

## MAJOR ARTICLE

# An Outbreak of Serotype 1 *Streptococcus pneumoniae* Meningitis in Northern Ghana with Features That Are Characteristic of *Neisseria meningitidis* Meningitis Epidemics

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(See the editorial commentary by Butler and Levine, on pages 189–91.)

**Background.** The Kassena-Nankana District (KND) of northern Ghana lies in the African meningitis belt, where epidemics of bacterial meningitis have been reoccurring every 8–12 years. These epidemics are generally caused by *Neisseria meningitidis*, an organism that is considered to be uniquely capable of causing meningitis epidemics.

**Methods.** We recruited all patients with suspected meningitis in the KND between 1998 and 2003. Cerebrospinal fluid samples were collected and analyzed by standard microbiological techniques. Bacterial isolates were subjected to serotyping, multilocus sequence typing (MLST), and antibiotic-resistance testing.

**Results.** A continual increase in the incidence of pneumococcal meningitis was observed from 2000 to 2003. This outbreak exhibited strong seasonality, a broad host age range, and clonal dominance, all of which are characteristic of meningococcal meningitis epidemics in the African meningitis belt. The case-fatality rate for pneumococcal meningitis was 44.4%; the majority of pneumococcal isolates were antibiotic sensitive and expressed the serotype 1 capsule. MLST revealed that these isolates belonged to a clonal complex dominated by sequence type (ST) 217 and its 2 single-locus variants, ST303 and ST612.

**Conclusions.** The *S. pneumoniae* ST217 clonal complex represents a hypervirulent lineage with a high propensity to cause meningitis, and our results suggest that this lineage might have the potential to cause an epidemic. Serotype 1 is not included in the currently licensed pediatric heptavalent pneumococcal vaccine. Mass vaccination with a less complex conjugate vaccine that targets hypervirulent serotypes should, therefore, be considered.

*Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type b (Hib) are the most common causes of acute bacterial meningitis [1]. Meningitis caused by *N. meningitidis* has been considered to be unique with respect to its epidemic occurrence. A region of sub-Saharan Africa extending from Ethiopia to Senegal, designated “the African meningitis belt,” has been particularly vulnerable to meningococcal disease

epidemics. In addition to sporadic disease, which occurs mainly during the annual dry season, epidemics have occurred in the African meningitis belt every 8–12 years over the past 100 years [2, 3].

Information on the epidemiologic profile of pneumococcal meningitis in the African meningitis belt is fragmentary, but some studies have found *S. pneumoniae* to be the most important causative agent of bacterial meningitis in certain areas [4]. The incidence in these areas is 10–20 cases/100,000 people/year, which is ~10 times higher than that in western Europe and the United States [5, 6]. Cases of *S. pneumoniae* meningitis occur throughout the year, and most studies report the youngest (<2 years) and the oldest (>60 years) people to be at greatest risk [4, 5]. For unknown reasons, the case-fatality rate for pneumococcal meningitis (~50%) is 5–10 times higher than that for meningococcal meningitis.

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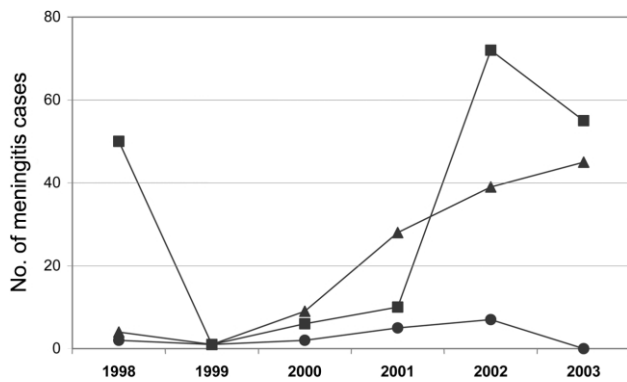
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**Figure 1.** No. of laboratory-confirmed (by culture and/or latex agglutination assay) meningitis cases in the Kassena-Nankana District of northern Ghana between 1998 and 2003. No laboratory data were available on the patients with suspected meningitis that was diagnosed during the wet season of 1998–1999. ■, *Neisseria meningitidis*; ▲, *Streptococcus pneumoniae*; ●, *Haemophilus influenzae* type b.

Although there are ~90 known pneumococcal serotypes, only a limited number account for most of the invasive infections. The serotype distribution varies with time, location, and age group [6]. Clonal dominance and global spread has been described for a small number of highly successful drug-resistant (and often multidrug-resistant) pneumococcal clones [7]. Serotype 1 is one of the most common serotypes that cause invasive disease worldwide, particularly in Africa [6, 8, 9]. It has a high attack rate but is rarely isolated from healthy carriers or from people with mild occult bacteremia. Outbreaks of invasive serotype 1 pneumococcal disease have occurred in several communities [4, 6, 10–14].

The present study was conducted between 1998 and 2003 in the Kassena-Nankana District (KND) of northern Ghana. After a large meningococcal meningitis epidemic occurred during the dry season of 1997, all patients with suspected meningitis were recruited prospectively. Cerebrospinal fluid (CSF) samples were collected and analyzed by standard microbiological techniques. Between 2000 and 2003, a continuous increase in the incidence of pneumococcal meningitis was observed. Here, we demonstrate that the epidemiological and bacteriological features of this outbreak closely resemble those usually associated with meningococcal meningitis epidemics, and the implications of these observations with respect to the control of bacterial meningitis in the African meningitis belt are discussed.

## PATIENTS, MATERIALS, AND METHODS

**Study area.** The KND has a population of 140,000 and lies within the Guinea savanna woodland area of northern Ghana. Two major seasons exist, a short wet season from May to October and a long dry season for the remainder of the year. The general population is rural, except for those living in the town

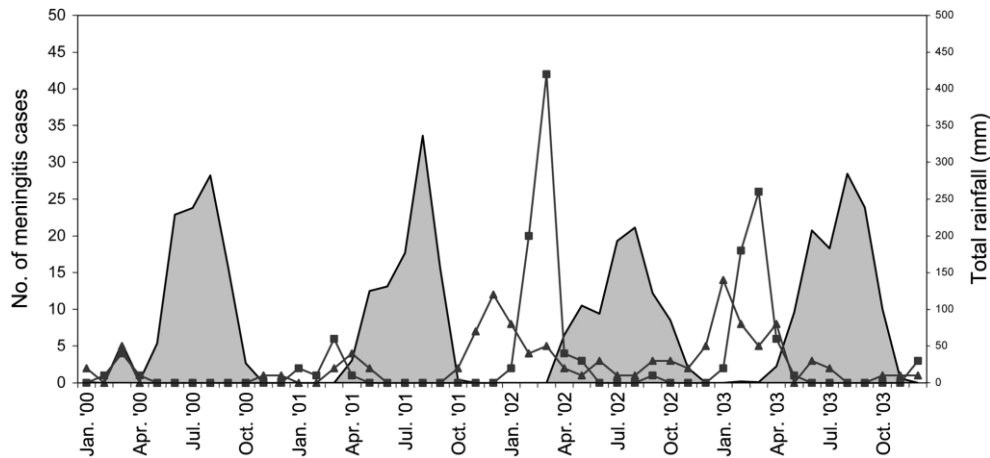
of Navrongo, which has a population of 20,000. People live in compounds with an average of 10 inhabitants.

**Patients.** CSF samples were collected between January 1998 and December 2003 from patients with suspected meningitis who reported to the War Memorial Hospital in Navrongo or to 1 of 4 health centers in the KND. In line with Ghana's standard diagnostic procedures, samples were analyzed at the laboratory of the War Memorial Hospital, for confirmation of the clinical diagnosis. Additional samples were obtained from the Bolgatanga Regional Hospital in the Upper East Region and from health facilities in the Bongo and Builsa Districts. In 1998–1999, only samples collected during the dry season were analyzed. Thereafter, samples collected from the few patients with suspected meningitis who presented during the wet season were also included. Ethical clearance for the study was obtained from the responsible institutional review boards and the Ghanaian Ministry of Health. Clinical and demographic information was recorded for all patients. Personal data were linked with the database of the Navrongo Demographic Surveillance System (NDSS). The denominators used for calculation of incidence rates represent the average annual population of the KND between 1995 and 1999 [15].

**Analysis of CSF samples.** CSF samples were analyzed by direct staining with Gram stain. Boiled CSF supernatants were tested serologically for capsular polysaccharide antigens of *N. meningitidis* (serogroups A, B, C, and W135), *S. pneumoniae*, and Hib (Slidex Meningite Kit, bioMérieux; Pasteurex Kit, Bio-Rad). CSF samples were inoculated onto blood, chocolate, and Thayer Martin agar and then incubated in candle jars for 24 h at 37°C. *S. pneumoniae* colonies were identified on the basis of colony morphological structure, Gram-stain behavior, and resistance to optochin (Taxo P discs, BD). All pneumococcal isolates were serotyped on the basis of the Quellung reaction, with antisera from the Statens Serum Institute (Copenhagen).

**Antibiotic resistance testing.** All isolates from the KND were tested for resistance to penicillin G and chloramphenicol (the 2 antibiotics commonly used in standard therapy for bacterial meningitis in Ghana) as well as cefotaxime and ciprofloxacin, by use of E-test strips (Diagnostic Medical Distribution) [16]. The breakpoints of the NCCLS protocol were applied. For ciprofloxacin, 4 µg/mL was taken as the breakpoint for resistance [17]. The ATCC 49619 strain was included as control.

**Multilocus sequence typing (MLST).** Bacteria were grown overnight in Todd-Hewitt medium. DNA extraction [18], MLST [19], and direct sequencing of polymerase chain reaction products by use of an ABI Prism 310 genetic analysis system was performed in accordance with standard protocols. Allelic profiles were analyzed by use of applications on the MLST home page (available at: <http://spneumoniae.mlst.net/>). For analysis of the relationships between closely related isolates, eBURST



**Figure 2.** Seasonal patterns of rainfall and no. of laboratory-confirmed (by culture and/or latex agglutination assay) pneumococcal and meningococcal meningitis cases in the Kassena-Nankana District (KND) of northern Ghana. Data on total monthly rainfall (indicated by shaded areas) are from the meteorological station of the KND. ■, *Neisseria meningitidis*; ▲, *Streptococcus pneumoniae*.

software (available at: <http://eburst.mlst.net/>) with the most-stringent group definition (6/7 alleles identical) was used. All allelic profiles obtained were compared with the complete listing of the sequence types (STs) available in the database.

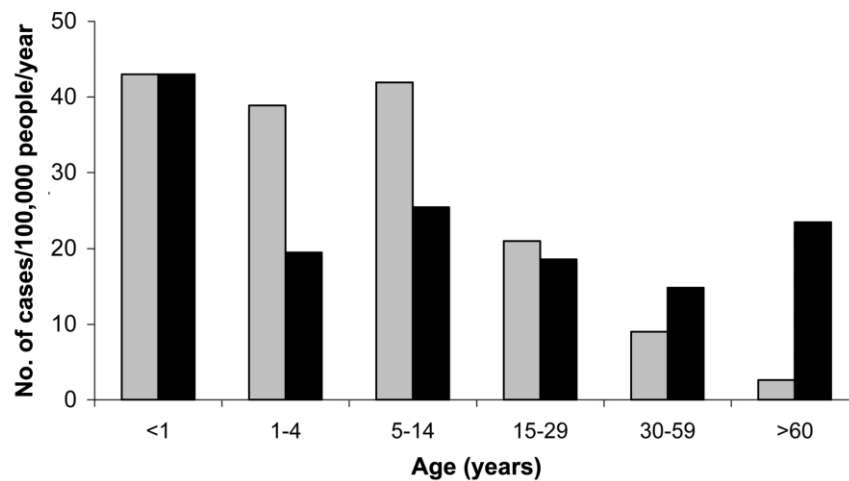
## RESULTS

**Meningitis cases.** Between 1998 and 2003, a total of 140 meningococcal, 117 pneumococcal, and 14 Hib meningitis cases were confirmed by culture and/or latex agglutination assay in the KND. The number of pneumococcal meningitis cases remained low during the first 2 years of the study but increased continuously during the following years (figure 1). Two subsequent outbreaks of serogroup A meningococcal infection were reported during the study period. After a large meningococcal

meningitis epidemic occurred in Ghana in 1997, 50 confirmed serogroup A meningococcal meningitis cases occurred in 1998 [20]. After 2 years of absence, from 2001 onward, serogroup A meningococcal meningitis cases reemerged, causing annual outbreaks until 2004 (authors' unpublished data). The number of Hib meningitis cases remained low throughout the study period and mainly occurred in children <7 years old (figure 1).

The vast majority of meningococcal and pneumococcal meningitis cases occurred during the dry season (figure 2). The pneumococcal meningitis cases peaked 1–2 months earlier than the meningococcal cases. During the remainder of the year, only sporadic meningitis cases, mostly caused by *S. pneumoniae*, were observed.

Both the patients with meningococcal meningitis and the pa-



**Figure 3.** Incidence of meningococcal (gray bars) and pneumococcal (black bars) meningitis in the Kassena-Nankana District of northern Ghana, by age. Cases were laboratory confirmed by culture and/or latex agglutination assay.

**Table 1. Host age distribution of serotype 1 and non-serotype 1 *Streptococcus pneumoniae* isolates from the Kassena-Nankana District of northern Ghana, found between 2000 and 2003.**

Category	Age group						NS	Total	Host age, range (median), years
	<1 year	1–4 years	5–14 years	15–29 years	30–59 years	>60 years			
No. of isolates									
Serotype 1 isolates	0	2	24	11	11	5	5	58	0.75–72 (15)
Non-serotype 1 isolates	2	2	5	1	3	4	1	18	0.33–85 (13)
Total	2	4	29	12	14	9	6	76	0.33–85 (14)
Serotype(s) of non-1 isolates	14 <sup>a</sup>	3 <sup>a</sup>	3, <sup>a</sup> 7F, 8, and 12F	8	6A, 8, and 10F	8, 12F, 14, and 38	2	...	...

**NOTE.** Data are no. of isolates, unless otherwise noted. NS, age not specified.

<sup>a</sup> Two isolates.

tients with pneumococcal meningitis exhibited a broad age range (figure 3). Infants (<1 year old) had the highest incidence for both pneumococcal and meningococcal meningitis (43 cases/100,000 people/year, for both). For pneumococcal meningitis, the incidences in all other age groups were 15–26 cases/100,000 people/year. For meningococcal meningitis, the incidences were comparable for children of all age groups and decreased steadily for the older age groups. As a result, in the patients >60 years old, the incidence of pneumococcal meningitis was significantly higher than the incidence of meningococcal meningitis (2.6 vs. 23.4 cases/100,000 people/year). The overall case-fatality rates were 43.6% (51/117) and 4.3% (6/140) for pneumococcal and meningococcal meningitis, respectively.

The geographic locations of the homes of 74 patients with pneumococcal meningitis and 102 patients with meningococcal meningitis were mapped by use of the NDSS, but neither pneumococcal nor meningococcal cases were geographically clustered (data not shown). Furthermore, no significant family clustering was observed.

**Characterization of pneumococcal isolates.** Between 1998 and 2003, 76 pneumococcal isolates were obtained from patients with meningitis in the KND. Fifty-eight (76%) of these belonged to serotype 1, which was the dominant serotype throughout the study (table 1). The 18 non-serotype 1 isolates belonged to 9 different serotypes. Only 33% (2/6) of the isolates from infants and children ≤4 years old belonged to serotype 1; the remainder belonged to serotypes 3 and 14. In contrast, in older children (5–14 years), young adults (15–29 years), and grown-ups (30–59 years), the proportions of isolates that belonged to serotype 1 were >80% (24/29, 11/12, and 11/14, respectively). In patients >60 years old, the proportion of isolates that belonged to serotype 1 was 56% (5/9).

Antibiotic-resistance testing showed that all but 2 of the 58 serotype 1 strains from the KND were completely susceptible to penicillin G, cefotaxime, chloramphenicol, and ciprofloxacin. The MICs for the 2 strains (both isolated in 2002) with antibiotic resistances were determined. For strain P1036, the

MICs were as follows: penicillin G, 0.5 µg/mL (intermediate); cefotaxime, 2 µg/mL (resistant); and chloramphenicol, 5 µg/mL (intermediate). For strain P1037, the MICs were as follows: penicillin G, 0.5 µg/mL (intermediate); cefotaxime, 1 µg/mL (intermediate); and chloramphenicol, 8 µg/mL (resistant).

All isolates from the KND and 15 isolates from neighboring districts were analyzed by MLST. The results showed that all serotype 1 isolates were clonally related (table 2). Ten distinct STs were identified, but they all shared at least 6 of 7 alleles with one other ST. ST217 and its 2 single-locus variants, ST303 and ST612, were dominant. In addition, single-locus variants of the 3 dominant STs were sporadically found. All isolates obtained in 1998 and 2000 had ST217. ST303 isolates were dominant from 2001 onward (6/15 in 2001, 9/18 in 2002, and 14/20 in 2003).

An eBURST analysis that included the STs of the Ghanaian strains and all strains available in the MLST database was performed (figure 4). Three of the 10 STs found in the Ghanaian isolates (ST217, ST303, and ST612) have been previously described in 34 serotype 1 lineage B isolates [9]; 16 of these isolates came from Africa, and the others came from either Israel, Europe, or the United States. In addition, Brueggemann et al. [9] defined 3 lineage B-associated STs (ST613, ST614, and ST618), represented by 4 African isolates and 1 European isolate. The eBURST diagram demonstrates that all Ghanaian serotype 1 strains found in the present study and all the lineage B isolates described by Brueggemann et al. are part of a single clonal complex in which all isolates share 100% genetic identity at 6 or 7 MLST housekeeping loci with at least 1 other member of the group.

Of the non-serotype 1 isolates, only the serotype 14 isolates exhibited allelic profiles that were closely related to those of the serotype 1 clonal complex (table 2). One of the serotype 14 isolates (ST1324) was a single-locus variant of ST1323 (shown in figure 4), 2 of the serotype 14 isolates (ST1314 and ST1315) were double-locus variants of ST1323, and the remaining sero-

**Table 2. Serotype distribution and sequence types (STs) of *Streptococcus pneumoniae* isolates from northern Ghana, found between 1998 and 2003.**

Serotype	ST	No. of isolates	Year of isolation	Allelic profile							Origin (district) <sup>a</sup>
				<i>aroE</i>	<i>gdh</i>	<i>gki</i>	<i>recP</i>	<i>spi</i>	<i>xpt</i>	<i>ddl</i>	
Serotype 1	217	15	1998–2003	10	18	4	1	7	19	9	KND (13), Bongo (1), and Builsa (1)
	612	8	2001–2003	10	18	4	1	7	19	31	KND (7) and Bolgatanga (1)
	303	36	2001–2003	10	5	4	1	7	19	9	KND (29) and Bolgatanga (7)
	1322	1	2001	10	5	4	1	7	19	31	KND
	1316	1	2002	2	18	4	1	7	19	9	KND
	1325	2	2002	10	8	4	1	7	19	9	KND
	1331	2	2002	13	8	4	1	7	19	9	KND
	1327	1	2003	10	18	4	1	13	19	31	KND
	1328	1	2003	10	18	4	1	7	21	31	KND
	1323	1	2003	10	5	4	1	7	21	9	KND
Serotype 2	74	1	1998	2	13	4	1	6	6	14	KND
Serotype 3	458	7	2001	2	32	9	47	6	21	17	KND (3) and Bolgatanga (4)
Serotype 4	1321	1	2002	8	8	47	18	46	122	31	Bolgatanga
Serotype 6A	1320	1	2002	7	13	8	6	6	8	8	KND
Serotype 7F	1326	1	2002	10	16	4	1	6	21	9	KND
Serotype 8	1317	1	2003	7	5	15	11	83	58	70	KND
	1318	1	2000	7	9	15	11	83	58	70	KND
	1335	1	2003	7	9	4	60	83	28	70	KND
	1319	1	2003	7	9	15	11	83	25	70	KND
Serotype 10F	909	1	2003	2	42	2	1	6	19	20	KND
Serotype 12F	989	1	2003	12	5	89	8	6	112	14	KND
	1330	1	2003	12	5	89	8	13	112	14	KND
Serotype 14	1324	1	2002	10	5	4	17	7	21	9	KND
	1313	1	2003	2	5	4	12	7	21	14	KND
	1315	1	2003	2	5	9	1	7	21	9	KND
	1314	1	2003	2	5	4	1	7	21	14	Builsa
Serotype 38	1329	1	2003	12	5	4	10	42	49	9	KND

**NOTE.** KND, Kassena-Nankana District.

<sup>a</sup> Values in parentheses indicate the no. of isolates found in each district (given only for those isolates found in >1 district).

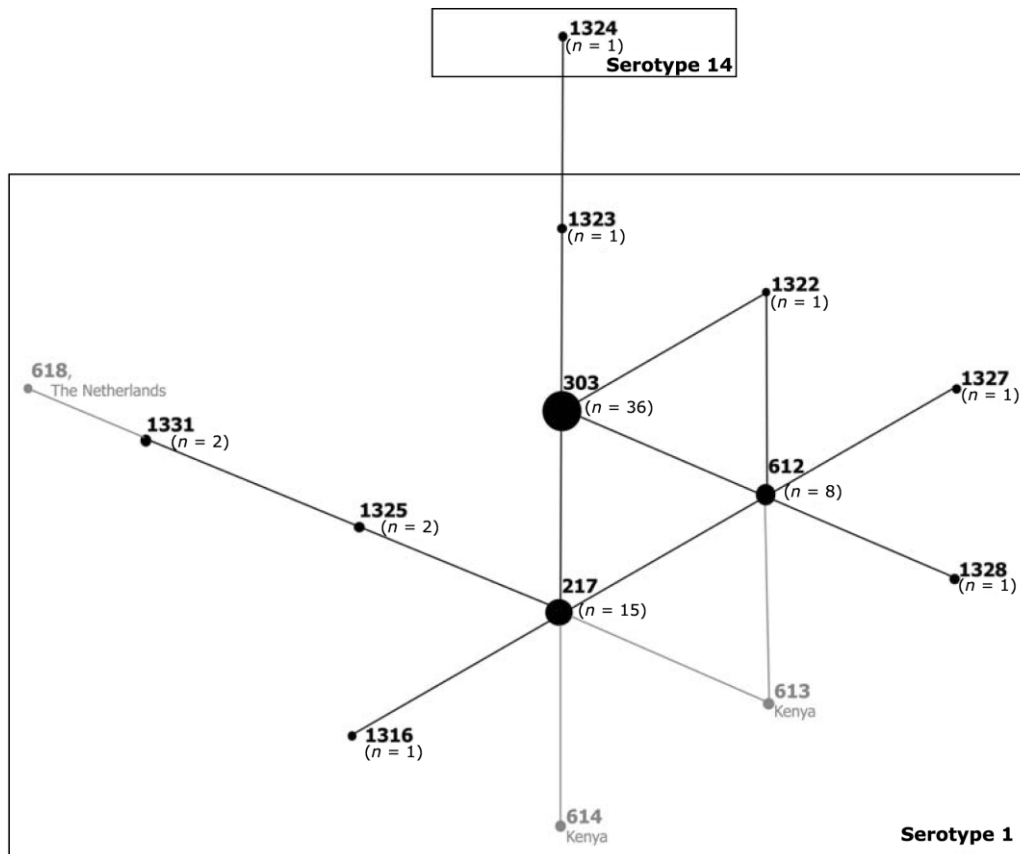
type 14 isolate (ST1313) shared 5 alleles with ST1314 and 4 alleles with ST1323.

## DISCUSSION

*N. meningitidis* is considered to be uniquely capable of causing bacterial meningitis epidemics. Our observation of a meningitis outbreak caused by *S. pneumoniae* in the KND of northern Ghana is, therefore, intriguing. The outbreak exhibited epidemiological and bacteriological features that are characteristic of African meningococcal meningitis epidemics [2], including strong seasonality, a broad host age range, and clonal dominance. The increase in pneumococcal meningitis cases was accompanied by 2 successive outbreaks of meningococcal meningitis. In the KND, the burden of disease for pneumococcal meningitis has met the criterion for the alert status included in the World Health Organization's definition of epidemic meningococcal outbreaks (a threshold of 5 cases/100,000 persons/week); in the neighboring Bolgatanga District, even the criterion for the epidemic status (a threshold of 10 cases/100,000 persons/week) has been fulfilled, in March 2001. Cases of both me-

ningococcal and pneumococcal meningitis were concentrated in the dry season, suggesting that similar factors might have triggered both types of outbreaks. Such factors may include mucosal defenses damaged by the extreme environmental conditions and/or coinfections of the nasopharynx [2]. Care was taken to avoid a bias associated with the well-known seasonality of meningococcal meningitis in the study area: to account for the fact that lumbar punctures were less likely to be performed during the wet season, standardized guidelines for lumbar puncture were applied.

Interestingly, the pneumococcal meningitis cases peaked 1–2 months earlier than the meningococcal meningitis cases. This finding may either (1) reflect a very high invasive capacity of the causative clonal complex of serotype 1 pneumococci or (2) indicate that the factors that trigger pneumococcal and meningococcal meningitis are not entirely the same. In this context, differences in climatic conditions between the early dry season (which includes the Harmattan period, with its cold nights and extremely dusty air) and the late dry season (which brings intense heat) may be relevant. The broad host age range for



**Figure 4.** e-BURST diagram of the sequence type (ST) 217 clonal complex. Included are all Ghanaian serotype 1 *Streptococcus pneumoniae* isolates and 1 Ghanaian serotype 14 *S. pneumoniae* isolate from the present study as well as all serotype 1 lineage B *S. pneumoniae* isolates described by Brueggemann et al. [9]. Lines connect all single-locus variants with each other. Black circles indicate STs found in northern Ghana in the present study, and the no. of isolates found are given. Gray circles indicate serotype 1 lineage B-associated STs not found in northern Ghana [9], and the countries of origin of the isolates are given. Shown is a modification of the original diagram produced by e-BURST, which was edited for the no. of isolates, the origin of non-Ghanaian isolates, and multiple single-locus variant connections.

both meningococcal and pneumococcal meningitis cases shows that age-related differences in the capacity of natural and adaptive immune effector functions are less important for susceptibility to invasive disease than for other epidemiological situations. Lack of spatial clustering suggests that colonization with serotype 1 pneumococci is not focal.

Clonally related bacteria from a common epidemiological source often show limited genotypic variation [21]. Groups of frequent genotypes plus their epidemiologically associated descendants have been designated “clonal complexes” [21] or “genoclouds” [22], which are determined on the basis of a threshold level of MLST allelic identity. The pneumococcal meningitis outbreak in the KND was caused by a serotype 1 clonal complex. The 3 most frequently found STs (ST217 and its 2 single-locus variants, ST303 and ST612) have been described previously [9], indicating that these genetic variants evolved before the outbreak in the KND. However, some of the infrequently isolated locus variants, such as ST1316, ST1322, ST1327, and ST1328, may have emerged locally. It is interesting to note that

ST1331 and ST1325, which were each found twice in the Ghanaian isolates, link an ST618 isolate from The Netherlands with the clonal complex.

Serotype 1 pneumococci are a common cause of invasive disease in many parts of the world but are found only rarely in healthy carriers [6, 9, 23]. Studies comparing the prevalences of *S. pneumoniae* subgroups in persons with invasive disease and in healthy carriers showed that individual serotypes may differ more than 100-fold in their potential to cause invasive disease [23, 24]. Individual clonal complexes that belong to the same serotype have different abilities to cause invasive disease [23], suggesting that clonal complex-specific virulence determinants might be important as well. It is not clear whether the virulence of the 3 major subgroups of serotype 1 pneumococci (which have distinct geographic distributions [9, 25]) is determined primarily by the capsular serotype—and is, therefore, uniform—or whether lineage-specific genetic differences modulate the potential to cause particular types of invasive disease. Our results suggest that the ST217 clonal complex might have

a particular propensity to cause meningitis. However, more studies are needed to verify whether this observation is reflective of a true bacterial phenotype or is merely the result of host and/or environmental factors.

We do not know whether the ST217 clonal complex was imported into northern Ghana recently or whether it has been present for a longer period of time without causing more than sporadic disease. Clonal dissemination of *S. pneumoniae* is usually associated with antibiotic resistance [7], but we observed no significant resistance in the Ghanaian isolates. Therefore, other factors must have led to the increased incidence of pneumococcal meningitis in the KND. Vaccination against *S. pneumoniae* is uncommon in Ghana. However, the massive immunization campaigns with a meningococcal A plus C carbohydrate vaccine that were repeatedly conducted throughout the study period might have played a role. *S. pneumoniae* and *N. meningitidis* both colonize the human nasopharynx, and effective interventions against one of these bacteria is likely to promote competing microorganisms. Vaccination with conjugate vaccines has been shown to reduce nasopharyngeal carriage of the bacterial types included in the vaccine and to lead to replacement by bacterial types not included in the vaccine [26, 27]. Even though polysaccharide vaccines, such as the unconjugated meningococcal A plus C carbohydrate vaccine used in the KND, are generally thought to not affect the prevalence of nasopharyngeal carriage [2], repeated immunization against *N. meningitidis* still might modify the bacterial flora of the nasopharynx [28]. Thus, it is conceivable that the increase in pneumococcal meningitis in the KND, as well as the recently observed outbreaks of non-serogroup A and non-serogroup C meningococcal meningitis [29–31], may have been promoted by mass vaccination against *N. meningitidis*. It will be important to investigate the interactions between these bacteria more closely, especially in the context of vaccination [32].

Serotype 1 is not included in the currently licensed pediatric heptavalent pneumococcal vaccine. This vaccine contains polysaccharides from the 7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) that cause >85% of severe pneumococcal infections in infants and young children in the United States and Canada [6, 26]. The vaccine covers 70% of pediatric isolates from Europe but only 67% and 43% of those from Africa and Asia, respectively [6]. In the KND, serotypes 3, 7F, 8, 12, and 14 accounted for the non-serotype 1 pneumococcal meningitis cases in patients <15 years of age. Excepting serotype 1, the so-called pediatric serotypes (e.g., 1, 5, 6, 9, and 14) [33] were either not found at all or found only rarely. In the present study, the pediatric heptavalent conjugate vaccine would have covered 6% (2/35) of all pneumococcal meningitis cases and 22% (2/9) of the non-serotype 1 pneumococcal meningitis cases in this age group. A nonavalent conjugate vaccine that includes serotype 1 is currently being developed, but such a complex conjugate vaccine may be too expensive for use in mass im-

munization in the African meningitis belt. However, mass vaccination with a less complex conjugate vaccine that targets hypervirulent serotypes should be considered, because increased incidences of pneumococcal meningitis have also been observed in other districts of Ghana (data not shown). Serotype 1 dominance and a broad host age range also seem to be features of the current pneumococcal meningitis situation in Burkina Faso [34, 35]. In view of the high case-fatality rate of pneumococcal meningitis, there is an urgent need for improved treatment options that are suitable for countries with limited resources as well.

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