Burden of Meningitis and Other Severe Bacterial Infections of Children in Africa: Implications for Prevention

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Apart from meningococcal disease in the sub-Saharan meningitis belt, the incidence and impact of life-threatening bacterial diseases in children across Africa have not been quantified. The clinical and epidemiological data on pneumococcal, *Haemophilus influenzae* type b (Hib), and other forms of bacterial meningitis, as well as data on other severe bacterial infections throughout the continent were scrutinized. Pneumococci were the leading causative agents of nonepidemic meningitis and other bacteremic diseases, followed by Hib. Meningococcal diseases were less common. Mortality rates associated with pneumococcal, Hib, and meningococcal meningitis were 549 (45%) of 1211 patients, 389 (29%) of 1352 patients, and 104 (8%) of 1236 patients, respectively; sequelae occurred in 50%, 40%, and 10% of cases. At 0–4 years of age, the estimated incidences of Hib meningitis and all classic Hib diseases were 70 and 100 cases per 100,000 population per year, accounting for approximately 90,000 and 120,000 cases per year, respectively. Including older age groups and, especially, nonbacteremic Hib pneumonia in the estimates of Hib disease in Africa increased the overall numbers manifold; the numbers of pneumococcal infections were even greater. The only realistic way to combat these severe infections efficaciously would be through widespread vaccination, starting with Hib conjugates.

The attention given to epidemics of meningococcal meningitis in the sub-Saharan meningitis belt [1, 2] tends to distort the overall picture of serious bacterial diseases in children during nonepidemic periods in Africa. Nontuberculous meningitis is a common life-threatening infection throughout Africa; in Nigeria, ≈1 in 60 infants dies of nontuberculous meningitis, a rate similar to the death rate of 1 in 20 infants for malaria or pneumonia [2]. The symptoms and signs are usually recognized, and most patients receive medical attention [2] (provided that any reasonable health care exists).

Consequently, fairly reliable information on its occurrence is available throughout the continent. This study surveyed the major bacterial pathogens affecting the 320 million children aged 0–14 years [3] in Africa. The epidemiology and outcomes of each disease (particularly for those aged 0–4 years) were delineated, and the preventive potential of existing vaccines for these life-threatening diseases was explored. Because meningococcal infections are well characterized [1, 2, 4–7], this analysis focused on infections caused by other pathogens. Of special interest were *Streptococcus pneumoniae* and *Haemophilus influenzae*, which, with the meningococcus, cause more than four-fifths of the cases of childhood meningitis elsewhere in the world [8, 9]. This first overall survey of Africa is timely because infections caused by *H. influenzae* type b (Hib) could be a target for vaccination [10, 11] even sooner than those caused by pneumococci.
PATIENTS AND METHODS

Cases diagnosed by means of positive culture or Gram stain of blood, CSF, or other normally sterile body fluids, or by means of lung-tap specimens were considered to be of bacterial etiology. Cases of meningitis in which latex agglutination or counterimmunoelectrophoresis tests of CSF were positive [12] were also included.

All modern data-search techniques were used, although some information was obtained from scientific meetings. Publications prior to the 1960s were excluded. If 2 sources provided essentially the same information, the latest or the larger series was used. Most of the articles included were in English, although many concerning West Africa were published in French. Very few relevant papers were published in other languages.

Incidence data were a priority, as were data obtained from prospective studies. For all of Africa, insufficient information prevented thorough analyses for agents other than Hib, but the incidence rates were calculated both for Hib meningitis and for all classic Hib infection manifestations, excluding nonbacteremic pneumonia. By combining all information, we could estimate the overall number of invasive Hib diseases in Africa.

For all demographic calculations, World Bank statistics [3] were used. According to these data, there were 719,202,000 people living in all of Africa in 1995; of these 121,483,000 (16.9%) were aged 0–4 years.

RESULTS

Meningitis

Table 1 lists 50 studies of bacterial meningitis in 25 countries and regions [13–62]. Prospectively collected data were obtained from Burkina Faso [13], Cameroon [15], Ghana [31], Libya [39], Nigeria [46, 48], South Africa [56, 57], Swaziland [59], and Zambia [61]. More than 30,000 cases were reported overall, but in only 37 studies (total no. of patients, 27,170) were both the total number of cases and the number of those infected with a particular agent disclosed; the average was 59% (16,129 of 27,170). In some studies, laboratory confirmation was successful in less than half of reported cases.

H. influenzae, pneumococcus, and meningococcus were the 3 leading microbial agents identified. In 11 series, at least 25% of cases were caused by other bacteria (Table 1), usually Salmonella species. This agent might be increasing in importance as a result of the AIDS epidemic [59, 63]. In Rwanda, where 30% of fertile women were positive for HIV [64], 13% of childhood bacterial meningitis was due to Salmonella species. Some authors regarded malnutrition as a risk factor [14], but others did not [41].

Pneumococcus was the most common agent in 20 (40%) of the 50 reports and was the second most common in another 19 (38%); the respective figures for H. influenzae were 11 (22%) and 13 (26%), and those for meningococcus were 13 (26%) and 10 (20%). It is not surprising that H. influenzae was of greater importance when only the pediatric cases were considered; sometimes it was more common than meningococcus, even in the meningitis belt: in Burkina Faso in 1986–1990 [13] and in northwestern Ethiopia in 1990–1994 [27]. This reflects the epidemic nature of meningococcal disease. When H. influenzae isolates were serotyped, 94%–100% were of type b (Hib) [11, 54, 65–67].

Figure 1 shows the distribution of Hib, pneumococci, meningococci, and other agents (usually Salmonella) in 9 regions within and 10 regions outside the meningitis belt [1, 2]. Although ≤95% of cases in the belt could be attributed to meningococci [33], in some studies the organism was not found there at all [15, 28]. Overall, pneumococci and Hib, not meningococci, were the most common causes of meningitis in Africa. In no study did pneumococci account for >50% of all cases, whereas this occurred twice with Hib [15, 58] and 3 times with meningococci [16, 24, 33].

A slight male predominance was observed in most studies, although whether this was mainly due to biological or social factors is unknown. Whether subjects with the SS hemoglobin genotype were especially prone to develop meningitis with bacterial species other than S. pneumoniae [2] varied by study: in Congo, an association with Hib disease was reported [19, 68], whereas in Zambia [61], The Gambia [65], and surrounding Senegal [69], it was not.

Complications and Sequelae

Differences in definitions prevented firm conclusions about the frequency of complications and sequelae. Subdural effusion, which often accompanies infant meningitis [70], was considered a complication in some studies, whereas in others, only events persisting long after discharge from the hospital were included. According to data culled from several resources, it is estimated that approximately half of the patients with meningitis developed long-term sequelae.

Seven studies evaluated sequelae according to etiology [13, 14, 25, 41, 43, 59, 71]. In 2 prospective studies (in Burkina Faso [13] and Swaziland [59]), Hib, rather than S. pneumoniae, proved to be the most likely bacterial species to lead to sequelae in patients recovering from bacterial meningitis; the rates in the Burkina Faso and Swaziland were 14% and 38% for Hib, 5% and 16% for pneumococci, and zero and 20% for meningococci, respectively. In contrast, a recent survey in The Gambia [71] revealed long-term sequelae (determined at examinations performed 11–90 months after illness) in 58% of cases of pneumococcal meningitis, compared with 38% of cases of Hib meningitis.

High rates of sequelae after Hib disease also emerged in 4 retrospective studies in Cameroon [14], Ethiopia [25], Malawi
Table 1. Etiology of bacterial meningitis in persons in Africa.

<table>
<thead>
<tr>
<th>Reference, country, city</th>
<th>Year(s) of study</th>
<th>Age</th>
<th>n</th>
<th>Bacteriologically confirmed, no. (%)</th>
<th>Hib</th>
<th>Pneumococci</th>
<th>Meningococci</th>
<th>Other a</th>
</tr>
</thead>
<tbody>
<tr>
<td>[15] Chad b</td>
<td>1980s a</td>
<td>2 mo to 8 y</td>
<td>64</td>
<td>49 (77)</td>
<td>57</td>
<td>37</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>[16] Chad b</td>
<td>1968–71</td>
<td>All ages</td>
<td>1445</td>
<td>1291 (89)</td>
<td>2</td>
<td>6</td>
<td>91</td>
<td>1</td>
</tr>
<tr>
<td>[18]</td>
<td>1970</td>
<td>ND</td>
<td>ND</td>
<td>156 (ND)</td>
<td>38</td>
<td>28</td>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>[19]</td>
<td>1960s–70s</td>
<td>≤15 y</td>
<td>553</td>
<td>303 (55)</td>
<td>38</td>
<td>27</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>[20]</td>
<td>1973–75</td>
<td>&lt;1 y</td>
<td>140</td>
<td>63 (45)</td>
<td>19</td>
<td>57</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>[21] Egypt</td>
<td>1971–75</td>
<td>All ages</td>
<td>1333</td>
<td>906 (68)</td>
<td>4</td>
<td>12</td>
<td>82</td>
<td>2</td>
</tr>
<tr>
<td>[22]</td>
<td>1977–78</td>
<td>All ages</td>
<td>1627</td>
<td>276 (47)</td>
<td>12</td>
<td>41</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>[23]</td>
<td>1966–89</td>
<td>All ages</td>
<td>5294</td>
<td>3211 (61)</td>
<td>10</td>
<td>18</td>
<td>66</td>
<td>6</td>
</tr>
<tr>
<td>Ethiopia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[26] Addis Abeba</td>
<td>1983–84</td>
<td>96% &lt;15 y</td>
<td>ND</td>
<td>53 (ND)</td>
<td>30</td>
<td>59</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>[27] Gonder b</td>
<td>1990–94</td>
<td>&lt;15 y</td>
<td>132</td>
<td>85 (64)</td>
<td>40</td>
<td>20</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>[28] Gabon</td>
<td>1983–84</td>
<td>≤15 y</td>
<td>30</td>
<td>25 (83)</td>
<td>16</td>
<td>40</td>
<td>0</td>
<td>44</td>
</tr>
<tr>
<td>[29] The Gambia b</td>
<td>1991–94</td>
<td>≤15 y</td>
<td>420</td>
<td>269 (64)</td>
<td>42</td>
<td>41</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>[31]</td>
<td>1989–90 a</td>
<td>3 mo to 14 y</td>
<td>ND</td>
<td>69 (ND)</td>
<td>14</td>
<td>51</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>[32]</td>
<td>1991–93</td>
<td>2 mo to 12 y</td>
<td>103</td>
<td>73 (71)</td>
<td>10</td>
<td>48</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>[33] Guinea b</td>
<td>1993</td>
<td>All ages</td>
<td>24</td>
<td>21 (88)</td>
<td>5</td>
<td>0</td>
<td>95</td>
<td>0</td>
</tr>
<tr>
<td>[34] Ivory Coast</td>
<td>1971–75</td>
<td>All ages</td>
<td>1393</td>
<td>833 (60)</td>
<td>14</td>
<td>39</td>
<td>6</td>
<td>41</td>
</tr>
<tr>
<td>[35]</td>
<td>1985–86</td>
<td>&lt;15 y</td>
<td>1392</td>
<td>839 (60)</td>
<td>23</td>
<td>46</td>
<td>7</td>
<td>24</td>
</tr>
<tr>
<td>[36]</td>
<td>1985–86</td>
<td>&lt;15 y</td>
<td>150</td>
<td>125 (83)</td>
<td>54</td>
<td>29</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>[37] Kenya</td>
<td>1970–81</td>
<td>All ages</td>
<td>ND</td>
<td>1631 (ND)</td>
<td>10</td>
<td>25</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>[38]</td>
<td>1985–86</td>
<td>≤12 y</td>
<td>ND</td>
<td>129 (ND)</td>
<td>19</td>
<td>25</td>
<td>12</td>
<td>44</td>
</tr>
<tr>
<td>[39] Libya b</td>
<td>1994–95</td>
<td>1 mo to 10 y</td>
<td>77</td>
<td>60 (78)</td>
<td>43</td>
<td>33</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>[40] Malawi</td>
<td>1972–73</td>
<td>All ages</td>
<td>177</td>
<td>ND (ND)</td>
<td>32</td>
<td>28</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>[41]</td>
<td>1996–97</td>
<td>≤15 y</td>
<td>267</td>
<td>174 (65)</td>
<td>25</td>
<td>35</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td>[42] Mali b</td>
<td>1979–91</td>
<td>All ages</td>
<td>2882</td>
<td>1541 (60)</td>
<td>29</td>
<td>21</td>
<td>50</td>
<td>0.2</td>
</tr>
<tr>
<td>[43] Mali and Niger b</td>
<td>1989–90</td>
<td>≥2 mo</td>
<td>528</td>
<td>426 (81)</td>
<td>31</td>
<td>27</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>[44] Mozambique</td>
<td>1989</td>
<td>2 mo to 6 y</td>
<td>70</td>
<td>51 (73)</td>
<td>24</td>
<td>49</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>Nigeria</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[45] Lagos</td>
<td>1970–73</td>
<td>&lt;13 y</td>
<td>410</td>
<td>246 (60)</td>
<td>17</td>
<td>38</td>
<td>31</td>
<td>14</td>
</tr>
<tr>
<td>[46] Ibadan</td>
<td>1976–80 a</td>
<td>≤10 y</td>
<td>ND</td>
<td>463 (ND)</td>
<td>28</td>
<td>34</td>
<td>6</td>
<td>32</td>
</tr>
<tr>
<td>[47] Benin City</td>
<td>1974–79</td>
<td>≤16 y</td>
<td>ND</td>
<td>34 (ND)</td>
<td>12</td>
<td>56</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>[48] Benin City</td>
<td>1986–89 a</td>
<td>1 mo to 6 y</td>
<td>22</td>
<td>13 (59)</td>
<td>8</td>
<td>38</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td>[49] Calabar</td>
<td>1981–84</td>
<td>1 mo to 12 y</td>
<td>ND</td>
<td>25 (ND)</td>
<td>24</td>
<td>48</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>[50] Maiduguri b</td>
<td>1988–92</td>
<td>1 mo to 14 y</td>
<td>107</td>
<td>75 (70)</td>
<td>12</td>
<td>29</td>
<td>36</td>
<td>23</td>
</tr>
<tr>
<td>[51] Enugu</td>
<td>1979–83</td>
<td>≤15 y</td>
<td>107</td>
<td>69 (64)</td>
<td>16</td>
<td>41</td>
<td>16</td>
<td>27</td>
</tr>
<tr>
<td>[52] Enugu</td>
<td>1989–93</td>
<td>≤15 y</td>
<td>1964</td>
<td>76 (4)</td>
<td>5</td>
<td>38</td>
<td>8</td>
<td>49</td>
</tr>
<tr>
<td>[53] Rwanda</td>
<td>1983–90</td>
<td>≤15 y</td>
<td>389</td>
<td>321 (82)</td>
<td>31</td>
<td>36</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>[54] Senegal</td>
<td>1970–81</td>
<td>All ages</td>
<td>4082</td>
<td>3125 (77)</td>
<td>29</td>
<td>39</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>[55] South Africa</td>
<td>1980–82</td>
<td>&lt;14 y</td>
<td>ND</td>
<td>321 (ND)</td>
<td>27</td>
<td>20</td>
<td>33</td>
<td>20</td>
</tr>
<tr>
<td>[56]</td>
<td>1981–84 a</td>
<td>&lt;14 y</td>
<td>422</td>
<td>281 (67)</td>
<td>17</td>
<td>12</td>
<td>50</td>
<td>21</td>
</tr>
<tr>
<td>[57]</td>
<td>1991–92 a</td>
<td>1 mo to 13 y</td>
<td>251</td>
<td>208 (83)</td>
<td>36</td>
<td>12</td>
<td>49</td>
<td>3</td>
</tr>
<tr>
<td>[58] Sudan</td>
<td>1985–86</td>
<td>3 mo to 14 y</td>
<td>96</td>
<td>44 (46)</td>
<td>57</td>
<td>16</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>[59] Swaziland</td>
<td>1991–92 a</td>
<td>All ages</td>
<td>85</td>
<td>51 (69)</td>
<td>16</td>
<td>49</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>[60] Togo b</td>
<td>1975–76</td>
<td>≤12 y</td>
<td>37</td>
<td>26 (70)</td>
<td>8</td>
<td>50</td>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td>[61] Zambia</td>
<td>1978–79 a</td>
<td>&lt;14 y</td>
<td>155</td>
<td>86 (56)</td>
<td>14</td>
<td>37</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>[62]</td>
<td>1980–81</td>
<td>≤15 y</td>
<td>219</td>
<td>176 (80)</td>
<td>8</td>
<td>36</td>
<td>12</td>
<td>44</td>
</tr>
</tbody>
</table>

NOTE. Dem. Rep., Democratic Republic; ND, no data available.

a At least partly prospective case collection.
b Regions in the meningitis belt.
Figure 1. Role of *Haemophilus influenzae* (Hib), pneumococcus (Pnc), meningococcus (Mnc), and other causative agents in childhood meningitis in Africa, among cases of proven etiology [13–62].

Permanent sequelae were often severe. Although such outcomes reported from high-quality centers were understandably few, every fifth case (21%) of profound deafness of known cause in Nigeria was due to meningitis [72], and even blindness resulted from the illness [51]. On the basis of data culled from several studies, it is estimated that approximately 40% of those surviving Hib, 50% of those surviving pneumococcal meningitis, or 10% of those surviving meningococcal meningitis had long-term sequelae. In one study of 105 deaf and mute individuals, bacterial meningitis was the cause of sequelae in 9% [73]. Concomitant malarial parasitemia did not seem to worsen the prognosis [41].

**Case Fatality**

Mortality was high (table 2), and deaths were predominantly due to pneumococcal meningitis: the overall hospital case-fatality rate in 17 studies was 45% (549 of 1211 patients). For Hib meningitis the rate was 29% (20 studies; 389 of 1352); for meningococcal meningitis, 8% (14 studies; 104 of 1236); and for other cases, 22% (12 studies; 175 of 803). The annual mortality associated with meningitis in Senegal was 17–20 persons per 100,000 total population in the 1960s, compared with 16.9 per 100,000 (and 160 of 100,000 infants) in the 1970s [54].

These rates are higher than those published in textbooks, which mostly cite data from high-quality hospitals. In affluent Cape Town, the case-fatality rates for pneumococcal, Hib, and meningococcal meningitis were only 5 (19%) of 26 patients, 4 (5%) of 74 patients, and 1 (1%) of 101 patients, respectively [57]. What remained unreported were the children in Africa...
Table 2. Case-fatality rates for bacterial meningitis in persons in Africa.

<table>
<thead>
<tr>
<th>Reference, country</th>
<th>Year(s) of study</th>
<th>Hib</th>
<th>Pneumococcal</th>
<th>Meningococcal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>[74] Burkina Faso</td>
<td>1986–90a</td>
<td>NG/82 (22)</td>
<td>NG (55)</td>
<td>NG (17)</td>
<td>NG</td>
</tr>
<tr>
<td>[17]</td>
<td>1958–77</td>
<td>15/115 (13)</td>
<td>24/83 (33)</td>
<td>0/4 (0)</td>
<td>17/43 (40)</td>
</tr>
<tr>
<td>[21] Egypt</td>
<td>1971–75</td>
<td>9/35 (26)</td>
<td>33/105 (31)</td>
<td>35/74 (44)</td>
<td>33/427a (8)</td>
</tr>
<tr>
<td>[22]</td>
<td>1977–78</td>
<td>24/42 (57)</td>
<td>63/144 (44)</td>
<td>19/89 (21)</td>
<td>19/77 (25)</td>
</tr>
<tr>
<td>[23]</td>
<td>1966–89</td>
<td>NG/322 (39)</td>
<td>NG/574 (41)</td>
<td>NG/2128 (9)</td>
<td>NG/187 (44)b</td>
</tr>
<tr>
<td>[25] Ethiopia</td>
<td>1975–76</td>
<td>NG/50 (19)</td>
<td>NG/26 (39)</td>
<td>NG/30 (7)</td>
<td>NG</td>
</tr>
<tr>
<td>[27]</td>
<td>1990–94</td>
<td>NG/34 (29)</td>
<td>NG/17 (35)</td>
<td>NG/31 (16)</td>
<td>NG/50 (41)</td>
</tr>
<tr>
<td>[65] Gambia</td>
<td>1985–87a</td>
<td>28/77 (37)</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>[71]</td>
<td>1990–95a</td>
<td>40/123 (33)</td>
<td>73/134 (54)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>[31]</td>
<td>1989–90</td>
<td>3/10 (33)</td>
<td>13/35 (37)</td>
<td>4/24 (17)</td>
<td>NG</td>
</tr>
<tr>
<td>[36] Ivory Coast</td>
<td>1985–86</td>
<td>15/67 (22)</td>
<td>NG (35)</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>[41] Malawi</td>
<td>1996–97a</td>
<td>18/42 (43)</td>
<td>27/59 (46)</td>
<td>0/7 (0)</td>
<td>17/48 (35)</td>
</tr>
<tr>
<td>[53] Rwanda</td>
<td>1983–90</td>
<td>22/80 (27)</td>
<td>54/103 (52)</td>
<td>3/29 (10)</td>
<td>20/50 (40)</td>
</tr>
<tr>
<td>[69] Senegal</td>
<td>1973–77</td>
<td>82/248 (33)</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>[54]</td>
<td>1970–79</td>
<td>NG/671 (34)</td>
<td>NG/983 (60)</td>
<td>NG/366 (14)</td>
<td>NG/495 (50)</td>
</tr>
<tr>
<td>[75] Zambia</td>
<td>1970–71a</td>
<td>5/13 (39)</td>
<td>12/24 (50)</td>
<td>0/1 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cases with full information</td>
<td>389/1352 (29)</td>
<td>549/1211 (45)</td>
<td>104/1236 (8)</td>
<td>175/803 (22)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Dem Rep., Democratic Republic; ND, not determined; NG, not given.
a Prospective study.
b Applies to purulent meningitis.

who died at home or on the way to the hospital [32, 59], or because their parents could not afford treatment [41, 76]. Furthermore, deaths occurring in the hospital did not necessarily reflect overall mortality: in The Gambia, 7 (8%) of 90 children and 9 (13%) of 70 children, respectively, who initially survived Hib or pneumococcal meningitis later died of illnesses that were probably related to their earlier episodes of meningitis [71].

Little if any progress was observed during the past several years. Excluding South Africa, 4 studies undertaken in the 1990s (Ethiopia [27], The Gambia [29], Malawi [41], and Swaziland [59]) showed fatality rates that remain astonishingly high: 42% for pneumococcal, 29% for Hib, and 17% for meningococcal meningitis. In summary, of every 100 children with pneumococcal or Hib meningitis, <35 fully recovered, one-third died, and one-half of the survivors were left with serious long-term sequelae. Because of the great potential and wide availability of Hib conjugate vaccines, Hib diseases were more closely analyzed, especially since a recent review of infections due to *S. pneumoniae* has been published recently [77].

**Characteristics of Hib Diseases**

*Hib meningitis versus age.* Figure 2 depicts the cumulative percentage of Hib meningitis cases as a function of age in 4 countries in the meningitis belt [13, 50, 67, 74] and 5 elsewhere [14, 19, 23, 57, 69]. These data are compared with prevaccination data from Finland [78] and the United States [79]. In Africa, children developed illness considerably earlier than did those in industrialized countries (some indigenous populations are familiar exceptions [80]). Up to 80% of all cases of Hib meningitis developed during the first year of life.

*Disease spectrum.* Three prospective studies (figure 3) [11, 57, 67] confirmed that meningitis represents only 50%–75% of all manifestations of Hib disease in Africa. The other entities occurring are the same as elsewhere [8, 9], except that epig-
lottitis was entirely absent (as in indigenous populations) [79, 80]. The variety of Hib entities complicates their detection. One prospective survey of childhood bacteremia in South Africa [81] disclosed a 23% case-fatality rate for Hib bacteremia, versus 22% for pneumococcal and 25% for meningococcal bacteremia.

**Hib pneumonia.** Bacteremic pneumonia represented one-quarter to one-third of all invasive Hib diseases (figure 3). However, bacteremia is rare in pneumonia, and the observed rates for bacteremic pneumonia undoubtedly underestimated the true role of Hib in acute lower respiratory tract infections [11]. The “gold standard” procedure for etiological diagnosis is percutaneous lung tap (aspiration), and this technique has been practiced in Africa at least since the 1930s [82]. Lung tap results were available from Nigeria [83–86], The Gambia [11, 87, 88], and Zimbabwe [89], but unfortunately, major methodological problems in bacteriology were obvious in some study reports [85, 86].

In The Gambia, in 54%–79% of all lung tap–proven or blood culture–proven cases of H. influenzae pneumonia, Hib was identified as the pathogen [87, 88]. Even more important was the epidemiological finding that not only did Hib-tetanus-toxoid conjugate prevent 100% (95% CI, 55–100) of cases of proven Hib pneumonia, but cases of severe pneumonia with or without effusion were reduced by 25% (95% CI, 0.24–44.1) [11]. Evidently, Hib causes pneumonia more frequently (probably <25% of severe cases in young children), than the earlier estimate of 5%–10% that was based on a hospital series [90]. Malnourishment does not greatly change the ratio of cases due to pneumococci versus Hib [88].

**Treatment and antimicrobial resistance.** Serious infections considered potentially due to Hib were treated by the traditional and inexpensive (and often still very effective [91]) combination of penicillin G or ampicillin and chloramphenicol [41]. Despite clinical success [15, 31], antimicrobial resistance caused by β-lactamase and other mechanisms are an emerging problem [14, 31, 32, 37, 49, 66]; in Malawi, 20% and 50% of Hib meningitis strains were resistant to chloramphenicol and ampicillin, respectively [41]. Third-generation cephalosporins were used, resources permitting. However, 3% of H. influenzae invasive isolates were already resistant to cefotaxime in Mali [42]. In one Ghana hospital, an average of 3.6 drugs per patient were prescribed [92].

**Incidence and Case Numbers**

**Meningitis.** In the absence of large prospective population-based studies, the few incidence data available provided a basis for some tentative calculations. When the high peaks of meningococcal epidemics (when local attack rates sometimes exceeded 1000 cases per 100,000 individuals) were ignored [1, 7], the annual incidence for all bacterial meningitis in the general population varied from 18 to 50 cases per 100,000 individuals in Senegal [18, 54] and was 13.5 per 100,000 individuals in Swaziland [59]. When a rate of 25 cases per 100,000 individuals was assumed for all of Africa (population, 720 million) [3], there were ~180,000 cases of nonepidemic bacterial meningitis each year. If 50% of cases were caused by Hib (a fair
Figure 3. The spectrum of invasive Hib diseases in 2 patient series in The Gambia and 1 in South Africa (data are from [11, 57, 67]).

estimate on the basis of published epidemiological and laboratory data) there were 90,000 cases of Hib meningitis per year. Since the vast majority affected children before their fifth birthday (figure 2), the incidence of Hib meningitis in this age group (121 million) [3] could be estimated to be ~74 cases per 100,000 children per annum.

This calculation agrees with information obtained from 5 African countries (figure 4). In the same age group, the annual incidence of Hib meningitis (per 100,000 children) was 72 in Senegal [54], between 56 [67] and 60 [93] in The Gambia, 62 in Burkina Faso [13], 53 in Niger [94], and 51 among black children (and 25 among white children) in South Africa [57, 95]. The overall incidence for Hib meningitis among children aged 0–4 years in all of Africa (with a relatively small white population) might easily have been 70 cases per 100,000 children per year, or 85,000 cases annually. Since Hib meningitis also affects older children (in Senegal and Ethiopia, 4%–9% of cases occurred at ages 5–14 years [27, 69]) and some cases occur in adults, 100,000 might be an appropriate estimate for the annual number of cases of Hib meningitis in all age groups.

**Other Hib diseases.** Estimates of incidence for other Hib manifestations were more difficult. Data from The Gambia [67] and South Africa [57] indicated that among children aged 0–4 years, the rates for nonmeningitis Hib diseases were 17 and 13 cases per 100,000 children per year, respectively. Since 23%–44% of the culture-proven cases of Hib disease were manifestations other than meningitis (figure 3), one would expect [8, 9] the combined incidence of all classic Hib diseases to be at least 30% higher than the incidence for Hib meningitis alone. Hence, the overall rate was probably close to 100 cases per 100,000 children (as among black children in South Africa [57]) (figure 4), or 120,000 cases per year at age 0–4 years. For all age groups in Africa, 150,000 cases of classic Hib disease each year is probably a realistic estimate.

If nonbacteremic Hib pneumonia is included, the figures rise considerably. The diagnosis and specific role of Hib in childhood pneumonia are matters of continuous discussion [96, 97]. One study in The Gambia showed that 47% of children aged <5 years had acute lower respiratory tract infection each year [90], and 17% had radiological evidence of pneumonia. For all such children in Africa (121 million) [3], this suggests 10 million yearly cases of radiologically positive pneumonia. Were 20%–25% to be caused by Hib [11], the number of cases would be up to 2 million per annum. A much lower number (slightly more than 300,000 cases) results from an estimation that the Hib pneumonia rate among infants is 5 times that of Hib meningitis, suggesting a lifetime risk of 1250 per 100,000 infants [98]. Both estimates are crude; on the other hand, the incidence of respiratory infections varies. Data from 6 developing countries suggested an incidence of 0.2–4.0 episodes of acute lower respiratory tract infection per year for each child during the first 5 years of life [99]. Whatever the true figure may be, it is large and exceeds the number of cases of all classic Hib manifestations (figure 3), probably being somewhere between these extremes.

**Death Rates**

The high case-fatality rates for meningitis (table 2) do not reflect the overall fatality rate for all Hib diseases. Nevertheless, in The Gambia, mortality attributable to Hib meningitis in children <5 years was 23 per 100,000 per year [90]—a rate as high as the overall incidence of Hib meningitis in many European countries [9]. Generalizing this figure to all of Africa yields a rate of ~56,000 fatalities per year.
**Severe Childhood Bacterial Infections in Africa**

Figure 4. The incidence data from Senegal [54], The Gambia [67, 93], Burkina Faso [13], Niger [94], and South Africa [57, 95], combined with the information obtained from a field trial with Hib vaccine in The Gambia [11], suggest for Hib meningitis and all classic Hib diseases an overall incidence of approximately 70 cases and 100 cases, respectively, per 100,000 children aged 0–4 years (suggesting a rate of approximately 90,000 and 120,000 cases per year among children aged <5 years in Africa). Inclusion of nonbacteremic Hib pneumonia probably would increase the overall number of invasive Hib infections manifold. *, black children. Bars in entries for South Africa and The Gambia indicate the highest and lowest rates of incidence; the columns indicate the average rates of incidence.

This estimate seems high. On the other hand, not all patients receive medical attention [32, 59], and some children (7% in Malawi) [41] are removed from the hospital before recovery. Hence, the true numbers of deaths are probably greater than those (28,000 caused by Hib meningitis and 36,000 to all classic Hib manifestations per year) that derive from the assumptions that there were 85,000 cases of Hib meningitis and 120,000 cases of Hib disease in this age group and that, of these cases, one-third overall were fatal.

Estimating the mortality caused by all Hib diseases, including nonbacteremic pneumonia, was extremely difficult [96, 100]. Mortality associated with pneumonia in the prevaccination era in The Gambia [101] was approximately 16 and 2.6 cases per 1000 infants and children aged 1–4 years, respectively. If it is assumed that one-fourth of these cases were due to Hib [11], then 160,000 children (on the basis of a 30% fatality rate; table 2) died as a result of this pathogen each year. In reality, the annual mortality from all Hib infections and in all age groups combined in all of Africa might have been ~750,000 if the calculations suggesting >2 million cases of Hib disease per year (see above) are accepted. The wide amplitude of these estimates underlines the urgent need of prospective epidemiological studies in Africa.

**DISCUSSION**

The likely occurrence of >1 million cases of Hib disease and countless pneumococcal infections per year [102], together with startlingly high attack rates of meningococcal disease in the meningitis belt [1, 4, 7], reveals the grim truth that the number of cases in Africa, when compared with any Western country, is much greater. Not only are these infections fatal (table 2); they frequently leave survivors with severe long-term sequelae. In prewar Somalia, 25% of newborn children died within a few years, and in some villages mortality was 40% [103]. In a teaching hospital series in Ghana, pyogenic meningitis and septicemia were responsible for 10% of all childhood deaths, next only to accidents, respiratory infections, and malaria in frequency [104]. Even when children are brought to medical centers, treatment might not be given at all [76], may be interrupted [41, 46], or may be suboptimal [51], almost always because of economic constraints. With this background it should be stressed, with some exceptions [41], that no clinical evidence supports the use of costly newer antimicrobials over inexpensive ampicillin or chloramphenicol against meningitis [91] or most other severe infections. If this is forgotten, indiscriminate use of antimicrobials throughout Africa may result in uncontrollable problems.

A view shared by many [32, 43] is that rapid diagnosis and institution of therapy would improve the prognosis of these diseases. Poor communication, particularly in rural areas, may add to the risk of complications, but surprisingly few data exist to support this view. Early deaths were not related to delays in presentation in Ghana [31], Swaziland [59], or The Gambia [71], and in fact a short history carried a considerably worse
immunity and induces clinical protection in expensive. doses in vaccination schedules, and they would be convenient [114]. Use of combinations would avoid the need for extra accounts for only 10%±20% of the overall costs. Furthermore, the excellent immunogenicity of lower doses in one country does not guarantee similar immunogenicity elsewhere, as has been discovered [113, 114].

Another approach would be to combine different vaccines [114]. Use of combinations would avoid the need for extra doses in vaccination schedules, and they would be convenient to administer. However, vaccine combinations are also expensive.

The most practical and efficient approach to implementing Hib vaccination would be to reduce the number of doses. As seen in both industrialized [115] and nonindustrialized countries [11, 112], a single dose of Hib conjugate triggers T-cell immunity and induces clinical protection in ~50% of subjects [11]. Even this modest level of effectiveness would prevent death and serious long-term sequelae in hundreds of thousands of children in Africa each year. Since 2 vaccine doses increase protection to 90% [11, 115] and a third dose increases it by only another 5% [116], many European countries have virtually eradicated invasive Hib disease with the use of a total of 3 doses [117]. Furthermore, longstanding vaccine-induced immunity is not imperative, because natural immunity develops early in childhood. An additional benefit of Hib conjugates is their effect on herd immunity observed in Africa [118].

The tiny country of The Gambia was the first in the continent to show the effectiveness of countrywide Hib vaccination [119]. One expects to see this soon in all of Africa.

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