 2/106 (1.9%) | 0 (0%) | 0 (0%) | 1.00 |
| Wheeze (*n* = 148) | 90/106 (84.9%) | 15/19 (78.9%) | 43/51 (84.3%) | 0.79 |
| Bronchial breathing (*n* = 96) | 57/106 (5.4%) | 11/19 (57.9%) | 28/51 (54.9%) | 0.97 |
| Reduced air entry (*n* = 106) | 47/106 (44.3%) | 10/19 (52.6%) | 18/51 (35.3%) | 0.38 |

IQR, interquartile range; HIV, human immunodeficiency virus; NVT, non-vaccine type; VT, vaccine type

[a]One-way ANOVA

cases each (5.6%) of serotypes 6B and 14, and two cases each (3.7%) of serotypes 7 F, 5 and 6 A.

Among the 500 children, 176 had PEP (35.2%) and 324 had no PEP (64.8%) on CXR. Among those with PEP, 51 were NVT (28.9%), 19 were VT (10.8%), and 106 had no pneumococcal growth (60.2%). Among non-PEP cases, 114 were NVT (35.2%), 35 were VT (10.8%), and 175 (54.0%) had no pneumococcal growth. Compared to those without pneumococcus, neither those with VT (OR 0.89, 95% CI: 0.46–1.64) nor NVT (OR 0.73, 95% CI: 0.49–1.11) had increased odds of PEP (Table 1).

There were no differences in the clinical characteristics of those with PEP when comparing those carrying VT v NVT v no pneumococcus (Table 2), no differences in clinical characteristics between children with PEP and no-PEP (Supplementary Table 1), and no significant association between NP serotypes and PEP in children hospitalized with ARI (Supplementary Table 2).

## Discussion

In this study, nearly half (43.5%) of children hospitalized with ARI had *S. pneumoniae* detected in their nasopharynx. PEP was detected in 10.8% of cases with VT serotypes and 29.0% of cases with NVT serotypes. However, no significant association was found between PEP and NP findings. Children with VT carriage were no more likely to have PEP than children carrying no pneumococcus or those with NVT carriage. There were no differences in clinical characteristics between those carrying VT v. NVT v. no pneumococcus.

This is the largest study in sub-Saharan Africa to evaluate pneumococcal serotypes in children hospitalized with ARI and the association with radiographic PEP. Pneumococcal serotypes vary in NP carriage prevalence, invasiveness, and disease incidence [19, 20], and therefore more invasive serotypes causing severe disease were selected for inclusion in conjugate vaccines.

In our analysis, VT serotypes accounted for 10.8% of radiographic PEP. A prior surveillance study in Malawi noted sustained VT carriage among infants, showing a post-PCV 13 carriage of 9.3% at 6–10 weeks compared to 24.2% before vaccine introduction (3). In the 1–4 year age group, VT carriage was sustained at 18.7% in a 2014 study and 16.5% in a 2018 study (3,4).

In PERCH, a pneumonia etiology study conducted in five sub-Saharan African countries (The Gambia, Mali, Zambia, South Africa, and Kenya), *S. pneumoniae* was the most common bacteria isolated, and one of the bacteria most associated with radiographic PEP [21, 22], but the role of pneumococcal serotypes was not specifically

evaluated. Other studies in Malawi and from sub-Saharan Africa have evaluated serotypes in invasive pneumococcal disease [17, 23–25], or effects of PCV on radiographic PEP [26], but not serotype association with radiographic PEP.

Radiographic pneumonia and their associated pneumococcal serotypes have been described in adults in high-income countries [27, 28], and demographic and clinical characteristics between PCV-13 and non-PCV-13, or proposed expanded PCV serotypes in an adult hospitalized population, were noted to be similar [27, 29]. In Zanzibar, a study of serotype distribution in preschool children with radiologically confirmed pneumonia compared to healthy controls prior to introduction of pneumococcal vaccination identified PCV-13 serotypes 9 A/V and 14 to be significantly associated with radiographic pneumonia [30]. However, in this dataset 294 children had a CXR collected, and only 39 children had radiographic pneumonia [30]. Our study involving 500 CXRs and 176 cases of PEP is the largest to date conducted in sub-Saharan Africa.

This study had some limitations. We examined children following WHO criteria for diagnosis of PEP, which is the methodology used for epidemiology studies and not routinely used in clinical practice. This, therefore, could have underestimated the number of cases of lobar pneumonia in our dataset. We did not capture information on previous admissions with respiratory illness at the time of PEP diagnosis and that could have affected the association between PEP and clinical features present at the time of diagnosis. We did not conduct serotyping for all serotypes, and therefore could not comprehensively evaluate what additional serotype coverage beyond PCV-13 would be beneficial. PCV-13 was introduced in Malawi in 2011, and the decreased incidence of cases over the subsequent decade may have made differences in disease severity less apparent. Finally, due to differences in the variables used in the two studies, after merging and aligning variables across the datasets, only a proportion of cases were included in the final analysis.

In conclusion, among children hospitalized with ARI in Malawi after introduction of PCV-13, carriage of *S. pneumoniae* remains pervasive, with high prevalence of VT and NVT serotypes. VT serotypes accounted for a moderate proportion of radiographic PEP. Further research is needed to understand the basis for the continued carriage of VT serotypes after PCV-13 introduction and evaluate interventions to reduce carriage and associated pneumonia morbidity and mortality.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41479-024-00147-7.

Supplementary Material 1

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**Author contributions**
TDS, NBZ, NF, RSH led PCPVA and VacSurv studies. PI provided training for CXRs, which were read by AK, NBZ, PH, MSJ, GM, LN, OO, and VM. GM merged the data with support from RW. GM conducted the statistical analysis with support from JC, TDS, NF, RSH, and PI. GM wrote the first draft of the manuscript, with support from PI. All authors reviewed and contributed to the final draft.

**Data availability**
Data is provided within the manuscript.

## Declarations

**Competing interests**
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## Publisher's note