The Changing Landscape of Epidemic Bacterial Meningitis in Africa: New Opportunities for Prevention

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(See the article by Leimkugel et al., on pages 192–9.)

Reports of epidemic meningitis in Africa typically lead one to imagine explosive outbreaks of meningococcal meningitis. Discussions of invasive pneumococcal disease generally bring to mind cases of sporadic infection that primarily involve the very young, the elderly, and the immunocompromised. Reported pneumococcal disease outbreaks mostly have occurred in institutional settings or in closed communities rather than in the general population. Against the background of these presuppositions, Leimkugel et al., in this issue of the Journal of Infectious Diseases, provide an important description of progressively larger annual epidemics of meningitis caused by Streptococcus pneumoniae that occurred throughout the Kassena-Nankana District of northern Ghana from 2000 to 2003 [1]. Disease occurred in a highly seasonal pattern, with cases occurring primarily during the dry seasons of each year. The annual outbreaks of S. pneumoniae meningitis occurred concurrently with the annual epidemics of Neisseria meningitidis meningitis that are characteristic of the African meningitis belt in sub-Saharan Africa. One intriguing characteristic of these annual outbreaks was that the majority of cases were caused by a single clonal complex of serotype 1 S. pneumoniae.

Even sporadic pneumococcal infections have long been noted to display seasonal fluctuations and year-to-year variability in incidence. In 1939, Heffron observed that “Lobar pneumonia may at times be unusually prevalent in certain regions or even over considerable portions of whole countries, at which time the opinion is frequently expressed that a ‘big pneumonia year’ is in progress” (p. 386) [2]. In temperate regions, rates of invasive infection are highest during the cooler, darker months of winter [3–5]. The seasonal pattern of annual outbreaks of pneumococcal infection has been attributed to a variety of factors that are more common during the winter months, including colder ambient air temperatures, lower humidity, greater air pollution, higher rates of infection with viral respiratory pathogens that may facilitate pneumococcal transmission and disease, and more crowding indoors.

Recent reports from elsewhere in Africa suggest that annual outbreaks of pneumococcal meningitis are not unique to Ghana and may represent an emerging facet of the epidemiologic profile of bacterial meningitis throughout sub-Saharan Africa. In neighboring Burkina Faso, pneumococcal meningitis epidemics occurred during the dry season of 2002–2003, concurrently with meningococcal meningitis epidemics [6]. In both Ghana and Burkina Faso, cases of pneumococcal meningitis occurred in persons of all ages, and serotype 1 accounted for the majority of cases for which an isolate was available. Although rates of disease were highest in infants (<1 year old), the majority of cases occurred in persons ≥5 years old. In a 1-year prospective study of adults with meningitis admitted to a hospital in Malawi during 1998–1999, S. pneumoniae surpassed N. meningitidis as a more-common causative agent [7]. As in Ghana and Burkina Faso, most cases occurred during the cooler dry months, when the incidence of meningococcal meningitis was also the highest. These epidemics highlight 3 important issues: (1) the large and underappreciated burden of bacterial diseases, especially pneumococcal diseases, in sub-Saharan Africa; (2) the peculiar propensity of serotype 1 S. pneumoniae to cause serious infection and disease epidemics; and (3) the potential for pneumococcal vaccination to prevent disease and death in developing areas.

Although direct comparison is difficult because of methodological differences in
surveillance and laboratory diagnosis, the incidence of pneumococcal meningitis in Ghana is remarkably high—at least 10-fold greater than that reported in the United States [1, 8]. Leimkugel et al. reported that, in Ghana, the case-fatality rate for pneumococcal meningitis is >40% and is several-fold greater than the case-fatality rate for meningococcal meningitis [1], which is consistent with findings from other recent studies in Africa and Europe [6, 7, 9]. The rates of pneumococcal meningitis reported by Leimkugel et al. likely underestimate the true burden of pneumococcal disease in Ghana. No data are provided to determine whether pneumococcal bacteremia and pneumonia also became more prevalent during the periods when the number of meningitis cases increased. Meningitis is usually a much less common manifestation of pneumococcal infection than are bacteremia and pneumonia. Additionally, the serotype distribution of invasive clinical isolates suggests that serotype 1 may be more prone to causing disease outside the central nervous system than are other serotypes [10].

Additional data are needed to determine whether the clonal complex that accounted for the majority of cases in Ghana has a unique propensity to cause meningitis. It is possible that each year’s meningitis outbreak was only the tip of a pneumococcal iceberg submerged in a sea of lower respiratory tract infections and febrile illnesses that can be attributed to other agents. A prospective study designed to identify bacteremia in hospitalized children <13 years old in rural Kenya demonstrates the burden of pneumococcal infection that usually goes unrecognized in the absence of diagnostic laboratory methods [11]. S. pneumoniae was the most common cause of bacteremia and, among children between the ages of 60 days and 5 years, accounted for 8.7% of all in-hospital deaths. Without microbiological evaluation, many of these deaths would likely have been attributed to other pathogens, such as malarial parasites [12].

More recently, Cutts et al. reported the results of a randomized, controlled trial of a nonavalent pneumococcal conjugate vaccine in The Gambia that shows the large proportion of disease and death caused by pneumococcal infections [13]. Compared with placebo recipients, children vaccinated against pneumococcal infection experienced 15% fewer hospital admissions for any cause and 16% lower all-cause mortality. Approximately 1 death was prevented for each 200 children vaccinated. The vaccine prevented approximately seven pneumonia cases for every case of culture-confirmed invasive pneumococcal infection, which demonstrates the limitations of microbiological testing alone for measurement of the burden of disease.

Serotype 1 S. pneumoniae has long been noted for its tendency to cause serious infection and epidemics of disease. In 1917, Stillman described serotype 1 as “highly parasitic” because it was the most frequent cause of lobar pneumonia but was rarely isolated from asymptptomatically colonized persons [14]. Nearly a century later, analysis of isolates from children with invasive pneumococcal infection and nasopharyngeal colonization confirmed that serotype 1 is more likely to cause invasive infection than are other serotypes, even in areas where it is an uncommon cause of disease [15]. In the United States, serotype 1 was the most common cause of sporadic and epidemic pneumococcal disease during the first half of the 20th century; however, in recent years it has become relatively uncommon and has accounted for a relatively small proportion of pneumococcal disease outbreaks [2, 16–18]. Despite the apparent decrease in serotype 1 disease in the United States, this serotype remains a leading cause of sporadic invasive pneumococcal disease in Africa [10, 11]. Leimkugel et al.’s study in Ghana confirms that serotype 1 is more common than other serotypes in certain areas but remains a threat to cause large epidemics.

Immunization with effective vaccines will be the cornerstone for control of bacterial meningitis, bloodstream infections, and pneumonia in developing countries. Leimkugel et al. suggest that multivalent pneumococcal conjugate vaccines currently under development may be too expensive for use in Africa and that a less complex vaccine should be considered as an alternative. More than 15 years and hundreds of millions of dollars have been invested in the development of highly efficacious conjugate vaccines that contain 7 or more serotypes. Two randomized, double-blind, controlled trials in Africa have now shown that vaccination of infants and young children with a nonavalent vaccine (which includes serotype 1) prevents invasive pneumococcal disease and radiographically confirmed pneumonia [13, 19]. Because of the time and economic investment needed to develop new vaccine formulations, more lives might be saved by speeding the introduction of multivalent conjugate vaccines that are in the final stages of development rather than starting over by initiating the development of less complex vaccines that target serotype 1. Moreover, the likelihood of replacement disease—that is, an increase in disease caused by pathogenic nonvaccine pneumococcal serotypes—may be greater with the use of limited-valency vaccines.

Prevention of epidemic pneumococcal meningitis might be achievable, at least in part, through routine immunization of infants and children with pneumococcal conjugate vaccine. In the United States, even with a relatively modest immunization coverage of <70% of all children <2 years old, routine immunization of infants appears to provide protection of unvaccinated children and adults through decreased transmission of vaccine serotypes [20]. Whether these indirect effects would be observed in Africa is unclear and warrants further evaluation. Additionally, the 23-valent pneumococcal polysaccharide vaccine is an option for control of invasive pneumococcal infection in persons ≥2 years old. In Leimkugel et al.’s study, all but 2 (98%) of the isolates from patients with meningitis in northern Ghana belonged to serotypes that are included in the 23-valent vaccine [1]. Recent com-
munity outbreaks of serotype 1 invasive disease in Israel and northern Canada subsided after 23-valent vaccine was provided to persons at risk for infection [21, 22].

Invasive bacterial infections are an important preventable cause of disease and death in sub-Saharan Africa. What barriers and questions remain? Better methods for the conduct of continuous laboratory-based surveillance for bacterial meningitis in Africa are needed for early detection of outbreaks, for assessment of the effectiveness of vaccination programs, and for detection of the emergence of pathogens not targeted by vaccines. The role that conjugate vaccines can play in immunization of older children and adults remains to be determined, and the role that the currently available 23-valent polysaccharide vaccine can play in controlling pneumococcal epidemics in Africa also needs careful consideration. Although the polysaccharide vaccine may be protective against invasive infections and could potentially provide boosting for persons immunologically primed with a conjugate vaccine, additional data are needed on vaccine safety and effectiveness for HIV-infected persons in Africa and for persons who receive multiple doses [23–25]. The most daunting question remaining to be answered may be: why not? Modern vaccinology has enabled us to overcome technological barriers to the prevention of invasive S. pneumoniae, N. meningitidis, and Haemophilus influenzae type b infections in sub-Saharan Africa. With the creation the Global Alliance for Vaccines and Immunization and its associated >$1 billion Vaccine Fund, overcoming the economic barriers to vaccine procurement and delivery may soon be possible as well. With political will and sustained commitment, the technology and resources available today could result in immediate and lasting reductions in the morbidity and mortality that result from invasive bacterial infections, both in Africa and elsewhere.

References