Emergence of Endemic Serogroup W135 Meningococcal Disease Associated with a High Mortality Rate in South Africa

Anne von Gottberg,1,3 Mignon du Plessis,1,3 Cheryl Cohen,2,4 Elizabeth Prentice,5 Stephanie Schrag,5 Linda de Gouveia,1 Garry Coulson,1,3 Gillian de Jong,2,3 and Keith Klugman,1,6,7 for the Group for Enteric, Respiratory and Meningeal Disease Surveillance in South Africa

1Respiratory and Meningeal Pathogens Research and 2Epidemiology and Surveillance Units, National Institute for Communicable Diseases, and Schools of 3Pathology and 4Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; and 5National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, and 6Hubert Department of Global Health, Rollins School of Public Health, and 7Division of Infectious Diseases, School of Medicine, Emory University, Atlanta, Georgia

Background. In the African meningitis belt, Neisseria meningitidis serogroup W135 has emerged as a cause of epidemic disease. The establishment of W135 as the predominant cause of endemic disease has not been described.

Methods. We conducted national laboratory–based surveillance for invasive meningococcal disease during 2000–2005. The system was enhanced in 2003 to include clinical data collection of cases from sentinel sites. Isolates were characterized by pulsed-field gel electrophoresis and multilocus sequence typing.

Results. A total of 2135 cases of invasive meningococcal disease were reported, of which 1113 (52%) occurred in Gauteng Province, South Africa. In this province, rates of disease increased from 0.8 cases per 100,000 persons in 2000 to 4.0 cases per 100,000 persons in 2005; the percentage due to serogroup W135 increased from 7% (4 of 54 cases) to 75% (221 of 295 cases). The median age of patients infected with serogroup W135 was 5 years (interquartile range, 2–23 years), compared with 21 years (range, 8–26 years) for those infected with serogroup A (P < .001). The incidence of W135 disease increased in all age groups. Rates were highest among infants (age, <1 year), increasing from 5.1 cases per 100,000 persons in 2003 to 21.5 cases per 100,000 persons in 2005. Overall case-fatality rates doubled, from 11% in 2003 to 22% in 2005. Serogroup W135 was more likely to cause meningococcemia than was serogroup A (82 [28%] of 297 cases vs. 11 [8%] of 141 cases; odds ratio, 8.9, 95% confidence interval, 2.2–36.3). A total of 285 (95%) of 301 serogroup W135 isolates were identified as 1 clone by pulsed-field gel electrophoresis; 7 representative strains belonged to the ST-11/ET-37 complex.

Conclusions. Serogroup W135 has become endemic in Gauteng, South Africa, causing disease of greater severity than did the previous predominant serogroup A strain.

Meningococcal disease remains an important cause of meningitis and sepsis worldwide [1–3]. Since the early 1970s, polysaccharide meningococcal vaccines have been used in industrialized countries and during outbreaks throughout the world [4]. Recent licensure of conjugate vaccines offers new scope for prevention of disease [5, 6]. Significant prevention challenges still exist for Africa. The African meningitis belt extends from Ethiopia to Senegal and has cyclical epidemics occurring every 5–10 years, resulting in attack rates of ≥1000 cases per 100,000 persons [7]. Historically, Neisseria meningitidis serogroup A has been the most common serogroup to cause disease in this region [7]. An international outbreak of N. meningitidis serogroup W135 meningococcal disease among Hajj pilgrims in 2000 and 2001 highlighted the importance of this serogroup [8–12]. Cases of W135 disease were also identified in Burkina Faso in 2001 [13], during an epidemic in the same country in 2002 [14], and in other countries in the meningitis belt [15, 16]. The causative isolates were characterized as a single clone belonging to the electrophoretic type (ET)–37 complex, sequence type (ST)–11 [11, 17].
South Africa does not fall in the meningitis belt, but for many decades, there has been documented endemic meningococcal disease, with seasonal increases during the winter and spring months (May–October) [18]. The burden of disease occurs in a cyclical pattern at intervals of 8–10 years [19]. The incidence of clinical notification to the national Department of Health (Pretoria, South Africa) has decreased since the late 1980s; for the period 1992–1997, there were 1–2 cases per 100,000 persons [19].

Two provinces have historically been responsible for highest rates of disease, and disease has typically been due to specific serogroups: serogroup B in Western Cape Province [20, 21] and serogroup A in Gauteng Province [22–24]. Western Cape Province has a Mediterranean climate, with wet winters and hot, dry summers; Gauteng Province lies on a plateau and has a temperate climate with summer rainfall [25].

Most South Africans have good access to health care; for example, 92% of all births are assisted by trained health personnel [26]. This rate ranges from 85% in Eastern Cape Province to 93.3% in Western Cape Province and 95.2% in Gauteng Province. In South Africa, it is standard practice to refer all patients with suspected meningitis to the hospital and to obtain CSF specimens for laboratory testing. Third-generation cephalosporins are available in hospitals and clinics for empirical treatment of acute bacterial meningitis [27]. Routine and large-scale use of meningococcal vaccines are not standard in South Africa.

During the period 1999–2002, serogroup W135 caused <10% of cases of meningococcal disease in South Africa [24]. In this article, we report the replacement of serogroup A disease in Gauteng Province with a hypervirulent clone of W135. This led to an increased incidence of disease among young infants and higher case-fatality rates.

**METHODS**

**National meningococcal surveillance.** In 1999, South Africa established a national laboratory–based surveillance system for invasive meningococcal disease [28]. Throughout the country, clinical microbiology laboratories were requested to send reports of laboratory-confirmed meningococcal cases and, when available, isolates to a central laboratory in Johannesburg. Basic demographic characteristics, including age, sex, date of specimen collection, and source of isolate, were supplied for patients. Annual laboratory audits and a review of laboratory-confirmed cases reported by clinicians to the Department of Health were performed to identify cases not captured by routine surveillance. Cases found on audit (up to 10%–20% of annual totals) were included, although no associated isolates were available for testing.

Approximately 80 laboratories participated in 2000. In 2003, we enhanced the surveillance system, initiating frequent communications and province visits to increase case reporting. The number of participating laboratories increased to 110 in 2003 and to 120 in 2005. In addition, we collected expanded clinical and demographic information on patients at 15 sentinel hospitals in 7 of 9 provinces. New captured data included discharge diagnosis, outcome, and HIV serological status.

**Definitions.** Case patients were defined as residents of South Africa for whom *N. meningitidis* was isolated from normally sterile specimens (e.g., CSF, blood, and joint fluid specimens) from January 2000 through December 2005. In addition, starting in 2003, the definition for case patients was broadened to include patients with culture-negative specimens that yielded positive results by latex agglutination and Gram stain microscopy or by latex agglutination and PCR. Laboratory-confirmed meningococcal meningitis was defined as growth of *N. meningitidis* on CSF cultures (with or without growth on blood cultures). Laboratory-confirmed meningococcal meningitis was defined as growth of *N. meningitidis* on blood cultures (without growth on CSF cultures).

**Strain characterization.** Bacteria were identified according to standardized procedures [29]. Serogroup was determined by slide agglutination with polyclonal antibodies to capsular polysaccharides A, C, X, Y, Z, and W135 and with monoclonal antibodies to polysaccharide B (Remel; Biotech). Strains not reacting with these antibodies were sent to the World Health Organization Collaborating Center for Reference and Research on Meningococci (Oslo, Norway) or to the Meningitis Laboratory, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (Atlanta, GA), for serogrouping. Two serogroup W135 strains related to the international outbreak in 2000 were obtained from the former institution [12]. Three patients with culture-negative disease diagnosed by latex agglutination had CSF specimens available for serogroup confirmation with PCR [30]. MICs were determined using Etest (AB-Biodisk) and the broth microdilution method, and results were interpreted using breakpoints recommended by Clinical and Laboratory Standards Institute guidelines [31].

PFGE of *NheI* restriction enzyme–digested genomic DNA was performed using a method adapted from Popovic et al. [32]. A PFGE cluster was defined as ≥3 isolates sharing ≥80% similarity on the dendrogram [32, 33]. Multilocus sequence typing (MLST) was performed as described by Maiden et al. [34]. Sequence types were assigned through the Neisseria MLST Web site (http://pubmlst.org/neisseria/).

**Incidence.** We calculated the incidence on the basis of the number of laboratory-confirmed cases reported each year from 1 January through 31 December divided by midyear population estimates for each year, as supplied by Statistics South Africa (Stats SA). In 2005, the estimated population of South Africa was 47 million (with 9 million in Gauteng Province). Sero-
Table 1. Number and incidence of laboratory-confirmed invasive meningococcal cases in South Africa reported to the National Institute for Communicable Diseases, by serogroup, 2000–2005.

<table>
<thead>
<tr>
<th>Serogroup</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>21 (11)</td>
<td>69 (30)</td>
<td>58 (30)</td>
<td>87 (33)</td>
<td>57 (20)</td>
<td>24 (6)</td>
<td>316</td>
</tr>
<tr>
<td>B</td>
<td>103 (52)</td>
<td>71 (31)</td>
<td>47 (24)</td>
<td>76 (29)</td>
<td>62 (22)</td>
<td>58 (14)</td>
<td>417</td>
</tr>
<tr>
<td>C</td>
<td>17 (9)</td>
<td>16 (7)</td>
<td>20 (10)</td>
<td>31 (12)</td>
<td>31 (11)</td>
<td>21 (5)</td>
<td>136</td>
</tr>
<tr>
<td>W135</td>
<td>10 (5)</td>
<td>13 (6)</td>
<td>24 (13)</td>
<td>26 (10)</td>
<td>77 (27)</td>
<td>257 (62)</td>
<td>407</td>
</tr>
<tr>
<td>X</td>
<td>4 (2)</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>2 (0.5)</td>
<td>11</td>
</tr>
<tr>
<td>Y</td>
<td>41 (21)</td>
<td>59 (26)</td>
<td>41 (21)</td>
<td>43 (16)</td>
<td>53 (19)</td>
<td>52 (13)</td>
<td>289</td>
</tr>
<tr>
<td>Z</td>
<td>2 (1)</td>
<td>...</td>
<td>...</td>
<td>2 (1)</td>
<td>...</td>
<td>...</td>
<td>4</td>
</tr>
<tr>
<td>29E</td>
<td>...</td>
<td>1 (0.4)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>Not groupable</td>
<td>...</td>
<td>...</td>
<td>1 (1)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>No isolate available</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>Total no. of cases reported</td>
<td>238</td>
<td>356</td>
<td>269</td>
<td>368</td>
<td>360</td>
<td>544</td>
<td>2135</td>
</tr>
<tr>
<td>Annual incidence, cases per 100,000 population</td>
<td>0.54</td>
<td>0.80</td>
<td>0.59</td>
<td>0.80</td>
<td>0.78</td>
<td>1.16</td>
<td>NA</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of cases, unless otherwise indicated. NA, not applicable.

a No isolates identified.
b Percentage of all cases reported.

Statistical analysis. The χ² test for trend was used to assess linear trends over time. Serogroup W135 disease was compared with serogroup A disease alone, because serogroup A has specific epidemiological features and a history of predominance in Gauteng Province. The prevalence of other serogroups in the province did not vary over time and caused minimal disease. Univariate assessment of characteristics associated with disease due to serogroup W135 infection and disease resulting in death was performed using Fisher’s exact test or the Mantel-Haenszel test for categorical variables, and the Kruskal-Wallis test was used for continuous variables. Multivariable analyses were limited to cases from Gauteng Province during 2003–2005. Variables available for evaluation as potential risk factors included age group, sex, year of infection, syndrome (laboratory-confirmed meningitis vs. meningococcemia), HIV infection, and nonsusceptibility to penicillin. Multivariable logistic regression models were evaluated starting with all variables that were significant at P <.1 on univariate analysis and dropping nonsignificant factors with stepwise backward selection. Independence of data was assumed, because the vast majority of cases were considered to be unrelated. All 2-way interactions in the final multivariable model were evaluated. Univariate and multivariable analyses were performed with EpilInfo software, version 6.04d (Centers for Disease Control and Prevention), and Stata version 9 (StataCorp). Two-sided P values of <.05 were considered to be statistically significant.

RESULTS

Trend over time. During 2000–2005, a total of 2135 cases of laboratory-confirmed invasive meningococcal disease were reported to the national surveillance system. Cases occurred throughout the year, and the incidence increased seasonally during the winter and spring months. Rates of reported disease increased from 0.54 cases per 100,000 population in 2000 to 0.80 cases per 100,000 in 2001 (P < .001) (table 1). In 2005, the incidence increased to 1.16 cases per 100,000 population. The majority of cases of disease nationally during the 6 years were reported to occur in 2 provinces: Gauteng Province (1113 [52%] of 2135 cases) and Western Cape Province (490 [23%] of 2135 cases). Rates of disease in Gauteng Province increased overall from 0.81 cases per 100,000 in 2000 to 3.98 cases per 100,000 in 2005 (P < .001) (figure 1A). Western Cape Province reported a gradual decrease in the incidence during the same period (from 2.48 cases per 100,000 in 2000 to 1.51 cases per 100,000 in 2005; P < .001) (figure 1B). The majority of nationally reported cases were laboratory-confirmed meningitis (1667 [78%] of 2135 cases); 244 of these cases yielded positive results of both CSF culture and blood culture. Four hundred sixty-four (22%) of 2135 patients presented with meningococcemia alone, and 4 cases were diagnosed by joint fluid culture. Since 2003, we have identified 46 culture-negative cases that fulfilled the surveillance case definition (25 cases in 2003, 11 in 2004, and 10 in 2005).

For all cases that occurred during 2000–2005, there were...
isolates available for 1582 (74%) for serogrouping and other characterization (table 1). The percentage of cases of disease caused by serogroup W135 increased from 5% (10 of 198 cases) in 2000 to 62% (257 of 414 cases) in 2005 ($P<.001$). The majority of these cases (326 [80%] of 407 cases) were reported from Gauteng Province, where the percentage of cases of disease due to serogroup W135 increased from 7% (4 of 54 cases) in 2000 to 75% (221 of 295 cases) in 2005. The incidence of serogroup W135 disease increased in this province from 0.06 cases per 100,000 population in 2000 to 2.99 cases per 100,000 population in 2005 ($P<.001$) (figure 1A). During the same period, the incidence of serogroup A disease in Gauteng Province was lowest in 2000 (0.21 cases per 100,000 population); it increased to ~1 case per 100,000 population during 2001–2003 and decreased to 0.25 cases per 100,000 population in 2005 ($P<.001$ for 2003–2005). For the period 2000–2003, a total of 201 (48%) of 418 cases of disease were due to serogroup A, with the number decreasing to 18 (6%) of 295 cases in 2005. The incidence of serogroup Y disease remained stable. In Western Cape Province, the overall incidence of meningococcal disease decreased over time ($P<.001$); this was mainly the result of a decrease in the incidence of serogroup B disease ($P<
Endemic W135 Disease in South Africa

Figure 2. *Neisseria meningitidis* serogroup W135 isolates (n = 406) causing invasive meningococcal disease in South Africa, by PFGE pattern and year, 2000–2005.

.001) (figure 1B). The incidence of disease due to serogroup Y and C remained stable.

During the 6-year period we analyzed, 92 (6%) of 1579 meningococcal isolates were not susceptible to penicillin (peak MIC, 0.25 μg/mL). The proportion of nonsusceptible isolates fluctuated by year, from 5 (3%) of 198 isolates in 2000 to a peak of 33 (13%) of 264 isolates in 2003. Children aged ≤5 years accounted for 45 (51%) of 88 penicillin-nonsusceptible isolates and 612 (45%) of 1369 penicillin-susceptible isolates (P = .24). Penicillin-nonsusceptible isolates were reported from all provinces and occurred in all serogroups (7 [2%] of 316 serogroup A isolates, 28 [7%] of 417 serogroup B isolates; 9 [7%] of 134 serogroup C isolates, 25 [6%] of 406 serogroup W135 isolates, and 23 [8%] of 289 serogroup Y isolates). All 1578 isolates tested were susceptible to ceftriaxone, chloramphenicol, and ciprofloxacin, and 6 isolates were resistant to rifampin.

**Characterization of serogroup W135 isolates.** PFGE results were available for 377 (93%) of 406 serogroup W135 isolates, of which 20 arbitrarily selected strains were further characterized by MLST. The isolates were found to be highly clonal by PFGE, with 1 distinct cluster (cluster 1) representing 350 (93%) of all 377 isolates. Eighty percent of isolates in this cluster were indistinguishable or differed by a single band from the pattern demonstrated by 2 Hajj-related outbreak isolates from 2000 (data not shown) [12]. All 13 selected isolates from this cluster were ST-11, of the ST-11/ET-37 complex. The proportion of isolates in cluster 1 increased from the first year, remaining high in the subsequent 5 years: 5 (50%) of 10, 12 (92%) of 13, 18 (82%) of 22, 19 (79%) of 24, 70 (92%) of 76, and 226 (97%) of 232 isolates for each year, respectively, and followed a seasonal pattern (figure 2). The majority of isolates from cluster 1 were from Gauteng Province (285 [81%] of 350 isolates), although isolates were identified in all 9 provinces. In provinces excluding Gauteng Province, 65 (87%) of 75 serogroup W135 isolates with PFGE results belonged to this cluster, whereas in Gauteng Province, 285 (95%) of 301 serogroup W135 PFGE patterns were identified as cluster 1 (P < .001). Seven representative strains from Gauteng Province belonged to the ST-11/ET-37 complex.

The remaining isolates comprised 1 small cluster of 12 (3%) of 377 isolates (cluster 2), a cluster of 4 isolates (1%; cluster 3), and 11 isolates that did not belong to any cluster. One isolate from cluster 2 was confirmed to be ST-4241 (ST-22 complex), and the 5 nonclustered isolates were ST-175, ST-3687, ST-4079 (ST-103 complex), ST-3181 (ST-22 complex), and ST-5753 (a new ST). One additional nonclustered isolate was identified as belonging to the ST-1 complex/subgroup I/II.
Descriptive epidemiology of meningococcal disease in Gauteng Province. In Gauteng Province, during the 6-year period reviewed, 889 (80%) of 1113 cases were classified as laboratory-confirmed meningitis, whereas 221 cases (20%) were classified as meningococcemia; 3 cases were diagnosed on the basis of positive joint fluid culture results. Six hundred fifty-eight (62%) of 1066 cases occurred in male patients. The median age of patients with serogroup A disease (during 2000–2005) was 21 years (interquartile range, 8–26 years), compared with 5 years (interquartile range, 2–23 years) for serogroup W135 disease ($P < .001$). Of the patients with a known age in 2004, the highest rates of disease for serogroup A and W135 disease occurred among infants aged <1 year (figure 3). Thirty-nine (85%) of 46 cases of serogroup A disease occurred among persons aged >4 years, compared with 32 (59%) of 54 cases of serogroup W135 disease ($P = .005$). The incidence of serogroup W135 disease increased for all age groups, but the most notable increase occurred among infants aged <1 year (from 5.08 cases per 100,000 population in 2003 to 21.45 cases per 100,000 population in 2005; $P < .001$).

From 2003 through 2005, case report forms were completed for 254 (79%) of 320 patients admitted to enhanced surveillance hospitals in Gauteng Province. There were no statistically significant differences in demographic characteristics between patients at sentinel sites with case report forms and those without case report forms; the only difference between patients who presented to sentinel sites versus those who presented to other hospitals in Gauteng Province was that a greater percentage of those who presented to sentinel sites received diagnoses on the basis of blood culture results in 2004.

When compared with serogroup A disease in univariate analysis, serogroup W135 disease was found to be more likely to affect children aged <5 years and to cause meningococcemia rather than meningitis (table 2). In multivariable analysis, the year of specimen collection, age <5 years, and meningococcemia were significantly associated with serogroup W135 disease.

Overall, case-fatality rates increased from 11% (6 of 53 patients) in 2003 to 22% (32 of 142 patients) in 2005 ($P = .045$). Among patients with invasive serogroup A or W135 disease, factors associated with death in univariate analysis were age of 25–44 years, infection with serogroup W135, and meningococcemia (table 3). In multivariable analysis, age group and meningococcemia were significantly associated with death; there was a marginal association between serogroup W135 infection and increased risk of dying (adjusted OR, 3.21; $P = .058$).

All cases reported to the surveillance network were considered to be sporadic, with the exception of a cluster of cases in 2005. These cases were part of an institutional outbreak of infection in an overcrowded residence for young adults identified in Gauteng Province. It involved 13 laboratory-confirmed cases over a period of 8 months, and 4 patients had isolates available for serogrouping; all were confirmed to be serogroup W135. No other geographic clustering or epidemiologically linked cases were identified.

Figure 3. Annual age-specific incidence for confirmed serogroup A and W135 invasive meningococcal disease in Gauteng Province, South Africa, as reported in 2004. *Serogroup-specific disease rates were calculated assuming that the distribution of serogroups for cases with missing serogroup data ($n = 31$; 17% of total reported) was the same as the distribution for cases with serogroup information available.
Endemic W135 Disease in South Africa • CID 2008:46 (1 February) • 383

DISCUSSION

The rate of invasive meningococcal disease in Gauteng Province doubled from 2003 to 2005. This increase was associated with a decrease in the incidence of serogroup A and the emergence of a clone of serogroup W135. Selected isolates of this clone were confirmed as belonging to the hypervirulent ST-11/ET-37 complex, (W)ET-37 clone, a strain that re-emerged internationally during a Hajj-related outbreak of meningococcal disease in 2000 [17]. Preliminary analysis of data from 2006 suggest that the emergence of serogroup W135 is sustained [36].

The overall case-fatality rate in Gauteng Province doubled from 2003 to 2005. We found that the (W)ET-37 clone was associated with meningococcemia, as was described in an outbreak in Saudi Arabia and in sporadic serogroup W135 disease in Taiwan [37, 38]. In addition, we report an increased case-fatality rate, compared with that for serogroup A; this was of borderline statistical significance in multivariable analysis, whereas meningococcemia was independently associated with serogroup W135 disease and with increased risk of death. Meningococcemia is well described to have a higher case-fatality rate than meningitis [1]. Previous clinical descriptions of disease due to this clone have reported an association with clinical severity but not with mortality [37, 38].

The increase in incidence of serogroup W135 disease goes beyond serogroup redistribution and is consistent with the introduction of antigens distinct meningococci [39–42]. In outbreaks caused by new strains for which there is little herd immunity, older persons generally are at increased risk of disease [39, 43]. This was not seen in our setting and may reflect immunity to this strain among older persons or an age-dependent risk factor (e.g., viral coinfection in infants) [1]. Serogroup-specific differences in age distribution have been reported elsewhere; in Burkina Faso, the highest rates of serogroup W135 meningitis occurred among infants, compared with serogroup A, which occurred among older children [44]. In contrast, sporadic serogroup W135 disease among 30 patients in Taiwan predominantly affected adults [38]. Most cases in Gauteng Province in 2005 were presumed to have been sporadic, with only 1 outbreak identified. In addition, our observations that infants were the most affected, that disease was seasonal, and that cases occurred throughout the province suggest that this strain has become endemic.

Although data are limited, to our knowledge, serogroup W135 has not been recognized as the predominant cause of sporadic or endemic disease in any of the countries where it has emerged, despite the potential, particularly in the African meningitis belt [16, 44]. This may have resulted from a lack of ongoing laboratory-based surveillance in some regions. Serogroup W135 has become a recognized cause of epidemic and endemic disease, and a multivalent conjugate vaccine may hold more promise than a monovalent serogroup A conjugate vaccine currently under development for use in this region [4].

It is of concern that this (W)ET-37 clone is causing severe endemic disease in South Africa. Meningococci belonging to the ST-11/ET-37 complex have been described as a hyperinvasive lineage, and serogroup C isolates belonging to this complex caused increased morbidity and mortality in Europe, Canada, and the United States in the 1990s, leading to a decision to introduce routine infant vaccination with the conjugate monovalent serogroup C vaccine in the United Kingdom [41,

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mortality rate, no. of deaths/no. of patients (%)</th>
<th>Univariate analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>15/76 (20)</td>
<td>Reference .81</td>
<td>...</td>
</tr>
<tr>
<td>Male</td>
<td>20/109 (18)</td>
<td>0.91 (0.43–1.92)</td>
<td>...</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>8/72 (11)</td>
<td>Reference &lt;.001</td>
<td></td>
</tr>
<tr>
<td>5–14</td>
<td>5/25 (20)</td>
<td>2.0 (0.59–6.81)</td>
<td>.001</td>
</tr>
<tr>
<td>15–24</td>
<td>5/38 (13)</td>
<td>1.21 (0.37–4.0)</td>
<td></td>
</tr>
<tr>
<td>25–44</td>
<td>17/46 (37)</td>
<td>4.69 (1.82–12.10)</td>
<td></td>
</tr>
<tr>
<td>&gt;44</td>
<td>0/4 (0)</td>
<td>Undefined</td>
<td></td>
</tr>
<tr>
<td>Syndromea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>12/135 (9)</td>
<td>Reference &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Meningococcemia</td>
<td>23/48 (48)</td>
<td>8.11 (4.02–16.31)</td>
<td>.001</td>
</tr>
<tr>
<td>Serogroup</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>4/50 (8)</td>
<td>Reference .01</td>
<td>...</td>
</tr>
<tr>
<td>W135</td>
<td>31/135 (23)</td>
<td>3.42 (1.14–10.27)</td>
<td>...</td>
</tr>
<tr>
<td>HIV infection status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seronegative</td>
<td>8/81 (13)</td>
<td>Reference .27</td>
<td>...</td>
</tr>
<tr>
<td>Seropositive</td>
<td>11/53 (21)</td>
<td>1.74 (0.64–4.70)</td>
<td>...</td>
</tr>
<tr>
<td>Strain’s susceptibility to penicillin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Susceptible</td>
<td>32/177 (18)</td>
<td>Reference .17</td>
<td>...</td>
</tr>
<tr>
<td>Nonsusceptible</td>
<td>3/8 (38)</td>
<td>2.72 (0.62–11.96)</td>
<td></td>
</tr>
<tr>
<td>Year of infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>4/30 (13)</td>
<td>Reference .1</td>
<td>...</td>
</tr>
<tr>
<td>2004</td>
<td>5/43 (12)</td>
<td>1.67 (0.29–4.77)</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>26/112 (23)</td>
<td>2.30 (0.82–6.44)</td>
<td>...</td>
</tr>
</tbody>
</table>

* Two cases of arthritis with positive synovial fluid culture results were excluded.

45]. It has been postulated that the (W)ET-37 clone may have emerged as a result of a capsular switch from serogroup C strains many years ago, because the clone has been identified since at least 1970 [17]. The South African clone was indistinguishable by PFGE from the Hajj-related outbreak strains from 2000, suggesting the possibility of reintroduction of this strain during the international outbreak. Serogroup W135 isolates belonging to this complex, however, were recognized in South Africa in 1986 and have been recognized elsewhere in Africa at least since 1993 [11, 17].

Because our laboratory-based surveillance system excludes disease diagnosed clinically without laboratory confirmation, observed rates represent a minimum estimate of the full burden of disease. However, the number of reported cases in Gauteng Province (before the increase in 2005) are similar to published figures of clinical disease notified to the South African Department of Health, with reports of 150–200 cases per year during the peak years since 1977 [19]. The recent reduction in the incidence of serogroup B disease in Western Cape Province has also been confirmed by clinical notifications [46]. The increase in reported cases without viable isolates in 2001 may have been due, in part, to audits that identified nonreporting laboratories and to increased awareness of the surveillance network as it became established. Although the number of laboratories increased over the years, most improvements occurred before the disease changes we describe. Audits estimated that >80% of all cases of laboratory-confirmed disease were reported to the network. Patients who died before presenting for care would also have been missed by the surveillance network. Clinical practice and laboratory diagnostics did not change systematically over the time reviewed.

Serogroup W135 has become the predominant serogroup in Gauteng Province and has caused severe disease in infants. Other countries in Africa, especially those where serogroup A disease is common, would benefit from routine, interepidemic laboratory-based surveillance. The potential importance of serogroup W135 disease should be considered in global vaccine development strategies.
THE GROUP FOR ENTERIC, RESPIRATORY AND MENINGEAL DISEASE SURVEILLANCE IN SOUTH AFRICA

Sandeep Vasaikar (University of Transkei, Mthatha, Eastern Cape); Nolan Janse van Rensburg and Peter Smith (University of the Free State, Bloemfontein, Free State); Khatija Ahmed, Ruth Lekalakala, and Pyu-Pyu Sein (University of Limpopo–Medunsa Campus, Garankuwa, Gauteng); Heather Crewe-Brown, Charles Feldman, Alan Karstaedt, and Olga Perovic (University of the Witwatersrand, Johannesburg, Gauteng); Mike Dove (University of Pretoria, Pretoria, Gauteng); Wim Sturm and Trusha Vannali (University of KwaZulu-Natal, Durban, KwaZulu-Natal); Ken Hamese (Polokwane/Mankweng Hospital Complex, Polokwane, Limpopo); Keith Bauer and Charles Mutanda (National Health Laboratory Service, Mpumalanga); Rena Hoffmann and Lynne Liebowitz (University of Stellenbosch, Stellenbosch, Western Cape); John Simpson and Andrew Whitelaw (University of Cape Town, Cape Town, Western Cape); Adrian Brink (AMPATH laboratories, Johannesburg, Gauteng); Claire Heney (Lancet laboratories, Johannesburg, Western Cape); and John Frean, Karen Keddy, Kerrigan McCarthy, Vanessa Quan, and Koshika Soma (National Institute for Communicable Diseases, Johannesburg, Gauteng)

Acknowledgments

We thank all laboratory and clinical staff throughout South Africa for contributing to national surveillance. We also thank Olga Hattingh, Kedibone Mothibeli, Ruth Mpembere, Thomas Rafundisani, Happy Skosana, and Nicole Wolter, for technical expertise and assistance; Muzi Hlanzi and Ethel Maringa, for data management; and Leonard Mayer and Thomas Clark, for kind review of the manuscript.

Financial support. National Institute for Communicable Diseases/National Health Laboratory Service, Centers for Disease Control and Prevention (cooperative agreement U60/CCU020088) and US Agency for International Development’s Antimicrobial Resistance Initiative.

Potential conflicts of interest. All authors: no conflicts.

References


