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Childhood pneumococcal disease in Africa – a systematic review and meta-analysis of incidence, serotype distribution, and antimicrobial susceptibility

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Abstract

Background—Determining the incidence, disease-associated serotypes and antimicrobial susceptibility of invasive pneumococcal disease (IPD) among children in Africa is essential in order to monitor the impact of these infections prior to widespread introduction of the pneumococcal conjugate vaccine (PCV).

Methods—To provide updated estimates of the incidence, serotype distribution, and antimicrobial susceptibility profile of *Streptococcus pneumoniae* causing disease in Africa, we performed a systematic review of articles published from 2000–2015 using Ovid Medline and Embase. We included prospective and surveillance studies that applied predefined diagnostic criteria. Meta-analysis for all pooled analyses was based on random-effects models.

Results—We included 38 studies consisting of 386,880 participants in 21 countries over a total of 350,613 person-years. The pooled incidence of IPD was 62.6 (95% CI 16.9, 226.5) per 100,000

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Author contributions

PI and ENJ conceived of the study; PI, BT, SKO and ENJ designed the study; PI and BT performed the literature review, with critical input and data interpretation from SKO and ENJ; PI performed the data analysis; AB, AK, and HC supervised and performed the meta-analyses; PI wrote the first draft; all authors reviewed, revised and approved the final draft.

Declaration of interests

PI has received an investigator-initiated grant from Pfizer. SKO is a scientific advisory board member of Gendrivax, and a research grant recipient of Pfizer and GSK. All other authors have no conflicts of interest.

Web Appendix: Methods to estimate the incidence, serotype distribution, and antimicrobial susceptibility profile of *Streptococcus pneumoniae* disease in children <5 years of age in Africa.

person-years, including meningitis which had a pooled incidence of 24.7 (95% CI 11.9, 51.6) per 100,000 person-years. The pooled prevalence of penicillin susceptibility was 78.1% (95% CI 61.9, 89.2). Cumulatively, PCV10 and PCV13 included 66.9% (95% CI 55.9, 76.7) and 80.6% (95% CI 66.3, 90.5) of IPD serotypes, respectively.

Conclusions—Our study provides an integrated and robust summary of incidence data, serotype distribution and antimicrobial susceptibility for *S. pneumoniae* in children 5 years of age in Africa prior to widespread introduction of PCV on the continent. The heterogeneity of studies and wide range of incidence rates across the continent indicate that surveillance efforts should be intensified in all regions of Africa to improve the integrity of epidemiologic data, vaccine impact and cost benefit. Although the incidence of IPD in young children in Africa is substantial, currently available conjugate vaccines are estimated to cover the majority of invasive disease-causing pneumococcal serotypes. These data provide a reliable baseline from which to monitor the impact of the broad introduction of PCV.

Keywords

Streptococcus pneumoniae; invasive pneumococcal disease; pneumonia; serotype; children; incidence; penicillin susceptibility; systematic review; meta-analysis

INTRODUCTION

Streptococcus pneumoniae is capable of causing a spectrum of disease in children, the most severe of which is invasive pneumococcal disease (IPD), which includes bacteremic pneumonia, meningitis and sepsis. In the developed countries where there is widespread coverage with the pneumococcal conjugate vaccine (PCV), rates of IPD have dropped substantially. For example, IPD rates in children under 5 years caused by vaccine serotypes decreased by 78% over a 3-year period.¹ In contrast to developed countries, which have robust surveillance systems for measuring the burden of pneumococcal disease, fewer systems exist for addressing the burden of disease in Africa. Nevertheless, rates of pneumococcal disease are estimated to be highest on the African continent, causing over 4 million cases a year in children under 5 years.² Pneumococcal disease also contributes to substantial mortality, driven predominantly by mortality from pneumococcal pneumonia. Thus, vaccines that could that could effectively reduce pneumococcal disease in Africa could have a major impact on morbidity and mortality on the continent.

Based on the success of PCV in developed countries and the large burden of pneumococcal pneumonia in Africa, the addition of PCV in African national vaccine schedules has been rapid, with six African countries introducing PCV this decade (Equatorial Guinea, Comoros, Seychelles, Gabon, Guinea, Cape Verde).³ By 2020, only three African countries will not have introduced the vaccine (Chad, Algeria, South Sudan).³ However, incorporation of PCV into national immunization schedules does not equate to broad uptake, and estimates of vaccine availability and coverage in high-burden countries have been low until recently.³ Secondly, PCV may be less effective when there is mismatch between circulating serotypes and those included in the vaccine. Substantial reductions in IPD in the United States occurred following introduction of a vaccine that consisted of seven serotypes, representing almost 90% of circulating pneumococcal serotypes in North America.⁴ Coverage in Africa

was previously estimated to be lower (49–88%).^{4,5} These estimates were based on reviews of published literature up to 2007,⁵ incorporating a handful of studies from disparate countries to reflect IPD data for the entire African continent. Moreover, these early studies relied primarily on less sensitive direct conventional culture⁶ rather than potentially more sensitive molecular techniques. Indeed, incorporation of real-time PCR into routine public health surveillance of bacterial meningitis has increased detection rates by up to 85%⁷ and are increasingly accessible and utilized in research-oriented laboratories in Africa. Moreover, while a limited number of serotypes have been attributed as the cause of most IPD worldwide in the pre-PCV era,⁵ including an increased incidence of nonvaccine serotypes,⁸ there has nevertheless been a sustained decrease in total burden of pneumococcal disease after the introduction of vaccine.⁹ Serotypes causing disease in other geographic regions in the post-PCV era may vary, differences that could affect the potential impact of the currently available vaccines. Thus, inclusion of more recent studies may help address whether this is occurring in Africa.

As a presage to the widespread rollout of PCV in Africa, as well as to incorporate data in the post-PCV era, the objective of this study was to provide a systematic review and meta-analysis of the current literature on the incidence, serotype distribution, and antimicrobial susceptibility of pneumococcal disease on this continent. These findings refine current estimates of disease epidemiology for the continent that are needed in order to reflect regions where disease is in transition with the rollout and widespread uptake of PCV, to control both invasive disease and pneumococcal pneumonia, and to reliably design and monitor the impact of current and future polysaccharide- and protein-based vaccines for children in resource-limited settings.

METHODS

A comprehensive search of relevant published papers from 2000 to 2015 was performed in Ovid Medline and Embase (Appendix Table 1). We excluded studies before 2000, to circumvent temporal variations in pneumococcal seroepidemiology that can occur over a period of decades.¹⁰ Prospective studies and prospectively collected surveillance on both invasive pneumococcal disease and nonbacteremic pneumonia that met our inclusion and exclusion criteria were selected. IPD was defined as pneumococcal isolates from a normally sterile source, and meningitis was considered a subset of IPD. A diagnosis of nonbacteremic pneumonia required clinical and/or radiographic findings consistent with pneumonia and a microbiological diagnosis of pneumococcus from a noninvasive site (nasopharyngeal and respiratory tract). Only data derived from symptomatic infections, but not nasopharyngeal carriage, were included. We restricted our criteria to studies with data for children 5 years of age or younger. For antimicrobial susceptibility studies, we included children up to and including 16 years of age. Only studies meeting our minimum requirements for data completeness were included. More detailed selection criteria are included in the Web Appendix.

Data was extracted from the articles independently by two authors (PI and BT) using predefined data fields. Information extracted from each study included: (1) characteristics of study (including age, location, study period, types of pneumococcal disease, methods of

diagnosis, inclusion and exclusion criteria); (2) microbiologic data (including sites of isolation, serotype distribution, and antimicrobial susceptibility profile based on criteria set by the Clinical Laboratory and Standards Institute (CLSI); and (3) epidemiologic measures (including incidence and case-fatality ratios). Two authors (PI and BT) independently established study quality and excluded studies with methodologic issues and inconsistencies in the data.

Data cleaning and imputation was carried out in Microsoft Excel 14.5.8 (Redmond, WA). Statistical analysis and modeling was performed using R 3.2.4.¹¹ Meta-analyses of the incidence, serotype distribution, and antimicrobial susceptibility of pneumococcal disease were conducted using random effects models,¹² to incorporate heterogeneity across studies. For the purposes of the meta-analysis, vaccine-related serotypes grouped with vaccine serotypes were considered vaccine types. Studies were also grouped by study-level characteristics and pooled proportions were calculated within these subgroups using random effects models. We used meta-regression to test differences in the incidence between particular subgroups. The significance level for all tests was set at 5%. Fieller's method was used to calculate the 95% CI for the percentage of cases attributable to meningitis as part of IPD overall.¹³

RESULTS

Of the original 1,868 records identified, 38 studies met review criteria (10 on incidence, 16 on serotype distribution, and 23 on antimicrobial susceptibility; Figure 1). The 38 studies reported on 386,880 children in 21 countries between 2000–2014, and included 23,357 children from Northern (6.0%), 47,017 from Eastern (12.0%), 302,107 from Western and central (77.2%), and 14,399 from Southern (3.7%) Africa (Figure 2). Of these 38 studies, only seven addressed the incidence, outcomes and microbiology of noninvasive respiratory disease.

Incidence of pneumococcal disease

Ten studies had data on incidence, five from Western and central,^{14–18} three from Eastern,^{19–21} and two from Southern Africa (Table 1).^{22,23} Incidence for IPD within and between studies ranged from 22.9–5,300/100,000 person-years for children under a year,^{14,15} to 5–1,870/100,000 person-years in those 1–5 years.^{15,16} The HIV prevalence was 1.7–70%,^{14,23} with highest rates in Southern Africa (Appendix Table 2). Case fatality ratios for IPD^{14,17,18,23–33} ranged from 1.7–75% (Appendix Table 2),^{27,28} and were generally higher than in (bacteremic and nonbacteremic) pneumonia (1.7–15%).^{28,32}

Among children with IPD, meningitis incidence ranged from 9.1–108/100,000 person-years,^{14,16,18,19} and for bacteremia ranged from 2–403/100,000 person-years.^{14,15,17,20,21,23} Four studies calculated the incidence of bacteremic pneumonia at 10–437/100,000 person-years.^{14,22} However, when nonbacteremic pneumonia was included with radiographic findings in its criteria, incidence was substantially higher at 1,280–5,300/100,000 person-years.¹⁵

In 350,613 person-years reviewed, the pooled incidence rate for IPD was 62.6 (95% CI 16.9, 226.5)/100,000 person-years and for meningitis was 24.7 (95% CI 11.9, 51.6)/100,000 person-years (Figure 3). Meningitis represented 33.7% (Fieller's method 95% CI 25.2, 44.5%) of all IPD in these venues.

The predominant microbiological methods used in these studies were direct culture^{15,17,19–21,23,28,31} or a combination of culture and latex agglutination.³⁰ One study confirmed culture results with molecular diagnostics (PCR),¹⁴ and four compared culture and PCR on all specimens.^{16,18,33,34} None of the studies assessing incidence of disease compared the performance of molecular versus culture methods. Studies that utilized molecular diagnostics for all specimens or to confirm culture-positive specimens documented an overall incidence rate of 86.7 (95% CI 22.6, 332.9)/100,000 person-years compared to 30.1 (95% CI 3.1, 289.8)/100,000 person-years for studies that used culture only. Meta-regression demonstrated that neither diagnostic approach had substantively different incidence rates of *S. pneumoniae* ($p=0.40$).

Serotype distribution

Serotype was reported in 15 studies, primarily from Southern Africa (92.3%),^{23,35,36} with 14,154 isolates from sterile sites^{15,23,29,30,33,35–44} and 4 studies with 333 isolates from noninvasive sites (nasopharyngeal and respiratory tract, ear pus, ocular).^{29,37,43,45} The most common serotypes causing invasive disease (12,896 isolates) were serotype 14 (16.7%), followed by serotypes 6B and 6A (14.1% and 12.6%, respectively), serotype 23F (12.0%), and serotypes 19F and 19A (10.7% and 7.6% respectively; Figure 4). The most common serotypes identified in noninvasive studies were 19B/C/F (20.4%), nontypeable/serotypes of unknown designation (16.8%), 6/A/B (15.6%), and serotype 14 (11.7%). Only 17.1% of isolates causing invasive disease were not included in either the current 10- or 13-valent vaccines.

The 10-valent pneumococcal conjugate vaccine (PCV10) included 62.0% (95% CI 50.0, 73.8) of serotypes causing meningitis and 66.9% (95% CI 55.9, 76.7) of those causing all forms of IPD, whereas the 13-valent pneumococcal conjugate vaccine (PCV13) covered 72.3% (95% CI 58.6, 85.0) of serotypes causing meningitis, 80.6% (95% CI 66.3, 90.5) causing IPD. Of note, 88.3% (95% CI 43.2, 99.6) and 98.6% (95% CI 70.6, 100.0) of serotypes causing nonbacteremic pneumonia and noninvasive disease were included in the available PCV10 and PCV13, respectively (Appendix Figure 1). Serotypes 1 and 5, which are the most commonly identified serotypes in previous studies in Africa^{46–49} and in more recent outbreaks,^{50,51} accounted for 12.8% (95% CI 4.9, 24.0) of meningitis, 10.2% (95% CI 5.7, 15.6) of IPD, and 6.1% (95% CI 0.0, 71.2) of nonbacteremic pneumonia/noninvasive cases, respectively.

Antimicrobial susceptibility

In 23 studies of children 16 years of age,^{14,17,20,23,27,30,31,37,38,42–44,52–62} antimicrobial susceptibility testing was conducted using Etest/microdilution methods and disk diffusion. In 21 studies^{14,17,20,23,27,30,31,37,38,43,44,52–59,61,62} representing 11,486 isolates (of which 82.0% were from Southern Africa)^{23,57,62}, the pooled prevalence of penicillin susceptibility

was 78.1% (95% CI 61.9, 89.2). The change in minimum inhibitory concentration breakpoints instituted by CLSI in 2008^{14,20,30,31,37,38,53–55,57,59,61,63} yielded susceptibilities of 82.5% (95% CI 60.7, 94.1) pre-CLSI^{14,17,20,30,31,37,38,53–55,57,59,61} and 69.0% (95% CI 42.6, 88.4) post-CLSI.^{23,43,52,56,58,62} Overall susceptibilities to beta-lactam antibiotics were high: ampicillin/amoxicillin 94.7% (95% CI 80.2, 99.4)^{17,30,38,42,43,54,55,57,59,60} and third-generation cephalosporins 98.5% (95% CI 95.1, 100.0).^{17,30,42,52,54,56,58–61} However, penicillin susceptibility was lower among invasive isolates in Northern (33.3–44.5%)^{27,37} and Eastern Africa (16.7–35.3%).^{30,58} Pooled susceptibilities were 90.8% (95% CI 80.6, 96.4) for chloramphenicol^{17,19,20,30,38,52–55,57–60} and 94.0% (95% CI 79.4, 99.6) for azithromycin/erythromycin,^{17,31,38,56,58,60,61} but substantially lower for trimethoprim-sulfamethoxazole (31.7% [95% CI 9.8, 61.8]),^{17,20,31,53–56,58,60} and tetracycline (51.0% [95% CI 36.4, 65.0]; Figure 5 and Appendix Figure 2),^{17,38,54,55,58} each of which is in common use in Africa.

A striking finding in these meta-analyses was the significant heterogeneity among studies. The I^2 measure of consistency of effects across studies in meta-analysis revealed a range from 90.9 to 99.7 for incidence studies, 40.1 to 99.1 for serotype distribution, and 0 to 99.5 for antimicrobial susceptibility (Table 2). The funnel plot of these studies confirms this heterogeneity (Appendix Figure 3).⁶⁴ The Begg and Mazumdar rank test resulted in an estimate of with, $\tau^2 = 0$ with $p = 1.000$, which suggests that some factor beyond publication bias, such as small study sizes, may account for the heterogeneity seen.⁶⁵

DISCUSSION

The incidence of IPD among children in the first five years of life in Africa is substantial, with a pooled incidence rate of 62.6 (95% CI 16.9, 226.5)/100,000 person-years, and 24.7 (95% CI 11.9, 51.6)/100,000 person-years for meningitis. The majority of circulating serotypes would be covered by the currently available PCV10 and PCV13, including those identified in nonbacteremic pneumonia, with only 17.1% of isolates causing invasive disease not included in either the current vaccines. Pneumococcal isolates have high susceptibility rates to penicillin and other beta-lactams, although rates are lower in Northern and Eastern Africa. The use of molecular diagnostics in incidence studies may lead to optimized detection and more precise estimates of pneumococcal disease incidence on the continent. Only a third of countries in Africa contributed data to this study, illustrating the need for further scale-up of laboratory facilities to optimize diagnosis and improve surveillance to better evaluate the need for and impact of PCV implementation.

The incidence of IPD among African children prior to the widespread introduction of PCV is 2–3 fold higher than that reported in Western European children⁶⁶ and comparable to that reported in US children¹ prior to broad immunization. The incidence of IPD in Western Europe prior to PCV introduction in children under 2 years of age was 27.0 cases,⁶⁶ and in the US in children under 5 years of age was 96.4 cases per 100,000 persons.¹ This is, however, considerably lower than high risk populations such as Alaskan Natives and White Mountain Apache, where the IPD incidence rate for children under 2 years has been documented at 1,195⁶⁷ and 1,820 cases⁶⁸ per 100,000 persons, respectively. As the highest morbidity and mortality affects young children, we restricted our study to the under 5 age

group, and noted that incidence rates in our data were highest in the first year of life. Moreover, pneumococcal disease causes significant morbidity and mortality, with case fatality ratios that had an outlier as high as 75% but which varied considerably based on syndrome, e.g., nonpneumonia/invasive (9–75%) or pneumonia (1.7–15%). Although IPD has a known and well-described association with HIV infection,^{69,70} we identified no clear correlation between the incidence of IPD or pneumonia with the prevalence of HIV infection in these pediatric populations.

The incidence of IPD may be underestimated given the lack of accessibility to and the sensitivity of laboratory diagnostic facilities in Africa. The adoption of molecular diagnostics may provide more precise estimates of disease. The promise of PCR, compared with culture-based methods, has been based on its sensitivity and specificity,^{71,72} the potential to overcome the difficulty of isolating *S. pneumoniae* by culture in the lab,⁷³ and the lower likelihood of being affected by prior antimicrobial therapy. The utilization of molecular diagnostics, primarily PCR, has been demonstrated to be more sensitive in detecting meningitis, though these only form a small proportion of all pneumococcal disease. This was performed in 85% of all the studies included in the analysis, and this usage was associated with increased detection of *S. pneumoniae*, although no statistically significant differences in the incidence was noted. This could be attributed to the relative lack of specificity of molecular diagnostics in blood specimens,⁷⁴ although this would have led to reduction in observed incidence, rather than an increase in incidence.

Although pneumococcal pneumonia in young children⁷⁵ contributes the largest proportion of pneumococcal disease and death in Africa, primary data on the incidence and outcomes of this syndrome are few. Detection of *S. pneumoniae* in all-cause pneumonia in children is particularly challenging as respiratory specimens are consistently difficult to obtain so accurate surveillance is challenging compared with invasive disease. The WHO definition of pneumonia, based on an increase in respiratory rate, is not pathogen-specific, and diagnosing all-cause pneumonia in resource-limited settings is primarily based on crude clinical data, which makes interpretation of studies¹⁵ with clinical all-cause pneumonia as an outcome problematic and poorly concordant with true pneumococcal disease.⁷⁶ In addition, studies that focus on bacteremic pneumonia represent only a fraction (4.2–9.9%)^{77,78} of all pneumococcal community-acquired pneumonia in children. Our results for nonbacteremic pneumonia reveal an incidence that is 3–12-fold higher than bacteremic pneumonia. Even though these results are based only roughly 2,600 children in five studies, they highlight the significant impact of pneumococcal pneumonia in these high-risk children and our currently restricted ability to reliably estimate this prominent syndrome. The Pneumonia Etiology Research for Child Health (PERCH) study implemented to improve diagnostic techniques and standardize clinical criteria for pediatric community-acquired pneumonia in resource-limited settings may further elucidate pneumonia etiology and help document the impact and efficacy of the introduction of *Haemophilus influenzae* type b and *S. pneumoniae* conjugate vaccines in the population.⁷⁵

Effective prevention of both IPD and pneumococcal pneumonia requires accurate microbiologic diagnostics to identify prominent local serotypes associated with clinical disease to formulate appropriate capsule-specific conjugate vaccines. Serotype data on the

African continent were available from only seven studies at the time of licensure of the 7-valent pneumococcal conjugate vaccine (PCV7) in the United States in 2000.⁷⁹ Based on those early results, PCV7 included only four of the seven most common serotypes in Africa.⁷⁹ Our included studies summarized in the current analysis confirmed that serotype 14 was the most common serotype in African children.⁸⁰ The two vaccines provided coverage for 66.9% and 80.6% of serotypes detected in IPD, respectively. The proposed PCV15, which adds serotypes 22F and 33F,⁸¹ would provide coverage against only an additional 0.11% of circulating strains compared with PCV13. Surprisingly, PCV13 was found to cover a higher proportion (98.6%) of serotypes causing nonbacteremic pneumonia/noninvasive disease, compared to IPD (80.6%). As a wider range of (non-PCV) serotypes are found in nonbacteremic pneumonia and noninvasive disease, these findings may instead reflect the limited number of studies that met our inclusion criteria. The relatively large number of nontypeable strains identified (16.8%) may more accurately reflect serotypes of unknown designation, as the included studies denote but did not clearly define a nontypeable serotype to be equivalent to unencapsulated pneumococci. Molecular assays for pneumonia also has limitations compared to meningitis as detection in blood can reflect colonization and be nonspecific for disease. As molecular approaches to diagnose and identify capsular serotypes causing pneumococcal disease are more consistently validated, such tests applied systematically to populations over time may more accurately predict the incidence, serotype distribution and consequences of pneumococcal disease, both invasive and respiratory, as well as the clinical and economic impact of the rollout of PCV in young children.

Microbiologic diagnostics is also essential for determining appropriate therapy of pneumococcal disease, as well as disease outcome and burden. Penicillin susceptibility for invasive isolates was surprisingly low in several studies (16.7–54.5%),^{30,37,58} more so after CLSI instituted changes in minimum inhibitory concentration breakpoints. This high frequency may be due to the large proportion of isolates from South Africa and, given their upper middle-income country status and established antimicrobial stewardship programs,^{82,83} may lead to increased detection of resistance and not be representative of the rest of the continent. In other settings, high rates of nonprescription antimicrobial use before patients present to health facilities⁸⁴ would lessen detection. Susceptibility of third-generation cephalosporins, macrolides, and aminopenicillins was high, and lowest for trimethoprim-sulfamethoxazole. The results are comparable to other data from the continent, including a meta-analysis demonstrating 76.2% susceptibility to penicillin among invasive isolates, and 66.1% and 52.5% susceptibility to tetracycline and trimethoprim-sulfamethoxazole, respectively, in naso/oropharyngeal carriage studies.⁸⁵ As a result, the Integrated Management of Childhood Illness (IMCI) guidelines for pneumonia, developed as part of an overall paradigm shift by the WHO away from an etiology-based to a syndrome-based approach to health, no longer recommend trimethoprim-sulfamethoxazole as a first-line agent.

A limitation of our analysis was that the studies reviewed were primarily hospital-based, and hence did not capture community incidence of disease. Moreover, variations in age groupings in each study did not allow us to specifically identify and characterize cases in children less than 2 years. Although we abstracted and used serotype proportions reported in each study in the analysis, some studies grouped serotypes by vaccine coverage. Only one of

the included studies was conducted in the post-PCV era,²² and hence our results may not reflect the most current data for the continent. PCR targets and molecular methods were not always described to allow for a direct methodologic comparison across studies. Given the significant heterogeneity and likely publication bias, our findings at a minimum suggest that there are still insufficient data for much of the African continent to precisely ascertain the prevalence and incidence of *S. pneumoniae* in these regions.⁸⁶ However, heterogeneity by region and population in Africa may also be a true biology and epidemiologic feature of disease. While improved diagnostics contribute to improved surveillance and data, they have to be used in the context of a planned and quality controlled health information system which at present are usually only achieved through high cost research programs such as PERCH.

S. pneumoniae continues to represent a leading vaccine-preventable disease among children, and funding from the Global Alliance for Vaccines and Immunization led to the introduction of PCV into national immunization programs in 34 African countries by 2014.⁸⁷ By 2016, only 10 countries on the African continent had still not introduced PCV, predominantly in Northern Africa.⁸⁸ Despite introduction of PCV in many African countries, vaccine availability and uptake are low to date,⁸⁶ with only 59% of the target population in the African region estimated to have received the third dose of PCV.³ This limits the ability to monitor the vaccine's impact and trends. Future efforts should focus on increasing the availability and performance characteristics of diagnostic tests by syndrome (e.g. pneumonia, bacteremia, meningitis) for more robust and predictive pneumococcal disease surveillance and to more accurately identify specific vaccine targets. Such infrastructure and data would facilitate the acceptability, deployment and evaluation of PCV and other vaccination programs throughout the African continent.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Incidence, serotype and antimicrobial susceptibility data for *S. pneumoniae* in children in Africa.
- The pooled incidence of invasive pneumococcal disease (IPD) was 61.1 per 100,000 person-years.
- The pooled prevalence of penicillin susceptibility to *S. pneumoniae* was 78.1%.
- Cumulatively, PCV10 and PCV13 included 66.9% and 80.6% of IPD serotypes, respectively.
- These data provide a reliable baseline from which to monitor the impact of broad PCV introduction.

Figure 1.
Study selection process

Figure 2.

Regional summary of study characteristics.

Regions of Africa are as defined by the United Nations geoscheme.⁸⁹

Figure 3.

Incidence rates of pneumococcal disease in children < 5 years in Africa for
(A) IPD; (B) Meningitis.

IPD, invasive pneumococcal disease

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Figure 4.

Pneumococcal serotypes of 12,896 isolates from IPD in children 5 years of age, Africa.^{15,23,29,30,33,35–44}

IPD, invasive pneumococcal disease; NTK, nontypeable/serotypes of unknown designation; PCV7, 7-valent pneumococcal conjugate vaccine; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal conjugate vaccine

*Serotypes 2, 8, 9A/N, 10/A, 11, 12A/B/F/44/46, 13, 15B/C, 16F, 20, 21, 22/A, 24/A, 28F, 32A, 33F, 35/B, 35F, 38/25A/F, 40

Figure 5.

Pneumococcal antimicrobial susceptibility in children 16 years of age, Africa. Forest plots show mean with 95% CI, and size of the square reflects the relative contribution to the meta-analysis; length of diamond reflects the 95% CI.

Table 1
Characteristics of included studies regarding incidence of IPD and/or pneumococcal pneumonia among children <5 years of age, Africa, 2000–2012

Study	Study period, PCV status	Country, location(s)	Design	No. of enrolled cases <5y	Diagnostic method	Syndrome	Age group (months)	Incidence (cases per 100,000/person-year) 95% CI
Western and Central Africa								
Cutts <i>et al.</i> 2005 ¹⁵	8/2000 – 4/2004, pre-PCV	Upper and Central River Division, The Gambia	Randomized, placebo-controlled, double-blind trial	17,437 (Vaccine group: 8,718; placebo group: 8,719)	Radiography, culture	Nonbacteremic pneumonia ^a	3–11 12–23 24–29	PCV group: 3,440 (2,880–4,100) 2,580 (2,230–2,990) 1,270 (880–1,840) Placebo group: 5,300 (4,590–6,110) 4,170 (3,710–4,680) 1,870 (1,370–2,540)
						IPD	3–11 12–23 24–29	30 (4–190) 79 (30–170) 130 (40–410) 390 (230–660) 280 (180–440) 180 (70–480)
Campbell <i>et al.</i> 2004 ¹⁴	6/2002–5/2003, pre-PCV	Bamako, Mali	Prospective surveillance	2,049	Culture, confirmed by molecular diagnostics; latex agglutination	Meningitis	0–11 12–48	26.1 (10.2–48.4) 9.1 (0.2–41.3)
						Bacteremic pneumonia ^b	0–11 12–48	10.5 (1.3–33.1) 30.0 (11.0–54.3)
						IPD	0–11 12–48	22.9 (12.0–37.3) 21.6 (9.8–38.2)
Parent du Chatelet <i>et al.</i> 2005 ¹⁸	4/2002 – 4/2003, pre-PCV	Burkina Faso	Prospective surveillance, some retrospectively identified	281	Culture, PCR testing for all cases	Meningitis	<12 <60	95(65–125) 41 (31–51)
Mueller <i>et al.</i> 2012 ¹⁶	3/2007 – 12/2009, pre-PCV	Bobo Dioulasso, Burkina Faso and surrounding urban and rural zones	Hospital-based surveillance	263,848	Culture, multiplex PCR, latex agglutination	Meningitis	0–5 6–11 12–48	57.5 (35.1–88.8) 43.1 (22.3–75.3) 5.0 (2.4–9.1)
Nielsen <i>et al.</i> 2012 ¹⁷	9/2007 – 7/2009, pre-PCV	Asante region, Ghana	Prospective survey	1,351	Culture	Bacteremia	<60	430 (250–610)
Eastern Africa								
Sigafoos <i>et al.</i> 2008 ²⁰	5/2001 – 4/2006, 1. 6% received PCV in 2003 as part of clinical trial	Manhiça, Mozambique	Prospective surveillance	15,962	Culture	Bacteremia	<12 12–<60	403 (307–529) 187 (151–232)
Roca <i>et al.</i> 2009 ¹⁹	1/2006 – 1/2007, PCV not part of routine immunization schedule	Manhiça, Mozambique	Surveillance	3,507	Culture	Meningitis	<2 2–11 12–48	0 108 (35–337) 18 (4–70)
Thriemer <i>et al.</i> 2012 ²¹	3/2009 – 12/2010, pre-PCV	Pemba Island, Zanzibar, Tanzania	Surveillance	637	Culture	Bacteremia	60	2 (0.4–6); Adjusted: 42 (32–54)

Study	Study period, PCV status	Country, location(s)	Design	No. of enrolled cases <5y	Diagnostic method	Syndrome	Age group (months)	Incidence (cases per 100,000/person-year) 95% CI
Southern Africa								
von Gottberg <i>et al.</i> 2013 ²³	2003–2008, pre-PCV	South Africa	Surveillance	8,673 (70% HIV-infected)	Culture	IPD	<12 12–48	HIV-uninfected: 48 (35–63) 6 (5–7) HIV-infected: 1,022 (923–1,123) 198 (178–220)
Tempia <i>et al.</i> 2015 ²²	2/2009 – 12/2012, post-PCV	Soweto, South Africa	Prospective surveillance	8,050	PCR	Bacteremic pneumonia ^c	<24	2009: 436.6 (375.9–504.2) 2011: 86.9 (62.1–118.3) 2012: 157.1 (123.2–197.6) 2009: 129.8 (97.8–168.9) 2011: 58.6 (38.7–85.3) 2012: 43.1 (26.3–66.5)

HAART, highly active antiretroviral therapy; IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PCR, polymerase chain reaction

^aRadiological pneumonia.

^bGrowth in *S. pneumoniae* in blood of children admitted with clinically diagnosed pneumonia.

^cCough/difficulty breathing and any of the following symptoms/signs: unable to drink/breastfeed, vomits everything, convulsions, lethargic or unconscious, stridor when calm and lower chest wall indrawing, O₂ saturation <90%.

Table 2

Summary of meta-analyses for incidence, serotype distribution, and antimicrobial susceptibility

Subgroup	Number of studies	Total cases	Estimate [95% CI]	I ² [95% CI]
Incidence (cases per 100,000 person-years)				
Meningitis	4	269,685	24.7 [11.9,51.6]	90.9 [79.7,95.9]
IPD	10	316,823	62.6 [16.9,226.5]	99.7 [99.6,99.7]
Culture	7	50,645	30.1 [3.1,289.8] ^a	–
Molecular diagnostics	3	266,178	86.7 [22.6,332.9] ^a	–
Serotype distribution (prevalence)				
PCV10 (percent in vaccine ^b)				
Meningitis	6	196	62 [50,74]	40.1 [0.0,76.3]
IPD	17	14,145	67 [55, 76] ^c	98.6 [98.3,98.8]
Pneumonia/Noninvasive	4	333	88 [43,100]	94.6 [89.2,97.3]
PCV13 (percent in vaccine ^d)				
Meningitis	6	196	72 [59, 85]	61.9 [7,84.4]
IPD	17	14,145	81 [66,90]	99.1 [98.9,99.2]
Pneumonia/Noninvasive	4	333	99 [71,100]	91.5 [81.5,96.1]
Serotypes 1 and 5 (proportion)				
Meningitis	6	196	13 [5,24]	57.5 [0.0,82.8]
IPD	16	14,145	10 [6,16]	82.3 [72.4,88.7]
Pneumonia/Noninvasive	4	333	6 [0,71]	95.3 [90.8,97.6]
Antimicrobial susceptibility (prevalence of susceptibility)				
Penicillin	21	11,486	78 [62,89]	99.5 [99.5,99.6]
Ampicillin/Amoxicillin	11	757	95 [80,99]	95 [92.7,96.6]
Cefotaxime/Ceftriaxone	14	3,365	98 [95,100]	0 [0.0,0.0]
Chloramphenicol ^e	12	1,058	91 [81, 96]	90.8 [85.8,94]
Azithromycin/Erythromycin	7	480	94 [79,100]	87.5 [76.5,93.3]
Trimethoprim-Sulfamethoxazole	10	797	32 [10, 62]	97.3 [96.3,98.1]
Tetracycline	5	403	51 [36,65] ^c	82 [58.5,92.2]

CI, confidence interval; I² measure of consistency of effects across studies in meta-analysis; IPD, invasive pneumococcal disease; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

^aThe Wald CI was used since profile likelihoods are not well agreed upon for calculating CI involving covariates for this model.

^bPCV10 serotypes include 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.

^cBootstrapping was used to calculate the CI instead of the profile likelihood method due to convergence issues.

^dPCV13 serotypes include 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

^eOverall convergence issues for the model, so an alternate method of estimation was automatically employed by the function.