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Epidemiology of invasive pneumococcal disease in the pre-conjugate vaccine era: South Africa, 2003–2008☆

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ABSTRACT

Introduction: Dynamics of pneumococcal disease incidence and serotype distribution prior to introduction of pneumococcal conjugate vaccines (PCV) will assist in understanding effects of the vaccine over time and will be important in choosing the optimal PCV formulation.
Methods: We conducted active, laboratory-based, national surveillance for invasive pneumococcal disease (IPD) through the Group for Enteric, Respiratory and Meningeal Disease Surveillance in South Africa (GERMS-SA) from 2003 through 2008. Over 130 laboratories report to this system. Pneumococci were serotyped using Quellung and isolates screened for resistance by disk diffusion; minimum inhibitory concentrations were determined on potentially resistant isolates. We used univariate and multivariable multinomial regression models to assess differences between serotypes.
Results: GERMS-SA identified 8674 cases among children <5 years. Overall, 58% (3849/6668), 65% (4314/6668), and 85% (5669/6668) of cases and 61% (455/751), 64% (482/751), 82% (616/751) of deaths were due to serotypes included in 7-valent PCV, 10-valent PCV and 13-valent PCV, respectively. Serotypes 6A and 19A accounted for 16% (527/3252) of penicillin non-susceptible disease. In 2008, reported incidence of IPD was 6-fold higher in children <1 compared to children 1–4 years of age: 87 per 100,000 population and 14/100,000, respectively. The relative risk of IPD was 21-fold (95% CI, 19–24) and 34-fold (29–41) greater in HIV-infected compared to HIV-uninfected children in the <1 year and 1–4-year-old age groups respectively. On multivariable analysis serotypes 6B (relative risk ratio (RRR) 0.7; confidence interval (CI) 0.5–0.9), 18C (RRR 0.3; CI 0.1–0.5), 1 (RRR 0.2; CI 0.1–0.4) and 8 (RRR 0.2; CI 0.1–0.4) were significantly less common in HIV-infected individuals than serotype 14.
Conclusions: All vaccine formulations have the potential to prevent most cases and deaths from IPD in children in South Africa. Vaccines with protection against 19A would be advantageous in South Africa.

1. Introduction

The World Health Organization (WHO) has advocated for polysaccharide–protein conjugate vaccine (PCV) immunization implementation for infants [1]. Globally, an estimated 826,000 deaths occur annually from pneumococcal disease in children <5 years, of which 447,000 occur in Africa [2]. South Africa, a middle-income country with high human immunodeficiency virus (HIV) prevalence, introduced a 7-valent PCV (PCV-7) into the public immunization program since April 2009 and transitioned to 13-valent PCV in April 2011.

☆ The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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PCV-7 implementation has been highly effective in developed countries. The United States, since the introduction of PCV-7 in 2000, has seen a reduction in disease in the age group targeted for immunization (young children) [3], and also a reduction in disease among adults as a result of decreasing nasopharyngeal acquisition and subsequent reduced transmission of vaccine serotypes from children [4,5]. This vaccine has also been shown to prevent antimicrobial-resistant pneumococcal disease [6]. The United Kingdom has documented the benefits of the introduction of PCV-13 [7]. These studies have highlighted the importance of good quality laboratory-based surveillance data prior to vaccine introduction to guide the choice of optimal PCV formulation and assist in understanding effects of the vaccine over time.

Clinical trial data suggest that PCV is also likely to be beneficial for lower-income and high-risk populations. Clinical trials of a 9-valent PCV documented a 16% reduction in all-cause mortality in The Gambia [8], and an 83% and 65% reduction of vaccine-type invasive pneumococcal disease (IPD) among HIV-uninfected and HIV-infected children, respectively, in South Africa [9]. Preliminary data from a population-based surveillance site in Kenya may suggest a reduction in IPD after PCV-10 introduction [10].

In this study, we describe the epidemiology of IPD in the pre-vaccine era (2003–2008) caused by serotypes covered by the different vaccine formulations and the burden which they may potentially prevent among HIV-infected and -uninfected children. These analyses also serve as an important baseline from which to monitor the effects of PCV.

2. Methods

2.1. Invasive disease surveillance

Surveillance for IPD began in 1999 [11], but was enhanced in 2003 through GERMS-SA (Group for Enteric, Respiratory and Meningeal Disease Surveillance in South Africa), a nation-wide, active, laboratory-based surveillance system. Over 130 laboratories (representing ~290 hospitals) sent reports of laboratory-confirmed IPD together with isolates to the National Institute for Communicable Diseases (NICD) in Johannesburg. Demographic details such as age, gender, date of specimen, and source of isolate were captured. Enhanced surveillance at 16 sentinel hospitals located in all nine provinces collected additional information including admission date, HIV serological status, discharge diagnosis and outcome. Annual laboratory audits using a laboratory-based information system (Disa*Lab Laboratory Information Management System) for all public-sector laboratories in 8 provinces was used to identify unreported cases. KwaZulu-Natal did not have an electronic information system during the study years. We added the cases identified by audit to the database.

Cases of IPD were defined as patients with known age <5 years with *Streptococcus pneumoniae* cultured from normally sterile site specimens (*e.g.*, cerebrospinal fluid [CSF], blood or joint fluid) from January 2003 through December 2008. Repeat isolates from the same child within 21 days of the initial positive culture were excluded. Specimens yielding *S. pneumoniae* were captured for all national laboratories. Specimen source was defined by the following hierarchical definition: CSF specimen regardless of other specimens; blood specimen regardless of other specimens (excluding CSF); and other *e.g.*, pleural fluid and joint fluid without CSF or blood. Clinical syndrome was only captured for enhanced surveillance sites and was defined in the following hierarchical manner: meningitis if the clinical diagnosis of meningitis was noted in the clinical records or the pneumococcus was isolated from CSF; bacteremic pneumonia if the clinical diagnosis of pneumonia was noted in the clinical records and the pneumococcus was isolated from blood culture; bacteremia without focus if no localizing clinical diagnosis was noted in the clinical records and the pneumococcus was isolated from blood culture; and other, included any diagnoses not including the preceding three, including localized pneumonia with pneumococcus isolated from pleural fluid only. Predisposing conditions other than HIV were defined as follows: asplenia; chronic illness; other immunocompromising conditions (excluding HIV); other ACIP (Advisory Committee on Immunization Practices) [12] risk factors; and other risk factors. Malnutrition was defined as the presence of malnutrition as recorded in the medical records.

2.2. Estimation of incidence rates

We calculated cumulative annual incidence of IPD by dividing the number of IPD cases identified by mid-year population (in 2008, national population of children aged ≤5 years was estimated to be 6,108,700 individuals) [13]. Incidence by HIV coinfection was estimated for 2008, the year with the most complete HIV data. For estimates of incidence by HIV status, HIV-infected and uninfected population estimates were extracted from the Actuarial Society of South Africa (ASSA) 2008 AIDS and Demographic model. We used multiple imputation to estimate the HIV infection status for pneumococcal cases not tested for HIV using a binomial distribution. The predictors for the multiple imputation model were age; hospital; province; specimen type; penicillin, rifampicin and trimethoprim-sulfamethoxazole susceptibility; serotype; and site (enhanced or non-enhanced).

2.3. Serotyping and susceptibility testing

Pneumococci were serotyped by Quellung using specific antisera (Statens Serum Institut, Copenhagen, Denmark). Serotype 6C was distinguished from 6A for the whole study period [14]. PCV-7 included serotypes 4, 6B, 9V, 14, 18C, 19F and 23F; PCV-10 included in addition 1, 5 and 7F; and PCV-13 included in addition 3, 6A and 19A. Isolates were screened for penicillin resistance by oxacillin disk diffusion (Mast Diagnostics, Merseyside, United Kingdom) [15]. Minimum inhibitory concentrations (MICs) were determined for potentially resistant isolates using agar dilution or Etest® (AB-Biodisk, Solna, Sweden). Results were interpreted as penicillin susceptible or non-susceptible (MICs ≥ 0.12 mg/L) [15]. MIC50 was defined as the MIC required to inhibit the growth of 50% of penicillin non-susceptible isolates.

2.4. Statistical analysis

Univariate analysis used the χ^2-test for comparison of categorical variables to assess differences within enhanced and non-enhanced surveillance site data. Significant trends in incidence by serotype were assessed using Poisson regression. To assess differences between serotypes we evaluated the association of age, clinical syndrome, and HIV coinfection for each serotype compared to serotype 14 (the commonest serotype). We used univariate and multivariable multinomial regression models, generating a separate estimate of effect for each predictor on each outcome relative to the base level. The effect measures are the ratios of two relative risks (relative risk ratios) with each relative risk describing the probability of the outcome in the category of interest relative to the baseline category [16].

All analyses were done using Stata Version 11 (StataCorp Limited). Two-sided p values <0.05 were considered significant. An inherent property of national surveillance systems is the potential for incomplete information. For each analysis, we used all available case information. Variables were binary (yes/no), defined as the presence or absence of the attribute excluding missing data.