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The emergence of multidrug-resistant (MDR) Streptococcus pneumoniae complicates disease management. We aimed to determine risk factors associated with MDR invasive pneumococcal disease (IPD) in South Africa and evaluate the potential for vaccination to reduce disease burden. IPD data collected by laboratory-based surveillance from 2003 through 2008 were analyzed. Multidrug resistance was defined as nonsusceptibility to any three or more different antibiotic classes. Risk factors for multidrug resistance were evaluated using multivariable logistic regression. Of 20,100 cases of IPD identified, 3,708 (18%) had MDR isolates, with the proportion increasing from 16% (461/2,891) to 20% (648/3,326) (P < 0.001) over the study period. Serotypes included in the 13-valent pneumococcal conjugate vaccine (PCV13) accounted for 94% of MDR strains. Significant risk factors for MDR IPD included PCV13 (1,486/6,407; odds ratio [OR] of 6.3; 95% confidence interval [CI] of 5.0 to 7.9) and pediatric (3,382/9,980; OR of 12.8; 95% CI of 1.4 to 2.1), previous antibiotic use (242/803; OR of 1.7; 95% CI of 1.4 to 2.1), previous hospital admissions (579/2,450; OR of 1.2; 95% CI of 1.03 to 1.5), urban location (883/4,375; OR of 2.0; 95% CI of 1.8 to 2.3) or age of 15 to 64 years, HIV infection (975/4,636; OR of 1.5; 95% CI of 1.2 to 1.8), previous tuberculosis treatment (246/1,021; OR of 1.2; 95% CI of 1.03 to 1.5). MDR IPD prevalence increased over the study period. The effect of many of the MDR risk factors could be reduced by more judicious use of antibiotics. Because PCV13 serotypes account for most MDR infections, pneumococcal vaccination may reduce the prevalence of multidrug resistance.

S. pneumoniae is a leading cause of bacterial infection worldwide, occurring with a high incidence in Sub-Saharan Africa (45). Annual mortality rates resulting from invasive pneumococcal infection, including bacteremia, pneumonia, and meningitis, are high (58). One of the risk factors for developing invasive pneumococcal disease (IPD) is HIV infection (25), occurring among 10.6% of the South African population in 2008 (1).

The prevalence of S. pneumoniae antibiotic resistance has increased around the world, including in South Africa (3, 20, 23), not only to penicillin, but also to non-β-lactam drugs, such as macrolides, tetracycline, chloramphenicol, fluoroquinolones, and cotrimoxazole. The emergence of such antimicrobial resistance complicates the management of pneumococcal infections and may lead to treatment failure (6, 17, 26).

The development of resistance has heightened interest in preventive measures, such as vaccination. The 7- and 13-valent pneumococcal conjugate vaccines (PCV7 and PCV13), calculated to be cost-effective for many countries (50), was introduced into the national Expanded Programme on Immunization (EPI) in South Africa in 2009 and 2011, respectively. The vaccines are effective in preventing IPD in children and adults (15, 21, 32, 54). Most antibiotic-resistant infections are caused by five of the seven serotypes in PCV7 (35). As such, after the introduction of this vaccine, several studies have reported a decrease in the rate of antibiotic-resistant invasive pneumococcal infections (19, 32, 35, 42, 54). Related to this, however, is an increase in infections caused by serotypes not included in PCV7, including strains resistant to antibiotics, such as 19A, an important cause of IPD in children (13, 19, 21, 35, 40). If PCV13 proves to be as effective against serotype 19A as PCV7 has been against PCV7 serotypes, it has the potential to further reduce rates of antibiotic-resistant IPD (19).

Following its emergence in South Africa in 1977 (23), the problem of S. pneumoniae resistance to three or more different classes of antibiotics, defined as multidrug resistance, is of increasing global concern. Epidemiologic studies have repeatedly identified recent antibiotic use as the strongest risk factor for resistance among patients with IPD (12). The majority of studies investigating risk factors for carriage and infection with antibiotic-resistant S. pneumoniae have focused on penicillin resistance. The few studies that have analyzed risk factors for multidrug resistance have documented risk factors as age (<5 and >65 years) and previous use of β-lactam antibiotics by patients with noninvasive disease (7); antibiotic use in the last month by patients with nasopharyn-
geal carriage (27); and antibiotic consumption, population density, geographic location, PCV7 serotype, and isolate source from patients with invasive disease (52).

No systematic evaluation of multidrug resistance has previously been published from southern Africa or a middle-income country with high HIV disease prevalence. Using national, laboratory-based surveillance data over a 6-year period, we aimed to assess risk factors associated with S. pneumoniae multidrug resistance in South Africa and to evaluate the potential benefits of reducing antimicrobial-resistant disease by introducing the higher-valency pneumococcal vaccines.

**MATERIALS AND METHODS**

**Isolates and definitions.** From 1 January 2003 through 31 December 2008, S. pneumoniae isolates were collected as part of national laboratory-based surveillance for IPD. National laboratories performing clinical microbiology diagnostic tests submitted reports of laboratory-confirmed IPD together with the corresponding isolates to the National Institute for Communicable Diseases in Johannesburg, South Africa. Repeated isolates received from the same patient within 21 days of the initial isolate were excluded. Basic demographic data were collected for all cases, and for cases that occurred at one of 24 sentinel hospital sites located nationwide, enhanced clinical and demographic data were collected by interview or medical record review. The total population under surveillance in 2008 was 48.9 million persons, based on Statistics South Africa data (51).

A case of IPD was defined as isolation of S. pneumoniae from specimens from normally sterile sites, such as cerebrospinal fluid (CSF), blood, pleural fluid, or joint fluid, from people of all ages residing in South Africa during the surveillance period.

HIV infection was defined as positive or negative at the time of hospitalization for IPD. According to standard practice in South Africa, HIV testing is requested by admitting physicians when clinically indicated. For patients older than 18 months, this includes screening and confirmatory HIV enzyme-linked immunosorbent assay (ELISA) testing. For children less than 18 months of age, screening involves an ELISA, which, if positive, is followed by HIV PCR testing for confirmation.

Underlying conditions were defined as a medical-record-documented, preexisting history of pulmonary disease, renal disease, cerebrovascular accident, hepatic disease, cardiac disease, diabetes mellitus, head injury, connective tissue disease, asplenia, pregnancy, premature birth, malignancy, burns, gastric acid suppression, aplastic anemia, organ transplant, primary immunodeficiency conditions, hormonal conditions, protein energy malnutrition, or alcohol dependency, current smoking, or immunosuppressive therapy.

**Microbiological analysis.** Bacterial isolation and identification were performed using standardized methodologies. All isolates were screened for resistance to penicillin, ceftriaxone, erythromycin, tetracycline, chloramphenicol, rifampin, clindamycin, cotrimoxazole (trimethoprim-sulfamethoxazole), and ofloxacin by disk diffusion (Mast Diagnostics, Merseyside, United Kingdom), and, if resistant, MICs were determined by the Etest (AB Biodisk, Solna, Sweden) or agar dilution. Antibiotic resistance was defined using the Clinical and Laboratory Standards Institute (CLSI) breakpoints for 2009 (8). Isolates defined as either intermediate resistant or resistant to any of the antibiotics were regarded as being non-susceptible. Non-susceptibility to the relevant drugs was therefore defined as follows: penicillin, \( \geq 0.12 \, \text{µg/ml} \); ceftriaxone, \( \geq 1 \, \text{µg/ml} \); erythromycin, \( \geq 0.5 \, \text{µg/ml} \); tetracycline, \( \geq 4 \, \text{µg/ml} \); chloramphenicol, \( \geq 8 \, \text{µg/ml} \); rifampin, \( \geq 2 \, \text{µg/ml} \); clindamycin, \( \geq 0.5 \, \text{µg/ml} \); cotrimoxazole, \( > 0.5 \, \text{µg/ml} \); and ofloxacin, \( \geq 4 \, \text{µg/ml} \). Penicillin nonsusceptibility was defined using the more conservative CLSI meningeal breakpoints and applied to both meningeal and nonmeningeal isolates, as this analysis was not to guide clinical therapy but to investigate risk factors associated with the acquisition of resistance determinants. Multidrug resistance was defined as non-susceptibility to any three or more different antibiotic classes, according to the 2009 definitions of the CLSI (8) and various studies (23, 41, 55).

Pneumococci were serotyped by the Quellung method using specific antisera (Statens Serum Institut, Copenhagen, Denmark). Serotypes were grouped into the pediatric serotypes (6A, 6B, 9V, 14, 19A, 19F, and 23F) and nonpediatric serotypes (all serotypes excluding 6A, 6B, 9V, 14, 19A, 19F, and 23F). Additionally, serotypes were grouped according to those in PCV7 (4, 6B, 9V, 14, 18C, 19F, and 23F), PCV10 (those included in PCV7 plus 1, 5, and 7F), and PCV13 (those included in PCV10 plus 3, 6A, and 19A) versus nonvaccine serotypes (all serotypes excluding those occurring in PCV7, PCV10, or PCV13, respectively).

**Statistical analysis.** Statistical analyses were performed with Stata version 9.0 (STATA Corporation, College Station, TX). The prevalence of multidrug-resistant IPD was calculated as the total number of cases with viable isolates resistant to three or more different classes of antibiotics divided by the total number of cases of IPD with viable isolates in the study.

Using only the cases from enhanced surveillance sites with viable isolates for which case report forms were completed, and which therefore had additional clinical data, univariate and multivariable logistic regression was performed to determine if any independent variables (HIV infection, previous antibiotic use in the last 24 h and in the last 2 months, pediatric serotypes, PCV13 serotypes, age group, gender, province, year, diagnosis, final outcome, specimen type, recent hospitalization, underlying conditions, tuberculosis treatment, cotrimoxazole use, antiretroviral [ARV] use) were significantly associated with the outcome variable, multidrug resistance. The variables with statistical significance of \( P \) values of \( \leq 0.1 \) on univariate analysis were evaluated as potential risk factors for multidrug resistance in the multivariable models using stepwise forward selection. The collinearity and interaction between variables were assessed in the final multivariable model. \( P \) values of less than 0.05 were considered to indicate statistical significance in all analyses.

**Ethics.** Ethical approval for the surveillance program, review of patients’ medical records, and patient interviews were obtained from the Human Research Ethics Committee (Medical), University of the Witwatersrand, Johannesburg. Written informed consent was obtained from all patients prior to conducting interviews.

**RESULTS**

**Invasive pneumococcal disease surveillance, 2003 to 2008.** From 1 January 2003 to 31 December 2008, 27,732 cases of IPD were reported, of which 20,100 (72%) had viable isolates for further testing. Of these, 20,093 (99.9%) had antimicrobial susceptibility data. The majority of viable isolates were from blood specimens (61%; 12,280/20,100), with the remaining being from CSF (34%; 6,773/20,100) and other specimen types (5%; 1,047/20,100). Among patients with viable isolates and available demographic data, 50% (9,868/19,685) were male and the median age was 26 years (\( n = 19,254 \)) (interquartile range of 2 to 38 years). In children <5 years of age, the most common serotypes were 14 (15%; 1,027/6,681), 6B (13%; 885/6,681), 6A (12%; 798/6,681), 23F (11%; 753/6,681), 19F (10%; 671/6,681), and 19A (7%; 478/6,681). In individuals age \( \geq 5 \) years, serotype 1 was the most prevalent serotype (18%; 2,356/13,413), followed by 19A (8%; 1,022/13,413), 6A (6%; 839/13,413), 4 (6%; 832/13,413), 14 (6%; 805/13,413), and 23F (6%; 795/13,413). Serotypes included in PCV7 accounted for 41% (8,213/20,093) of all isolates, those in PCV10 accounted for 57% (11,362/20,093), and those in PCV13 accounted for 76% (15,204/20,093). Fifty percent (9,980/20,093) of isolates comprised the so-called pediatric serotypes (6A, 6B, 9V, 14, 19A, 19F, and 23F).

Of the cases from enhanced surveillance sites with viable isolates for which case report forms were completed, 57% (4,806/8,476) were diagnosed with pneumonia, 32% (2,729/8,476) with
meningitis, 6% (337/5,476) with bacteremia without focus, and 5% (404/8,476) with other diagnoses. Twenty-eight percent (2,386/8,407) of patients with known outcome data died. Of 5,665 patients with known HIV status, 82% (4,637) were seropositive.

**Antimicrobial resistance.** The highest levels of antimicrobial nonsusceptibility among isolates from 2003 through 2008 were observed for cotrimoxazole at 55% (10,951/20,094) (Fig. 1). The prevalence of nonsusceptibility to penicillin was 33% (6,569/20,094). The majority (32%; 6,488/20,094) of these isolates displayed intermediate resistance to penicillin, with only 0.4% (81/20,094) showing high-level resistance. When using CLSI meningitis breakpoints on meningeal isolates only and applying nonmeningitis breakpoints (8) to nonmeningeal isolates, penicillin nonsusceptibility was 10% (2,066/20,094). Overall, 18% (3,644/20,094) of all isolates were nonsusceptible to tetracycline, with 17% showing high-level resistance, 14% (2,873/20,094) of isolates were erythromycin nonsusceptible, and 10% (2,090/20,094) were clindamycin nonsusceptible. Very few IPD isolates were nonsusceptible to rifampin (4%), chloramphenicol (3%), or ceftriaxone (<1%) (Fig. 1). In addition, as discussed in detail elsewhere for 2003 to 2006 (53, 56), very few isolates were fluoroquinolone nonsusceptible, with 0.4% (12/3,329) in 2007 and 0.1% (2/3,327) in 2008.

**Trends in pneumococcal resistance.** Penicillin nonsusceptibility increased from 23% in 2003 to 38% in 2008 (P < 0.001) (Fig. 1). There were also significant increases from 2003 to 2008 in the proportion of isolates that were nonsusceptible to other antimicrobial agents: tetracycline, 15% to 20% (P < 0.001); erythromycin, 13% to 15% (P < 0.001); clindamycin, 10% to 11% (P < 0.05); and chloramphenicol, 3% to 5% (P < 0.001). Cotrimoxazole nonsusceptibility decreased overall between 2003 and 2008 (51% to 48%; P = 0.007). There were no significant changes in nonsusceptibility for rifampin and ceftriaxone over this period.

**Multidrug resistance.** Penicillin-susceptible isolates were likely to be susceptible to most of the other antimicrobials tested. Isolates with intermediate or high-level resistance to penicillin were significantly more likely to be resistant to the β-lactam ceftriaxone and to chloramphenicol, clindamycin, cotrimoxazole, erythromycin, rifampin, and tetracycline than when the isolates were susceptible to penicillin.

Of the 20,100 cases with viable isolates, 18% (3,708) were multidrug resistant. Serotypes included in PCV7, PCV10, and PCV13 accounted for 83% (3,072/3,708), 85% (3,153/3,708), and 94% (3,503/3,708) of multidrug-resistant strains, respectively. Additionally, the so-called pediatric serotypes accounted for 91% (3,382/3,708) of MDR strains. The serotype most commonly displaying multidrug resistance was 14 (85%) (Fig. 2). The overall incidence rate of MDR IPD for 2008 was 1.3 cases per 100,000 population. The age-specific incidence rate for the same year was highest in children age <1 year at 18.6 cases per 100,000 population. From 2003 through 2008, the percentage of isolates that were multidrug resistant increased significantly from 16% to 20% (P < 0.001), peaking at 21% in 2007 (Fig. 1).

In a repeat of the analysis utilizing CLSI penicillin meningitis and nonmeningitis breakpoints (8) for meningeal and nonmeningeal isolates, respectively, the prevalence of multidrug resistance was 16% (3,176/20,094).

**Risk factors associated with multidrug-resistant IPD.** In a multivariable logistic regression model, PCV13 serotypes and pediatric serotypes were the two strongest independent risk factors for MDR IPD, with adjusted odds ratios of 6.3 and 12.8, respectively (Table 1). Compared to adults 15 to 64 years old, children

![FIG 1](https://example.com/fig1.png) Frequency of nonsusceptibility, including multidrug resistance, of pneumococcal isolates causing invasive disease in all ages, by antimicrobial agent and year, South Africa, 2003 to 2008. P values were calculated using a nonparametric test for trend across ordered groups.
less than 5 years old were at the greatest risk of infection with MDR strains, as were adults ≥65 years old. MDR IPD prevalence was significantly elevated among HIV-infected persons overall and was significant for all age groups except individuals 15 to 64 years of age. Additionally, the following factors were found to be significant independent risk factors for MDR IPD: previous antibiotic use, previous hospital admissions in the last year, provincial location, and tuberculosis treatment (Table 1).

**DISCUSSION**

Active laboratory-based surveillance in South Africa from 2003 through 2008 demonstrated that the percentage of multidrug-resistant invasive pneumococcal isolates increased significantly, peaking at 21% in 2007. Overall, the prevalence of multidrug-resistant IPD in this study was 18%, equating to an incidence rate of 1.3 cases per 100,000 population in 2008. We identified ages of <15 years (particularly <5 years) and ≥65 years, HIV infection, PCV13 and pediatric serotypes, previous antibiotic use, previous hospital admissions, urban location, and tuberculosis treatment as significant risk factors for multidrug-resistant IPD in South Africa over this time period.

As shown in our study and corroborated by numerous other studies (4, 10, 11, 55), isolates with resistance to penicillin are significantly more likely to be resistant to multiple other antimicrobial agents than when the isolates are susceptible to penicillin, suggesting that penicillin resistance acts as a marker of resistance to other drugs. Thus, the increase in penicillin nonsusceptibility from 23% to 38% over the study period was paralleled not only by an increase in nonsusceptibility to tetracycline, erythromycin, clindamycin, and chloramphenicol but also by an increase in the prevalence of multidrug resistance.

Antibiotic resistance patterns are very dependent on local patterns of prescribing and purchasing (29). The frequency of multidrug resistance in this study is much higher than those reported previously among large numbers of systematically collected invasive pneumococcal isolates from South Africa up to 1998 (16, 22, 33) but lower than levels observed in an international multicenter survey using both limited invasive and respiratory isolates from South Africa in 2004 (14). The significant increase in multidrug resistance observed over the 6-year period of our study is consistent with trends reported in other prevaccine era studies (10, 22, 55), suggesting that the problem of MDR IPD is worsening.

The global increase in multidrug-resistant pneumococci appears to result from the spread of a few highly resistant pneumococcal clones within serotypes 6B, 9A, 9V, 14, 19A, 19F, and 23F, the so-called pediatric serotypes, which are particularly associated with carriage and disease in children (28, 33, 39). As such, in our study, pediatric and PCV13 serotypes were the strongest risk factors for multidrug-resistant IPD, accounting for 91% and 94% of multidrug-resistant strains, respectively. Consistent with a 1994 Zambian pediatric study in which all but one of the multidrug-resistant isolates were serotype 14 (57), this serotype displayed the highest percentage (85%) of multidrug resistance in our study. In another South African study in 1993 to 1995, a higher proportion of isolates from HIV-positive patients compared with HIV-negative patients were serotype 14 (9). Corresponding to the predominance of pediatric serotype MDR IPD, younger children in our study had a greater risk of multidrug resistance, reflecting both the prolonged duration of carriage of pneumococci in children compared to that in adults and their greater per capita use of antibiotics (30). Our study additionally corroborates reports of an age of <5 or ≥65 years as a risk factor for drug-resistant IPD (7, 46).

HIV infection is a powerful risk factor for IPD, with disease occurrence ranging from 30 to 100 times higher in HIV-infected patients than in age-matched HIV-uninfected individuals (24, 25). Additionally, pneumococci causing invasive disease among HIV-infected adults (5, 9, 25) and children (38) are more resistant to antibiotics. Our study extends this association to HIV infection and multidrug resistance and may be explained by the propensity of HIV-infected adults to infection with antibiotic-resistant pediatric pneumococcal serotypes (9, 25), as well as to the increased hospitalization and exposure to antibiotics given as treatment and prophylaxis among HIV-infected patients (37). Previous hospitalization was confirmed to be a risk factor for MDR IPD in our study (23), likely due to nosocomial acquisition of these strains. Of concern is the impact of cotrimoxazole prophylaxis on resistance to
TABLE 1 Factors significantly associated with MDR IPD in South Africa among all patients with IPD having viable isolates and completed case report forms, 2003 to 2008

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of MDR isolates/total no. of isolates</th>
<th>Multidrug resistance (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2003</td>
<td>195/1,212</td>
<td>16.1</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>264/1,611</td>
<td>16.4</td>
<td>1.02 (0.84–1.25)</td>
<td>1.12 (0.90–1.38)</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>291/1,584</td>
<td>18.4</td>
<td>1.17 (0.96–1.43)</td>
<td>1.38 (1.12–1.71)</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>276/1,522</td>
<td>18.1</td>
<td>1.16 (0.94–1.41)</td>
<td>1.42 (1.15–1.76)</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>301/1,418</td>
<td>21.2</td>
<td>1.41 (1.15–1.72)</td>
<td>1.68 (1.35–2.07)</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>244/1,127</td>
<td>21.7</td>
<td>1.44 (1.17–1.78)</td>
<td>1.79 (1.43–2.24)</td>
<td></td>
</tr>
<tr>
<td>Age group (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;1</td>
<td>416/1,652</td>
<td>25.2</td>
<td>2.21 (1.92–2.55)</td>
<td>2.07 (1.77–2.41)</td>
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</tr>
<tr>
<td>1–4</td>
<td>386/1,458</td>
<td>26.5</td>
<td>2.37 (2.05–2.74)</td>
<td>1.95 (1.66–2.28)</td>
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</tr>
<tr>
<td>5–14</td>
<td>156/783</td>
<td>19.9</td>
<td>1.64 (1.35–1.99)</td>
<td>1.39 (1.13–1.71)</td>
<td></td>
</tr>
<tr>
<td>15–64</td>
<td>571/4,327</td>
<td>13.2</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>39/239</td>
<td>16.3</td>
<td>1.28 (0.90–1.83)</td>
<td>1.49 (1.02–2.16)</td>
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</tr>
<tr>
<td>PCV13 serotypesc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>85/2,067</td>
<td>4.1</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Yes</td>
<td>1,486/6,407</td>
<td>23.2</td>
<td>7.04 (5.62–8.82)</td>
<td>6.28 (5.00–7.88)</td>
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</tr>
<tr>
<td>Pediatric serotypesb</td>
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<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
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<td>No</td>
<td>326/10,114</td>
<td>3.2</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
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<tr>
<td>Yes</td>
<td>3,382/9,980</td>
<td>33.9</td>
<td>13.33 (11.13–15.96)</td>
<td>12.8 (10.62–15.42)</td>
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<tr>
<td>HIV status</td>
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<td></td>
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<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Negative</td>
<td>172/1,028</td>
<td>16.7</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>975/4,636</td>
<td>21.0</td>
<td>1.33 (1.11–1.58)</td>
<td>1.49 (1.23–1.81)</td>
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<td>Antibiotics in last 24 h</td>
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<td></td>
<td>&lt;0.001</td>
</tr>
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<td>No</td>
<td>1,107/6,184</td>
<td>17.9</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Yes</td>
<td>98/375</td>
<td>26.1</td>
<td>1.62 (1.28–2.06)</td>
<td>1.46 (1.12–1.90)</td>
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<td>Antibiotics in last 2 months</td>
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<td>16.6</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Yes</td>
<td>242/803</td>
<td>30.1</td>
<td>2.17 (1.83–2.57)</td>
<td>1.68 (1.38–2.06)</td>
<td></td>
</tr>
<tr>
<td>Previous hospital admissions in last yr</td>
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<td></td>
<td></td>
<td></td>
<td>0.017</td>
</tr>
<tr>
<td>No</td>
<td>722/4,472</td>
<td>16.1</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
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<td>579/2,450</td>
<td>23.6</td>
<td>1.61 (1.42–1.82)</td>
<td>1.19 (1.03–1.37)</td>
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<td>Provincec</td>
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<td>&lt;0.001</td>
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<tr>
<td>LP</td>
<td>15/138</td>
<td>10.9</td>
<td>1.00</td>
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<td>EC</td>
<td>25/168</td>
<td>14.9</td>
<td>1.43 (0.72–2.84)</td>
<td>1.14 (0.56–2.33)</td>
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<td>FS</td>
<td>108/671</td>
<td>16.1</td>
<td>1.57 (0.89–2.79)</td>
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<td>GA</td>
<td>883/4,375</td>
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<td>2.07 (1.21–3.56)</td>
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<td>2.31 (1.13–4.72)</td>
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<td>NW</td>
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<td>1.92 (0.78–4.71)</td>
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<td>WC</td>
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<td>1.84 (1.06–3.19)</td>
<td>1.19 (0.67–2.10)</td>
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<td>TB treatment</td>
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<td>Yes</td>
<td>246/1,021</td>
<td>24.1</td>
<td>1.46 (1.24–1.71)</td>
<td>1.23 (1.03–1.47)</td>
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<td>ARV use</td>
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<td>No</td>
<td>601/2,942</td>
<td>20.4</td>
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<td>190/662</td>
<td>28.7</td>
<td>1.73 (1.45–2.06)</td>
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<td>Cotrimoxazole use</td>
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<td>746/4,584</td>
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<td>Yes</td>
<td>371/1,390</td>
<td>26.7</td>
<td>1.87 (1.62–2.16)</td>
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</table>

(Continued on following page)
that drug and its role in multidrug resistance. The prevalence of
cotrimoxazole resistance has increased markedly in South Africa
since 1977 and has been found to be associated with multidrug-
resistant strains in children (31). Over half of the isolates in our
study were cotrimoxazole nonsusceptible, and use of this drug was
more commonly reported in patients with multidrug resistance,
although this was not statistically significant on multivariable lo-
gistic regression analysis. Also of interest is that tuberculosis treat-
ment was a risk factor for MDR IPD, possibly reflecting the in-
creased exposure of patients to rifampin, which is widely used in
South Africa for the treatment of tuberculosis in children. In our
study, IPD patients who had received TB treatment were signifi-
cantly more likely to have rifampin-resistant isolates than those
who had not received the treatment (data not shown) and, al-
though such resistance in the former group was high at 18%, only
16% of all IPD cases were documented to have received TB treat-
ment, equating to very little rifampin resistance overall. The emer-
gence of fluoroquinolone-resistant pneumococci is of concern
(53), but ongoing screening for resistance during this study period
has not detected significant increases.

Our study confirms that a patient’s prior use of antibiotics,
both in the 24 h and the 2 months preceding sample collection, is
a risk factor associated with MDR IPD (7). It is thought that re-
petitive use of antibiotic agents exerts a selective pressure on the
pneumococcal strains in the nasopharynx or at the site of infec-
tion, thus leading to the emergence of resistant strains and their
rapid spread (4, 18, 33). The relationship between antimicrobial
resistance and exposure is complicated by the emergence of mul-
drug-resistant pneumococci that may be selected by several
classes of antibiotics (30). However, resistance typically imposes a
bacterial fitness cost, expressed as reduced growth, virulence, or
transmission (2), and as a result, models predict that significantly
reduced consumption of antimicrobials will result in decreases in
resistance (36), as shown in campaigns in Finland (48) and Iceland
(34). Less commonly, the acquisition of an additional resistance
plasmid or of a resistant mutation increases the fitness of a bac-
terial strain already resistant to antibiotics (49). Further investiga-
tion is required to determine the extent to which MDR
*S. pneumoniae*
strains are affected by fitness costs and changes in
antibiotic selective pressure. In South Africa, the sale of antibiotics
is reasonably well controlled; however, incorrect prescribing prac-
tices by physicians in the public and private sectors is of concern
and could be improved by the more prudent and appropriate
prescription of antibiotics in an attempt to prevent the emergence
and spread of resistance (47).

Consistent with a Belgian study (52), we found provincial lo-
cation to be associated with MDR IPD, with those residing in
urban locations at a higher risk than individuals in more rural
locations, probably due to increased exposure of the urban chil-
dren to recent antibiotic use, past hospitalization, and more day
care attendance.

As with most surveillance studies, this study had several limi-

**TABLE 1 (Continued)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of MDR isolates/ total no. of isolates</th>
<th>Multidrug resistance (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>P value&lt;sup&gt;d&lt;/sup&gt;</th>
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<tr>
<td><strong>Specimen type</strong></td>
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<td>Cerebrospinal fluid</td>
<td>401/2,223</td>
<td>18.0</td>
<td>1.00&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>Blood</td>
<td>1,100/5,893</td>
<td>18.7</td>
<td>1.04 (0.92–1.18)</td>
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<td>Other</td>
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<td>19.6</td>
<td>1.10 (0.83–1.47)</td>
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<td><strong>Diagnosis</strong></td>
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<td>Meningitis</td>
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<td>18.1</td>
<td>1.00&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>Pneumonia</td>
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<td>1.03 (0.91–1.16)</td>
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<td>Bacteremia</td>
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<td><strong>Gender</strong></td>
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<td>Male</td>
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<td>18.1</td>
<td>1.00&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>Female</td>
<td>796/4,203</td>
<td>18.9</td>
<td>1.06 (0.95–1.18)</td>
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<td><strong>Comorbid conditions&lt;sup&gt;f&lt;/sup&gt;</strong></td>
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<tr>
<td>Yes</td>
<td>127/782</td>
<td>16.2</td>
<td>0.83 (0.68–1.01)</td>
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<tr>
<td><strong>Immunocompromising conditions&lt;sup&gt;f&lt;/sup&gt;</strong></td>
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<td>Yes</td>
<td>278/1,433</td>
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<td>1.07 (0.92–1.23)</td>
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<td><strong>Outcome</strong></td>
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<td>Recovered</td>
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<td>18.8</td>
<td>1.00&lt;sup&gt;e&lt;/sup&gt;</td>
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<td></td>
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<td>Died</td>
<td>432/2,386</td>
<td>18.1</td>
<td>0.96 (0.85–1.08)</td>
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</table>

<sup>a</sup>Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.

<sup>b</sup>Serotypes 6A, 6B, 9V, 14, 19A, 19F, and 23F.

<sup>c</sup>EC, Eastern Cape; FS, Free State; GA, Gauteng; KZ, KwaZulu Natal; LP, Limpopo; MP, Mpumalanga; NC, Northern Cape; NW, North West; WC, Western Cape.

<sup>d</sup>Overall P value for all levels of the variable. NS, not significant.

<sup>e</sup>Referent.

<sup>f</sup>Excluding HIV.
tations. Surveillance studies represent a sample of isolates obtained from patients with specimens taken and may not represent the larger population. However, annual audits are conducted on all isolate data retrieved from a central data warehouse and detect any cases missed by surveillance (about 18% of all cases), although such cases do not have viable isolates for laboratory analysis. An additional potential source of bias is that the multivariable analysis is conducted only on data from enhanced surveillance sites which have completed case report forms. A limitation of surveillance systems is that certain data, such as underlying conditions, may not be filled out uniformly or completely. Because we evaluated a wide variety of potential risk factors for MDR IPD, some of the observed associations may have been a chance occurrence related to multiple comparisons. As such, we have included precise P values and confidence intervals for evaluation.

In a British study on the vaccine effectiveness (VE) of PCV13, VE in children was estimated to be 78% and IPD due to PCV13 serotypes was halved in children less than 2 years old (43). In the United States, rates of resistant disease caused by PCV7 serotypes decreased 87% following vaccine introduction (35). In our study, serotypes included in PCV13 accounted for 94% of multidrug-resistant strains. Thus, the identification of PCV13 serotypes as a significant risk factor for multidrug resistance development suggests that the newly licensed pneumococcal vaccine, which reduces pneumococcal disease in both HIV-infected and -uninfected children (32) and which prevents the transmission of pediatric serotypes to adults (54), may reduce both antibiotic resistance and the burden of pneumococcal disease due to pediatric serotypes in South Africa (32, 35, 54). However, it should be noted that following PCV7 introduction in the United States, nonvaccine serotypes acquired multidrug resistance at a rate proportional to the replacement of vaccine serotypes over a 5-year period (40). As such, the low prevalence of multidrug-resistant nonvaccine strains may increase following PCV7 and PCV13 introduction in this country.

In conclusion, we found that younger and older age, HIV infection, PCV13 and pediatric serotypes, previous antibiotic use, previous hospital admissions, urban location, and tuberculosis treatment were associated with multidrug-resistant IPD in South Africa. These risk factors affecting individuals or groups of individuals could impact decision-making regarding prevention and treatment of pneumococcal disease in this and other developing countries. The effect of many of the risk factors could be reduced by the introduction of the pneumococcal conjugate vaccine (35) as well as highly active antiretroviral therapy (HAART) (44) and more judicious use of effective antibiotics. Continued comprehensive laboratory surveillance of IPD will assist in monitoring changes in antimicrobial resistance, as well as the impact of vaccination on both decreasing vaccine serotypes currently associated with resistance and the emergence of resistant nonvaccine serotypes.

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REFERENCES

Multidrug-Resistant Pneumococcal Disease in South Africa