Bacterial Meningitis in Burkina Faso: Surveillance Using Field-Based Polymerase Chain Reaction Testing

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(See the editorial commentary by Robbins et al. on pages 26–7)

Background. In addition to frequent epidemics of group A meningococcal disease, endemic bacterial meningitis due mostly to Neisseria meningitidis, pneumococcus, and Haemophilus influenzae type b is a serious problem in sub-Saharan Africa. The improved ability to identify the etiologic agent in cases of bacterial meningitis will facilitate more rapid administration of precise therapy.

Methods. To describe the epidemiology of bacterial meningitis and evaluate the usefulness of field-based polymerase chain reaction (PCR) testing, we implemented population-based meningitis surveillance in Burkina Faso during 2002–2003 by use of PCR, culture, and antigen detection tests.

Results. Among persons aged 1 month to 67 years, the incidences of meningococcal meningitis, pneumococcal meningitis, and Haemophilus influenzae type b meningitis were 19 cases ( ), 17 cases ( ), and 7.1 n 179 n 162 cases ( ) per 100,000 persons per year, respectively. Of the cases of meningococcal meningitis, 72% were due to N. meningitidis serogroup W135. Pneumococcal meningitis caused 61% of deaths and occurred in a seasonal pattern that was similar to that of meningococcal meningitis. Of cases of pneumococcal meningitis and N. meningitidis serogroup W135 meningitis, 71% occurred among persons >2 years of age. Most patients, regardless of the etiology of their illness and the existence of an epidemic, received short-course therapy with oily chloramphenicol. Compared with culture as the gold standard, the sensitivity and specificity of PCR in the field were high; this result was confirmed in Burkina Faso and Paris.

Conclusions. Precise and rapid identification of etiologic agents is critical for improvement in the treatment and prevention of meningitis, and, thus, PCR should be considered for wider use in Africa. Vaccines against Streptococcus pneumoniae, N. meningitidis (including serogroup W135), and H. influenzae type b all will have a major impact on the bacterial meningitis burden. Antibiotic recommendations need to consider the importance of S. pneumoniae, even during the epidemic season.

Sub-Saharan Africa has experienced frequent epidemics of Neisseria meningitidis meningitis, mostly due to serogroup A [1–3], N. meningitidis serogroup W135 meningitis has been recognized since 1982 [4], but outbreaks have been documented only recently [5–8]. In addition, serogroup X has recently been associated with disease epidemics [9, 10]. The importance of endemic, as well as epidemic, bacterial meningitis in sub-Saharan Africa has also recently been reported [1, 11].

Surveillance of meningitis in Africa is hampered by difficulty with the timely transport of CSF specimens from outlying clinics to reference centers that have the capacity to identify etiologic agents and serogroups. The lack of field-based routine laboratory surveillance capacity may contribute to a failure to appreciate the contribution of such agents as Haemophilus influenzae and Streptococcus pneumoniae, in addition to meningococcal meningitis, to the overall burden of meningitis [1, 11], especially during the epidemic (or “dry”) season. PCR technology offers the possibility of overcom-
ing these obstacles. We conducted a prospective PCR-based meningitis surveillance study to document the meningitis burden due to various etiologic agents, to track the ongoing role of serogroup W135 in epidemics of meningococcal meningitis, and to evaluate the usefulness of PCR technology as a tool for conducting surveillance in the regions in Africa where meningitis is endemic (i.e., the African “meningitis belt”).

METHODS

Study sites. We conducted the study from April 2002 through April 2003 in 3 administrative districts of Burkina Faso, including 2 mainly urban districts centered around Bobo-Dioulasso (2002 population estimate, 646,856) and the adjacent, primarily rural, district of Hounde (2002 population estimate, 192,219). Both areas experience a climate typical of the sub-Saharan meningitis belt: a dry, or epidemic, season from November through April and a rainy season from May through October. Study site selection was based on the experience of previous meningitis epidemics and the availability of a reference laboratory in the areas selected. During the 2001–2002 epidemic season, only the Hounde district passed the World Health Organization (WHO) epidemic threshold of 10 suspected cases of bacterial meningitis per 100,000 persons per week, and no districts passed the threshold during the study period (Burkina Faso Ministry of Health, unpublished data).

Study design, case definitions, and case recruitment. Persons with suspected cases of meningitis were identified at the regional referral hospital (Centre Hospitalier National Sourou Sanou, Bobo-Dioulasso) and at all 59 local health care centers. Two mechanisms were used to enroll persons with suspected cases. First, local study staff prospectively identified persons with suspected cases of meningitis that were identified by health care staff. A standard form was used to record the district of residence and other demographic characteristics, vaccination history, date of disease onset, clinical symptoms at admission, treatment, and outcome for each case-patient. The study protocol required PCR testing for all cases, culture for cases in which the time between the collection of CSF samples and the samples’ arrival at the reference laboratory was <2 h, and latex agglutination testing (Pastorex; Biorad) if the CSF sample was visibly cloudy.

Second, we reviewed patient registers at all health centers within the study area to identify cases that had been reported as suspected bacterial meningitis but were not prospectively included in the study by local staff. Information available from the patient registers included only residence, sex, age, date of admission, outcome, and meningitis etiology for each patient. A latex agglutination test (Pastorex) was the only test performed to determine the etiology of bacterial meningitis in this group of patients.

Bacterial meningitis was categorized as “N. meningitidis,” “H. influenzae,” or “S. pneumoniae” meningitis on the basis of a positive culture, PCR, or latex agglutination test result, for each person residing in 1 of the 3 study districts who presented with a suspected case of meningitis during the study period. Persons of all ages were eligible for inclusion in the study; however, we did not attempt to evaluate or collect data on additional organisms, such as those associated with meningitis in neonates. Any positive test result was counted as representing a case of meningitis, even if other test results were negative; this was because of concern with regard to low culture sensitivity and because, occasionally, PCR was not performed for several days after the collection of specimens, but a latex agglutination test was performed immediately. For H. influenzae strains, latex agglutination and PCR identified serotype b but not other serotypes [5, 12]; because all H. influenzae strains for which a serotype was identified as serotype b, we assumed, for incidence calculations, that all nontyped H. influenzae strains were also serotype b. For 7 CSF specimens, different tests identified different etiologies. We assumed that the additional positive test results were the result of contamination, and we thus included only 1 positive test result per case; the culture result was used if it was available, and, if it was not, the PCR result was used.

Laboratory methodology. Primary PCR analysis was performed at the Neisseria Unit, Institut Pasteur, Paris, France, for samples collected until July 2002 and, thereafter, at the molecular biology laboratory at Centre Muraz in Bobo-Dioulasso. PCR identification was based on the amplification of the crgA gene, for N. meningitidis [13, 14]; the bexA gene, for H. influenzae [5, 12, 15]; and the lytA gene, for S. pneumoniae [5, 12, 15]. For meningococcal serogroup prediction, multiplex PCR was developed that simultaneously used oligonucleotides for the siaD gene (for serogroups B, C, Y, and W135) and the mynB gene (for serogroup A) [15]. Identification by established bacteriological methods was performed according to WHO recommendations [16].

Bacterial strains and CSF specimens were stored at −80°C. For quality control of PCR testing that was performed locally in Burkina Faso, a sample of isolated strains and CSF specimens with either positive or negative results from Centre Muraz was sent to the Institut Pasteur (Paris, France). For CSF specimens that initially yielded negative results at the Institut Pasteur, the Qiaquick kit (Qiagen) was used to test for the presence of PCR inhibitors.

At the Institut Pasteur, the phenotype (i.e., serogroup, serotype, and serosubtype) of all meningococcal isolates was determined as described elsewhere [17, 18]. N. meningitidis strains were tested for susceptibility to penicillin G, amoxicillin, cefotaxime, chloramphenicol, rifampin, and spiramycin, which are agents of interest for use either for treatment (β-lactams and chloramphenicol) or for chemoprophylaxis (rifampin and
spiramycin); testing involved use of the disk diffusion technique, as well as the measurement of MICs by Etest (AB Biodisk), as described elsewhere [19]. Serotype was determined by PCR for \textit{H. influenzae} serotype b [5].

Of 34 pneumococcal isolates, 14 were randomly selected and were sent to the French National Reference Center for Pneumococci (Paris) for quality-control purposes. The age range of the patients from whom these isolates were recovered was 3 months to 60 years (median age, 6 years), and all 3 study districts were represented. Cases of meningitis that were associated with the isolates occurred during 7 different months, ranging from the first to the last month of the study. Serotype determination was performed using latex particles that were sensitized with antisera provided by the Statens Seruminstitut (Copenhagen, Denmark); these antisera enable the identification of 90 known serotypes. Strains of known serotypes were used as internal controls. Antibiotic resistance to oxacillin, chloramphenicol, and/or erythromycin was determined using disk diffusion methodology and standard breakpoints [20].

\textbf{Analysis.} Data entry was done using EpInfo software, version 6.04d (US Centers for Disease Control and Prevention), and data were analyzed using SPSS software, version 10.0 (SPSS).

\textbf{Study approval.} This surveillance project was approved by the ethical review board of Centre Muraz and was supported by the Ministry of Health of Burkina Faso.

\section*{RESULTS}

\textbf{Patient characteristics.} We identified 1477 patients whose illness met a clinical definition of meningitis (365 persons were identified retrospectively through patient registers). Of these 1477 patients, an etiologic agent for meningitis was identified for 409 patients (76 of whom were identified through patient registers). We identified an additional 200 patients from whom we had obtained a visibly cloudy CSF sample or who had a WBC count of $>100$ cells/mm$^3$ and did not have an etiologic agent identified, including 99 patients for whom there was no record of culture, antigen detection, or PCR having been performed (figure 1). The laboratory methodology that was used to identify cases of meningitis varied by etiology (table 1). The age range of the case patients was 27 days to 67 years (median age, 5 years). Sixteen percent of case patients reported or had documentation that stated that they had received meningococcal A/C polysaccharide vaccine during the 4 years before enrollment in the study, although, for most patients, the vaccination status was unknown.

\textbf{Etiologic agents and seasonality.} The most commonly

![Figure 1. Characteristics of persons with suspected bacterial meningitis in Burkina Faso in 2002–2003](https://academic.oup.com/cid/article-abstract/40/1/17/304728)
identified etiologic organism was *N. meningitidis* (44% of cases), followed by *S. pneumoniae* (40% of cases) and *H. influenzae* type b (17% of cases), with the occurrence of cases of *N. meningitidis* meningitis and pneumococcal meningitis demonstrating similar seasonal patterns (figure 2). The predominant serogroup associated with cases of meningococcal meningitis was serogroup W135 (72% of cases), followed by serogroup A (23% of cases) (serogroup could not be determined for 5% of cases of meningococcal meningitis). Pheno-type determination was performed for 19 meningococcal strains collected during the 2001–2002 epidemic season and for 29 meningococcal strains collected during the 2002–2003 season. All 39 serogroup W135 strains were 2a:P1–2,5. Genotyping of representative strains showed that these strains belonged to the electrophoretic type 37 (ET-37) clonal complex. Eight serogroup A strains had the phenotype 4:P1–9, and 1 other strain was nongroupable and nontypeable. Fourteen of 34 *S. pneumoniae* isolates were evaluated; of these, 9 were serotype 1; 2 were serotype 6A; and 1 each belonged to serotypes 14, 21, and 25F.

**Incidence and case fatality proportions.** The annual in-

<table>
<thead>
<tr>
<th>Category, method(s)</th>
<th><em>Neisseria meningitidis</em> (<em>n</em> = 179)</th>
<th><em>Streptococcus pneumoniae</em> (<em>n</em> = 162)</th>
<th><em>Haemophilus influenzae</em> (<em>n</em> = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutually exclusive categories</td>
<td>Culture alone</td>
<td>2 (1.1)</td>
<td>1 (0.62)</td>
</tr>
<tr>
<td></td>
<td>PCR alone</td>
<td>66 (37)</td>
<td>43 (27)</td>
</tr>
<tr>
<td></td>
<td>LAT alone</td>
<td>15 (8.4)</td>
<td>57 (35)</td>
</tr>
<tr>
<td></td>
<td>Culture and PCR</td>
<td>12 (6.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Culture and LAT</td>
<td>2 (1.1)</td>
<td>6 (3.7)</td>
</tr>
<tr>
<td></td>
<td>PCR and LAT</td>
<td>13 (7.3)</td>
<td>28 (17)</td>
</tr>
<tr>
<td></td>
<td>Culture, PCR, and LAT</td>
<td>69 (39)</td>
<td>27 (17)</td>
</tr>
</tbody>
</table>

| Summary categories | Any positive culture result | 85 (48) | 34 (21) | 17 (25) |
|                   | Any positive PCR result | 160 (89) | 98 (61) | 49 (72) |
|                   | Any positive LAT result | 99 (55) | 118 (73) | 39 (57) |

**NOTE.** LAT, latex agglutination test.
Table 2. Annual incidence of acute bacterial meningitis per 100,000 persons in Burkina Faso in 2002–2003, by etiologic agent and age group.

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>Neisseria meningitidis</th>
<th>Streptococcus pneumoniae</th>
<th>Haemophilus influenzae type b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All serotypes</td>
<td>Serogroup A</td>
<td>Serogroup W135</td>
</tr>
<tr>
<td></td>
<td>n Incidence (95% CI)</td>
<td>n Incidence (95% CI)</td>
<td>n Incidence (95% CI)</td>
</tr>
<tr>
<td>&lt;1</td>
<td>38 96 (65–125)</td>
<td>42 106 (73–136)</td>
<td>31 77 (60–106)</td>
</tr>
<tr>
<td>&lt;5</td>
<td>62 41 (31–51)</td>
<td>55 36 (27–46)</td>
<td>84 56 (44–67)</td>
</tr>
<tr>
<td>5–14</td>
<td>34 11 (7.4–15)</td>
<td>70 23 (18–28)</td>
<td>23 7.5 (4.4–11)</td>
</tr>
<tr>
<td>&gt;14</td>
<td>65 13 (9.9–16)</td>
<td>25 5.0 (3.1–7.0)</td>
<td>8 1.6 (0.50–2.7)</td>
</tr>
</tbody>
</table>

* Age was not known for 1 patient.

Incidence of bacterial meningitis for persons of all ages was 43 cases/100,000 persons. The annual incidences of meningococcal meningitis, pneumococcal meningitis, and *H. influenzae* type b meningitis were 19 cases (n = 179), 17 cases (n = 162), and 7.1 cases (n = 68) per 100,000 persons, respectively. The highest incidences occurred among infants and children who were <5 years of age (table 2). For children who were 5–14 years of age, *N. meningitidis* was the most common etiologic agent, but for persons who were ≥15 years of age, the incidence of *S. pneumoniae* was more than twice as high as that of *N. meningitidis* and *H. influenzae* type b combined.

The incidence of *N. meningitidis* serogroup W135 was higher than that of *N. meningitidis* serogroup A among persons in all age groups (table 2), with the greatest difference observed among persons in the youngest age groups. Although age-specific incidences of *N. meningitidis* serogroup W135 and *S. pneumoniae* were highest among infants, 71% of cases in each group occurred among persons who were ≥2 years of age.

Annual incidences in urban areas were higher than those in rural areas for *N. meningitidis* (19 cases vs. 10 cases per 100,000 persons), *S. pneumoniae* (19 cases vs. 7.6 cases per 100,000 persons), and *H. influenzae* type b (8.2 cases vs. 3.0 cases per 100,000 persons).

The case-fatality proportion was 43% for persons with *S. pneumoniae* meningitis, 24% for persons with *H. influenzae* type b meningitis, and 16% for persons with *N. meningitidis* meningitis. The proportion of case fatalities due to *S. pneumoniae* was high for all age groups (figure 3), and *S. pneumoniae* accounted for 61% of the 115 deaths that were recorded during the study.

**Antibiotic use and antibiotic sensitivity.** Of 116 patients with pneumococcal meningitis and 54 patients with *H. influenzae* type b meningitis for whom data on treatment regimens were available, 68 patients received 1 or 2 doses of oily chloramphenicol in accordance with recommendations for empiric antibiotic therapy. Thirteen patients received longer courses (of

Figure 3. Case fatality proportions for cases of bacterial meningitis in Burkina Faso in 2002–2003, by age group and etiologic agent.
PCR testing, including purification if indicated (a step not performed in the field), found identical results for 164 of 183 tested specimens. Of the 19 discrepant results, those for 5 specimens were negative in the field but were positive at the Institut Pasteur (3 were positive for \(S.\) pneumoniae, 1 for \(H.\) influenzae, and 1 for \(N.\) meningitidis serogroup W135), and results for 10 specimens were negative at the Institut Pasteur but were positive in the field (2 were positive for \(S.\) pneumoniae, 3 for \(H.\) influenzae, 4 for \(N.\) meningitidis serogroup W135, and 1 for nongroupable \(N.\) meningitidis). The 4 remaining discrepant results involved different etiologies that were identified at the 2 testing sites.

DISCUSSION

Systematic surveillance is the basis for the development of public health policy. Surveillance of meningitis in Africa has been hampered by a lack of laboratory facilities—particularly in outlying areas, which may have substantially different patterns of disease than those seen in urban centers. The present study indicates that PCR technology can be used in African settings to overcome these limitations [21]. PCR has a high sensitivity and specificity [12, 13, 15], and the lower limit of bacterial concentrations necessary for detection are such that false-positive results caused by transient contamination (e.g., nasopharyngeal carriage) are unlikely to occur [22–24]. PCR technology is also rapid. Thus, PCR could be used as the basis for implementing etiology-specific treatment guidelines and for determining the appropriate vaccines for use in the response to and prevention of epidemics. The primary limitation of PCR in the present study was the relatively low sensitivity of PCR for the detection of pneumococcus and \(H.\) influenzae type b, a result that is apparently unrelated to field-based methodology errors but that may be because of a low DNA yield on extraction. The cost of PCR may also prove to be a substantial barrier to more-widespread use.

During the present study, serogroup W135 of the ET-37 clonal complex [5, 6] was the most common meningococcal serogroup identified. While awaiting the development of a monovalent conjugate serogroup A vaccine designed for use in Africa, earlier studies have focused on the relative merits of a

### Table 3. Sensitivity and specificity of PCR, compared with those of culture, for 434 persons with suspected bacterial meningitis in Burkina Faso in 2002–2003.

<table>
<thead>
<tr>
<th>Organism isolated</th>
<th>Positive by PCR and culture/positive by culture(^a)</th>
<th>Sensitivity, %</th>
<th>Negative by PCR and culture/negative by culture(^a)</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neisseria meningitidis</td>
<td>81/85</td>
<td>95</td>
<td>331/349</td>
<td>95</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>27/34</td>
<td>79</td>
<td>378/400</td>
<td>95</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>13/16</td>
<td>81</td>
<td>407/418</td>
<td>97</td>
</tr>
</tbody>
</table>

\(^a\) Data are no. of patients with specified PCR and culture results/total no. of specified culture results.
short-term strategy of using serogroup A vaccine only as a response to an epidemic [25, 26] or in combination with preventive vaccination [27–29]. If confirmed in other areas, the occurrence of W135 as a predominant pathogen—including among patients who are >2 years of age, an age when polysaccharide vaccine might be expected to be efficacious—may make this argument moot, at least for the moment. Immediate strategies should, instead, focus on the appropriate use of polysaccharide vaccines that confer protection against serogroups A and W135 (at least for patients who are >2 years of age, as has been recommended [30]). Long-term routine prevention strategies may need to address how to make available to Africa the polyvalent meningococcal conjugate vaccines currently under development for developed countries [31–33] rather than solely attempt to develop a monovalent serogroup A conjugate vaccine for use in Africa.

We found that S. pneumoniae caused the majority of cases of adult meningitis and the majority of deaths due to meningitis and that it had an incidence similar to that of N. meningitidis, even during the epidemic season. Although S. pneumoniae causes a high proportion of meningitis in Africa [34, 35], only a few studies have reported incidence rates [1]. Pneumococci contribute disproportionately to the burden of meningitis because of the substantially worse outcome associated with pneumococcal disease, compared with that associated with meningococcal disease [1, 34, 36]; moreover, pneumococci are the predominant cause of bacterial pneumonia in the developing world. Our data, if confirmed in other locations, suggest that prevention and treatment may need to focus as much on pneumococcus as on meningococcus, even in the African meningitis belt. Vaccine recommendations will need to consider that serotype 1, a serotype that is not included in the currently licensed 7-valent conjugate vaccine, predominated in our tested sample. Because 71% of pneumococcal cases occurred among persons >2 years of age, the polysaccharide vaccine—which contains serotype 1—may have a role in Africa.

The WHO recommends the use of single-dose oily chloramphenicol for the treatment of suspected cases of meningitis in sub-Saharan Africa when a meningitis outbreak has been declared [37, 38]. Part of the reason for this strategy is the assumption that most disease will be due to the meningococcus. However, we found that pneumococcal meningitis had a seasonal pattern and an incidence similar to those associated with N. meningitidis meningitis. Moreover, short-course therapy with oily chloramphenicol was common throughout the study period, even in the absence of an epidemic. Although few data exist with regard to efficacy, the use of chloramphenicol therapy for pneumococcal meningitis may lead to treatment failure [39], a situation that likely will worsen with the spread of chloramphenicol-resistant organisms [40, 41]. Thus, there is a need for the monitoring of patterns of antibiotic resistance, additional data from clinical trials of short-course chloramphenicol therapy, ongoing reviews of treatment guidelines, and accurate and rapid clinical diagnosis, such as can be provided by PCR.

In the present study, we underestimated incidence, because persons may have died without seeking care or may have received care without having a lumbar puncture performed. In addition, an etiologic agent was not identified in 37% of cases of purulent meningitis, including many for which no diagnostic tests were performed. It is unlikely that we overestimated the number of cases, because we included only study subjects who had documentation that stated that they resided in the study district. However, errors in population estimates could have led to inaccurate estimation of incidence.

An annual incidence of meningitis of 43 cases/100,000 persons implies that, during the 47 years that is the average life expectancy of a Burkian, 1 in 50 persons will experience bacterial meningitis; of these persons, 28% will die and many more will experience sequelae. Vaccination and treatment policies should reflect the primary etiologic agents, including pneumococcus and meningococcal serogroups W135 and A and, among children, H. influenzae type b. Moreover, policies should be responsive to ongoing changes in the epidemiology of meningitis. We recommend the further evaluation and expansion of PCR-based surveillance in Burkina Faso and neighboring countries in Western Africa.

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Acknowledgments

We thank Jean-Michel Alonso, Magaly Duclos-Galand, Annie Guiyoule, Dario Giorgini, and René Pires. We also thank Dr. Bonkoungou Méte (Directeur Regional de la Santé) and his staff, for their help in implementing the study in the Sanitary Region of Bobo-Dioulasso, and Dr. Roger Sié Hien (Director of Centre Muraz), for his support in implementing PCR technology for bacterial meningitis in Bobo-Dioulasso. We thank Caroline Douay, for data management; Mathilde Lourd, for epidemiology assistance; Emmanuel Duquesnoy, for logistics; and Regina Hidohou for data review. We are grateful to Christophe Sanou, Seydou Bambara, and Mathieu Sanou (from the field team of Association pour l’Aide à la Médecine Préventive in Bobo-Dioulasso), as well as the health care staff working in the pediatrics and infectious diseases wards in Centre Hospitalier National Souro Sanou,
the health workers from the administrative districts of Bobo-Dioulasso 15, Bobo-Dioulasso 22, and Houndé, and the bacteriology laboratory techni-
cians in Centre Hospitalier National Sounou Sanou, in Centre Muraz, and
in the medical center in Houndé, for their active contribution to the study. We
thank Dr. Anne le Fleéche (Unité Biodiversité des Bactéries Pathogènes
Emergentes, Institut Pasteur, Paris, France) for the control of Haemophilus
influenzae strains.

Financial support. Aventis Pasteur, Institut Pasteur, and the Bill and
Melinda Gates Foundation.

Potential conflicts of interest. None of the authors has a commercial
interest in any products that might be affected by the results of this in-
vestigation. L.P., B.D.G., and B.-M. N.-L. were employees of Association
pour l’Aide à la Médecine Préventive, which receives substantial financial
support from Aventis Pasteur—one of the funders of the study and a
manufacturer of meningococcal, pneumococcal, and H. influenzae type b
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