Prospective Study of a Serogroup X *Neisseria meningitidis* Outbreak in Northern Ghana

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After an epidemic of serogroup A meningococcal meningitis in northern Ghana, a gradual disappearance of the epidemic strain was observed in a series of five 6-month carriage surveys of 37 randomly selected households. As serogroup A *Neisseria meningitidis* carriage decreased, an epidemic of serogroup X meningococcal carriage occurred, which reached 18% (53/298) of the people sampled during the dry season of 2000, coinciding with an outbreak of serogroup X disease. These carriage patterns were unrelated to that of *Neisseria lactamica.* Multilocus sequence typing and pulsed-field gel electrophoresis of the serogroup X bacteria revealed strong similarity with other strains isolated in Africa during recent decades. Three closely related clusters with distinct patterns of spread were identified among the Ghanian isolates, and further microevolution occurred after they arrived in the district. The occurrence of serogroup X outbreaks argues for the inclusion of this serogroup into a multivalent conjugate vaccine against *N. meningitidis.*

Neisseria meningitidis can be classified into ⩾13 distinct serogroups on the basis of the antigenicity of the polysaccharide capsule [1]. Serogroups A, B, and C are responsible for >90% of invasive meningococcal infections worldwide. Most large meningitis epidemics are caused by serogroup A meningococci. Since World War II, such epidemics have been rare in industrialized countries but they occur periodically in the African meningitis belt and in China [2–6]. Serogroup C meningococci also cause disease outbreaks and occasionally epidemics [7, 8]. Endemic disease usually is caused by meningococci belonging to serogroup B or C, but occasionally disease is caused by bacteria in other serogroups, including W135, Y, and X. *N. meningitidis* serogroup X was described in the 1960s [9, 10], and a limited number of serogroup X meningococcal disease cases have been reported in North America [11], Europe [12, 13], Australia [14], and Africa [15, 16]. Some have been associated with complement deficiencies [17, 18] or AIDS [19]. Recently, 2 outbreaks of serogroup X meningococci occurred in Niger [20, 21]. Serogroup X bacteria were found to be very efficient in colonizing a group of military recruits in the United Kingdom [22].

In the African meningitis belt, epidemics of serogroup A meningococci occur in cycles every 8–12 years, and each epidemic wave follows a multiyear crescendo-decrescendo pattern [23]. Disease incidence is seasonally dependent, peaking during the dry season (December–May) and declining rapidly with the onset of the rainy season [24]. Even during major epidemic waves, case numbers are low during the rainy season [23]. The underlying mechanisms leading to the spread of meningococci and to epidemics of meningococcal disease remain unknown. Carriage rates of 15% can occur during epidemics in Africa [25, 26]. A population's susceptibility to epidemic disease might return as antibody levels decline and herd immunity is diluted by new birth cohorts and migration [23]. Variation in virulence between strains of *N. meningitidis* and the introduction of a new meningococcal clone into a susceptible population also might contribute to an epidemic. The extreme environmental conditions present in the sub-Saharan meningitis belt during the dry season—high temperature, low absolute humidity, and the Harmattan (a dusty wind that blows from the Sahara)—plus respiratory coinfections are thought to contribute to an enhanced susceptibility to meningococcal disease by damaging the local mucosal defenses [23].

Most persons infected with meningococci are only colonized. They carry the bacteria asymptomatically in the nasopharynx, and only a small proportion of these carriers develop invasive meningococcal disease. Therefore, epidemiologic analysis of meningococcal infection in defined populations should include both carrier and case patient studies. However, even carriage studies probably detect only a small proportion of the strains colonizing humans [27]. Meningococci can acquire foreign genes by DNA transformation from unrelated bacteria, including commensal neisseriae [28]. Serologic cross-reactions between *Neisseria lactamica* and *N. meningitidis* have been demonstrated, and it has been argued that the carriage of *N. lactamica* may have a role in the development of natural immunity to meningococcal disease [29]. Despite the importance of meningococcal

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infection as a cause of morbidity and mortality in countries of the African meningitis belt, few longitudinal carriage studies have been undertaken in this region [25, 26].

In the dry seasons between November 1996 and May 1997, a meningitis epidemic occurred in northern Ghana [30]. In total, 18,551 cases and 1403 deaths were reported [31]. During the 1996–1997 epidemic, 1396 cases and 65 deaths were registered in the Kassena-Nankana District (KND; Upper East Region) [32]. One year later, a smaller meningitis outbreak occurred in the same district with 50 serogroup A subgroup III cases and 10 deaths [16]. To investigate the dynamics of meningococcal carriage, we conducted a longitudinal carriage study in the KND during 1998–2000 when an outbreak of serogroup X meningococcal meningitis with a high carriage rate occurred.

Methods

Study area and population. The study was conducted in the KND of the Upper East Region of Ghana. The district lies within the guinea savannah woodland area, has a population of 140,000, and has 2 main seasons: a short wet season from June to October and a long dry season the rest of the year. The general population is rural except for those living in the town of Navrongo (population ~20,000). People live in residential compounds with an average of 10 inhabitants each.

Suspected meningitis patients presenting at the War Memorial Hospital, Navrongo, or at 1 of the 3 health centers in the KND were recruited throughout the study period. In accordance with World Health Organization guidelines [5], a suspected case was defined by sudden onset of fever and stiff neck or fever and stiff neck and altered mental status. A lumbar puncture was done before treatment, and the cerebrospinal fluid specimen was analyzed as described elsewhere [16]. Because of the 1997 epidemic and the various vaccination campaigns in KND, the population was clearly attuned to the danger of meningitis, and most patients were likely to present at a health facility.

Residential compounds were selected randomly from a complete listing of the district population (Navrongo Demographic Surveillance System [33]). One compound refused to participate and was replaced by the next eligible one on the random listing. The 37 selected compounds were sampled 5 times between March 1998 and April 2000, once in each dry and rainy season. At the time of the visit, a throat swab was taken from all compound members who agreed to participate. The swabs were inoculated directly on Thayer-Martin agar plates (Difco) that were transported to a laboratory within 2 h. The agar plates were incubated in candle jars for 24 h at 37°C.

Characterization of bacteria. Up to 10 random colonies with neisserial morphology were subcultured from each plate. Bacteria that were gram-negative diplococci that produced cytochrome oxidase from N,N,N′,N′-tetramethyl-1,4-phenylene-diammoniumdichloride (Merck) and utilized glucose and maltose but not sucrose in cystine-trypticase agar (Difco) were analyzed further. Those with β galactosidase (ONPG disks; Oxoid) were classified as *N. lactamica,* and those with γ-glutamyltransferase activity (MPR 2-kit; Boehringer Mannheim) were classified as *N. meningitidis.* Isolates from these species were stored in 10% skim milk (Difco) on glass beads at −70°C. The frozen samples were transported to Switzerland in liquid nitrogen or on dry ice.

Meningococci were serogrouped by slide agglutination with serogroup-specific antisera (Murex) and were serotyped or subtyped with monoclonal antibodies by whole cell ELISA [4]. They also were screened for diversity by pulsed-field gel electrophoresis (PFGE) after digestion with *Nhe* I and *Spe* I [34]. Multilocus sequence typing (MLST) was performed [35] on a subset of 20 isolates representing the different PFGE variants of the different serogroups.

Data analysis. We calculated the prevalence of carriage with STATA statistical software [36]. To evaluate age and sex effects on prevalence, we used logistic regression models including random effects, to allow for repeated assessment of the same persons. The incidence (acquisition) of carriage was estimated by using paired samples from successive surveys with the following formula: number of new acquisitions/(person-intervals at risk × duration of interval). The person-intervals at risk were defined as pairs of samples where bacteria were not present in the first sample, and new acquisitions were defined as pairs in which bacteria were present in the second sample. Age and sex effects on incidence of infection (acquisition) were assessed by logistic regression analysis.

For serogroup X isolates, distinct *Nhe* I and *Spe* I fragments were assigned arbitrary numbers. The presence or absence of each fragment was scored in a data matrix as plus (1) or minus (0). We used the data matrix to construct a neighbor-joining tree (MEGA version 2b3 [37]) based on the number of band differences between PFGE patterns. For serogroup X strains, a matrix of pairwise geographic distances between the compound of isolation was compared with the data matrix of genetic distances by a Mantel test with 10,000 permutations (GENETIX version 4.01 [38]).

Results

The longitudinal carriage rate of *N. meningitidis* and *N. lactamica* was investigated between 1998 and 2000 in the KND. Throat swabs taken on 5 occasions from 292–308 inhabitants of 37 randomly selected residential compounds were investigated bacteriologically. Only 2 persons refused to participate further after the first survey and were excluded from the analysis. Overall, 493 persons (43% males) participated in the study. The mean age of the participants was 25 years (SD, 20 years). The study population did not get older because we also recruited babies. Retrospective questionnaire responses regarding immunization with A/C polysaccharide were available for 377 participants (76%). The estimated vaccine coverage in KND was 84%.

Prevalence and incidence of carriage. The carriage rate of *N. lactamica* remained constant at ~9% with no difference between the dry and the wet season. However, the carriage rate of *N. meningitidis* of different serogroups changed dramatically. Carriage of serogroup A meningococci dropped continuously from 3% in April 1998 to ≤0.3% in April 2000 (table 1). All 14 serogroup A isolates were A:4,21:P1.9 and possessed PFGE patterns similar to those of disease isolates from the 1998 meningitis outbreak (data not shown). Three representative isolates

Table 1. Carriage of *Neisseria lactamica* and different serogroups of *Neisseria meningitidis* during 5 longitudinal carriage surveys in northern Ghana.

Bacterial strain present	MLST type	Subgroup complex	April 1998, DS (n = 300)	Nov 1998, RS (n = 299)	April 1999, DS (n = 292)	Nov 1999, RS (n = 308)	April 2000, DS (n = 298)	Total (n = 1497)	Percentage of meningococcal isolates	Change over time	
										LRT χ^2_1	P
N. lactamica	—	—	28 (9.3)	26 (8.7)	24 (8.2)	30 (9.7)	25 (8.4)	133 (8.9)	—	—	NS
N. meningitidis	—	—	14 (4.7)	9 (3.0)	15 (5.1)	13 (4.2)	59 (19.8)	110 (7.4)	100		
A:4,21:P1.9	ST5	III	9 (3.0)[a]	4 (1.3)[b]	2 (0.7)	1 (0.3)	0 (<0.3)	16 (1.1)[a,b]	14.5	15.6	<.001
X:NT:P1.5	ST181/ST751	—	0 (<0.3)	0 (<0.3)	10 (3.4)	7 (2.3)[a]	53 (17.8)[a]	70 (4.7)	63.6	94.3	<.001
Y:4:P1.5	ST168	—	4 (1.3)	3 (1.0)[a]	2 (0.7)	3 (1.0)[a]	5 (1.7)[a]	17 (1.1)[d]	15.5	—	NS
W135:2a:P1.2,5	ST11	ET-37	1 (0.3)	1 (0.3)	0 (<0.3)	0 (<0.3)	0 (<0.3)	2 (0.1)	1.8		
PolyAG:NT:NST	ND	—	0 (<0.3)	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)	5 (0.3)	4.5		

NOTE. Data are no. (%) of subjects, except where noted. DS, dry season; LRT, likelihood ratio test from logistic regression; MLST, multilocus sequence typing; ND, not done; NS, not significant; NST, nonsubtypeable; NT, nontypeable; polyAG, polyagglutinable; RS, rainy season.

[a] PolyAG, 1 isolate.

[b] Nongroupable, 1 isolate.

[c] PolyAG, 2 isolates.

[d] PolyAG, 3 isolates.

were MLST sequence type ST5, as is typical of subgroup III bacteria from Africa [39].

Serogroup X bacteria were first isolated in 1999 (3% of samples) and comprised 18% of samples in the dry season of 2000 (table 1). The estimated incidence (acquisition rate) was 0.6 per 100 person months for *N. lactamica,* 1.0 for serogroup X meningococci, and 0.2 for meningococci of other serogroups (table 2).

The carriage rate of *N. lactamica* was highest among children <5 years old and decreased continuously with age (figure 1). In contrast, serogroup X carriage was highest among 5–14-year-olds. Females were more likely to acquire *N. lactamica* (table 2). Males were at higher risk of carrying serogroup X meningococci than were females (odds ratio [OR], 2.0; 95% confidence interval [CI], 1.2–3.3), but there was no significant difference in acquisition (table 2). Males were also more likely to carry (OR, 3.9; 95% CI, 1.4–10.9) and to acquire meningococci of other serogroups (table 2).

Only 3 persons were colonized simultaneously by *N. meningitidis* and *N. lactamica,* which was fewer than expected, assuming independence ($P < .02$, Fisher's exact test). However, persons carrying *N. lactamica* at any one time were equally likely to become serogroup X carriers in subsequent surveys as those who did not carry *N. lactamica.* The acquisition of serogroup X bacteria did not differ significantly between compounds with *N. lactamica* carriers and compounds without carriers.

People living in compounds with ⩾1 *N. lactamica* carrier were more likely to acquire *N. lactamica* (secondary colonization) than were persons living in compounds without carriers (OR, 5.0; CI 95%, 2.1–12.1). As expected for an epidemic outbreak, most persons from whom serogroup X bacteria were isolated lived in compounds where these organisms had not been recovered previously. Nearly 60% of the compounds sampled became newly infected with serogroup X bacteria at some point during the study. On average, 35% of a compound's inhabitants (2.5 ± 2.0 persons; range, 1–8 persons) carried serogroup X meningococci on the first occasion that the bacteria were detected in that compound. Vaccination with A/C polysaccharide had no effect on colonization with serogroup X.

Cases of meningococcal meningitis. The last confirmed serogroup A meningococcal meningitis case occurred in the second epidemic year—during the 1998 dry season [16]. In contrast, 9 cases (56% in males) of meningitis were caused by serogroup X meningococci from March 1998 to April 2000. One of these cases occurred in the 1998 dry season during the serogroup A outbreak and was fatal. A second fatal case occurred during the 1999 dry season. During the 2000 dry season, 7 patients were identified and all survived. The median age of the 9 patients was 6 years (mean, 9.7 years; range, 1–32 years). Serogroup X disease was not associated with complement or properdin deficiency in any of the 4 serum samples tested [41].

Table 2. Sex differences in incidence (acquisition) of carriage of *Neisseria lactamica* and different serogroups of *Neisseria meningitidis* (per 100 person months) estimated from sequential samples.

Serogroup acquired	Total	Males[a]	Females[a]	Age-adjusted odds ratio	LRT χ^2_1	P
Serogroup X	1.0 (0.7–1.3)	1.2 (0.8–1.7)	0.8 (0.5–1.1)	1.6 (0.9–2.7)	2.4	.12
Other serogroups	0.2 (0.1–0.4)	0.3 (0.1–0.6)	0.1 (0.02–0.3)	3.4 (0.9–12.8)	3.6	.06
N. lactamica	0.6 (0.4–0.8)	0.3 (0.1–0.6)	0.8 (0.5–1.2)	0.4 (0.2–0.9)	6.0	<.02

NOTE. Data are odds ratio (95% confidence interval). LRT, likelihood ratio test from logistic regression.

[a] Binomial exact odds ratio.

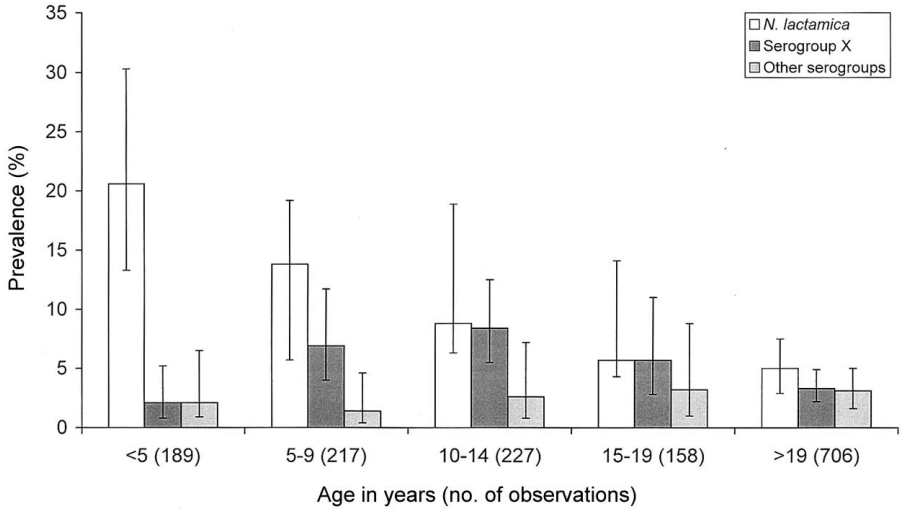

Figure 1. Age distribution by prevalence of carriage of *Neisseria lactamica* and different serogroups of *Neisseria meningitidis.* Error bars indicate 95% confidence intervals on the basis of a logistic model that allowed for repeated measurements with the SAS GENMOD procedure [40].

Population structure and spread of serogroup X meningococci. We obtained serogroup X meningococcal isolates from Africa (dating from 1970 to 2000); all the isolates, including both disease and carrier isolates, could be assigned to 2 groups, a and b, by PFGE (authors' unpublished data). Most serogroup X isolates from Chad, Mali, and Niger were group a; strains from Burkina Faso were group b. These PFGE patterns differ in 4 *Nhe* I and 3 *Spe* I fragments. Of the 79 serogroup X isolates from Ghana, 78 belonged to group b and 1 belonged to group a (figure 2, *track 14*). The group a isolate was MLST type ST181; 12 representative group b isolates were ST751, which differs at 2 of the 7 MLST loci. The group b isolates from Ghana were not totally uniform by PFGE. They shared 11 uniform *Nhe* I bands (figure 2), but 8 other bands were polymorphic. Four smaller fragments could not be evaluated because of lack of resolution. Similarly, the group b isolates contained 19 uniform *Spe* I fragments, 6 that

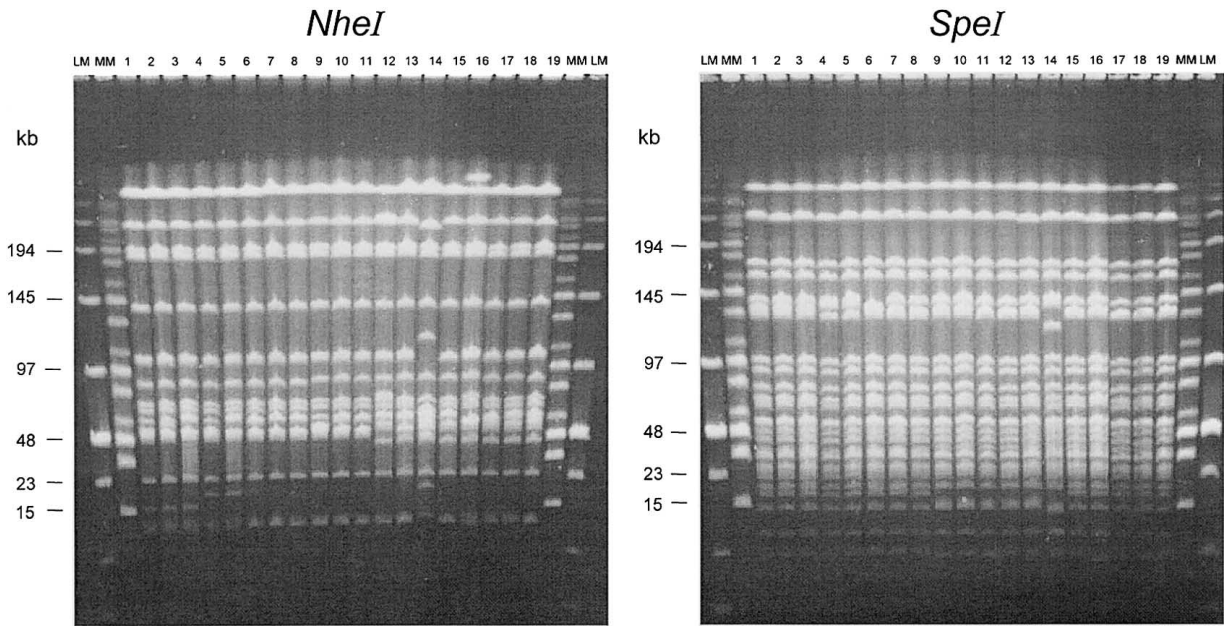

Figure 2. Pulsed-field geld electrophoresis patterns of *Nhe* I- and *Spe* I-digested chromosomal DNA of representative serogroup X meningococci from northern Ghana. Strains were loaded in tracks 1–19 in the following order (*track,* strain): *1,* Z9389; *2,* Z9396; *3,* Z9381; *4,* Z9292; *5,* Z9295; *6,* Z9399; *7,* Z9401; *8,* Z8329; *9,* Z8331; *10,* Z9301; *11,* Z9300; *12,* Z9297; *13,* Z9383; *14,* Z9413; *15,* Z9294; *16,* Z7091; *17,* Z8336; *18,* Z9392; and *19,* Z9293. Molecular weight markers were loaded in the flanking tracks as indicated (LM, low range marker; MM, midrange marker). Molecular weights are at left.

were polymorphic, and 3 that could not be evaluated. The combined data from both restriction digests resulted in 9 PFGE subtypes within the group b Ghanaian isolates (figure 2).

Phylogenetic analysis of the PFGE data showed that 8 of the 9 subtypes from group b belonged to 3 clusters (1–3) and that 1 subtype represented by the sole isolate from 1998 was very different. Both neighbor-joining (figure 3) and maximal parsimony algorithms (data not shown) yielded comparable results. For the cluster 1–3 isolates, there was significant correlation between the pairwise genetic distances and the geographic distances between the compounds of isolation (Pearson $r = 0.34$; $P < .0001$, Mantel test). The correlation was even stronger between geographic distances and cluster assignment (Pearson $r = 0.43$; $P < .0001$, Mantel test). All 3 clusters were isolated from both carriers and meningitis patients (cluster 1, 4 patients; cluster 2, 1 patient; and cluster 3, 3 patients). There was no significant difference in the patient:healthy carrier ratio among clusters.

All 3 clusters were found in 1999. Clusters 1 and 3 also were isolated in Burkina Faso from 1996 to 1998 (figure 3). These results suggest that the 3 clusters evolved outside the district and were imported concomitantly in 1999. The 3 clusters showed different patterns of spread. Cluster 1 bacteria colonized only 1 compound in 1999 and spread extensively through the central part of the district in 2000 (figure 4). Cluster 2 colonized a few compounds in the eastern part of the district in 1999 and spread to only 3 other compounds thereafter. Cluster 3 spread from east to west and continued to diversify (figure 3). Cluster 3 isolates from 1999 and Burkina Faso (1998) were located in branches nearer the root of the tree and seem to be ancestral. Most cluster 3 isolates from 2000 were in descendent twigs, indicating recent descent.

Discussion

Meningococcal carriage rates of up to 30% are observed during serogroup A epidemics in Africa [23], but lower carriage rates have occurred in some epidemics [42], and carriage is generally infrequent during interepidemic periods [8, 25, 26]. A major serogroup A epidemic occurred in northern Ghana in 1996–1998 [16]. The data presented here show that, in 1998, the carriage prevalence of the epidemic strain was only 3%. During the following 2 years, serogroup A carriage decreased even further, and no serogroup A carrier was identified in 2000. These results resemble those for a serogroup A subgroup IV-1 epidemic in The Gambia in the 1980s [26].

There was an initial increase in carriage of serogroup X during the 1999 dry season followed by a second strong increase during the 2000 dry season. Season has no effect on meningococcal carriage in temperate zones and in Africa [24, 43, 44] and is, therefore, unlikely to account for the observed increase in serogroup X carriage. In contrast, similar temporal patterns are typical of serogroup A epidemics in the African meningitis belt, where large epidemics are often preceded by localized outbreaks 1 year earlier [23]. The prevalence of serogroup X carriage was highest in 10–14-year-olds, which is similar to the age patterns frequently observed for both serogroup A carriage and disease [45]. Although there were sex differences in carriage prevalence and incidence in *N. lactamica* and meningococci of other serogroups, there was no such difference in acquisition of serogroup X bacteria, reflecting the epidemic nature of the colonization process—that is, the whole population was at risk. Furthermore, serogroup X meningococci were acquired mostly through primary colonization, which suggests that a new bacterial wave was entering the area.

Our findings are consistent with the hypothesis that, in the African meningitis belt, meningococci of different serogroups invade specific populations in successive waves. Low carriage rates during interepidemic periods alternate with periods of high carriage, which can result in epidemics of disease if the bacteria are particularly virulent. However, frequent carriage of bacteria of low virulence normally would not be documented because of the low burden of disease. The ratio of cases of serogroup A disease per carrier in 1998 was 40-fold higher than that for serogroup X meningococci in 2000. These different case-to-carriage ratios possibly reflect such differences in virulence. However, it has been postulated that epidemic disease reflects a lack of herd immunity [23], and it is possible that carriage of serogroup A bacteria during 1996–1998 stimulated protective immunity against subsequent disease by serogroup X meningococci. Secondary factors, such as respiratory tract coinfections, also may be necessary for epidemics to occur [8] and might have been lacking during the epidemic of colonization by serogroup X meningococci. Meningococcal disease (as opposed to carriage) is highly seasonal in the African meningitis belt [24], and all 9 cases of meningococcal meningitis in our study occurred exclusively during the dry season.

It has been suggested that exposure to *N. lactamica* may stimulate natural immunity to meningococcal disease [29, 43]. A negative correlation between carriage of *N. lactamica* and either carriage of *N. meningitidis* or meningococcal disease was found in the Faroe Islands [46]. In one African study involving *N. lactamica,* there was no association between carriage of *N. meningitidis* and *N. lactamica* [25]. We found a negative association between the carriage of both species in this study. However, carriage of *N. lactamica* did not correlate with the acquisition of serogroup X meningococci or its absence, either at the individual or the compound level. Thus, it appears that, in the African meningitis belt, carriage of *N. lactamica* does not reduce colonization of the nasopharynx with serogroup X meningococci but could still protect against serogroup A infections. The age and sex patterns of prevalence and acquisition of *N. lactamica* differed from those of *N. meningitidis. N. lactamica* was carried predominantly by infants and young children, which is similar to data from Europe and other African studies [25, 43, 46, 47]. *N. lactamica* was acquired mainly in compounds where carriers were already present, indicating that it is transmitted from per-

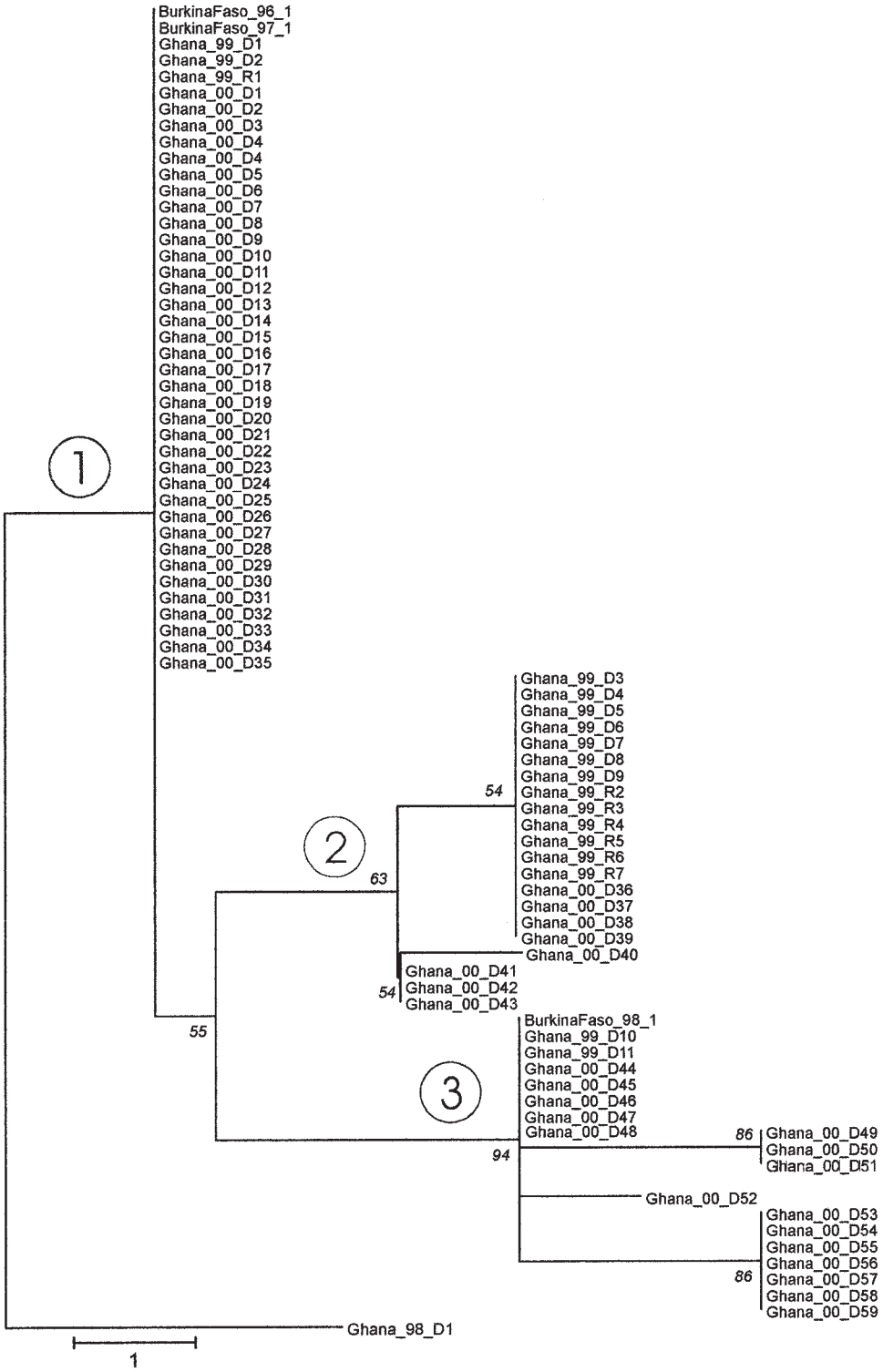

Figure 3. Neighbor-joining tree based on the pulsed-field gel electrophoresis subtypes of serogroup X meningococci isolated in northern Ghana. Distance used was no. of band differences. Nos. at nodes are percentages of 1000 bootstrap replicates in which the nodes appeared. Only nodes with >50% are indicated. Strains labeled "D" or "R" were isolated during the dry or rainy seasons, respectively.

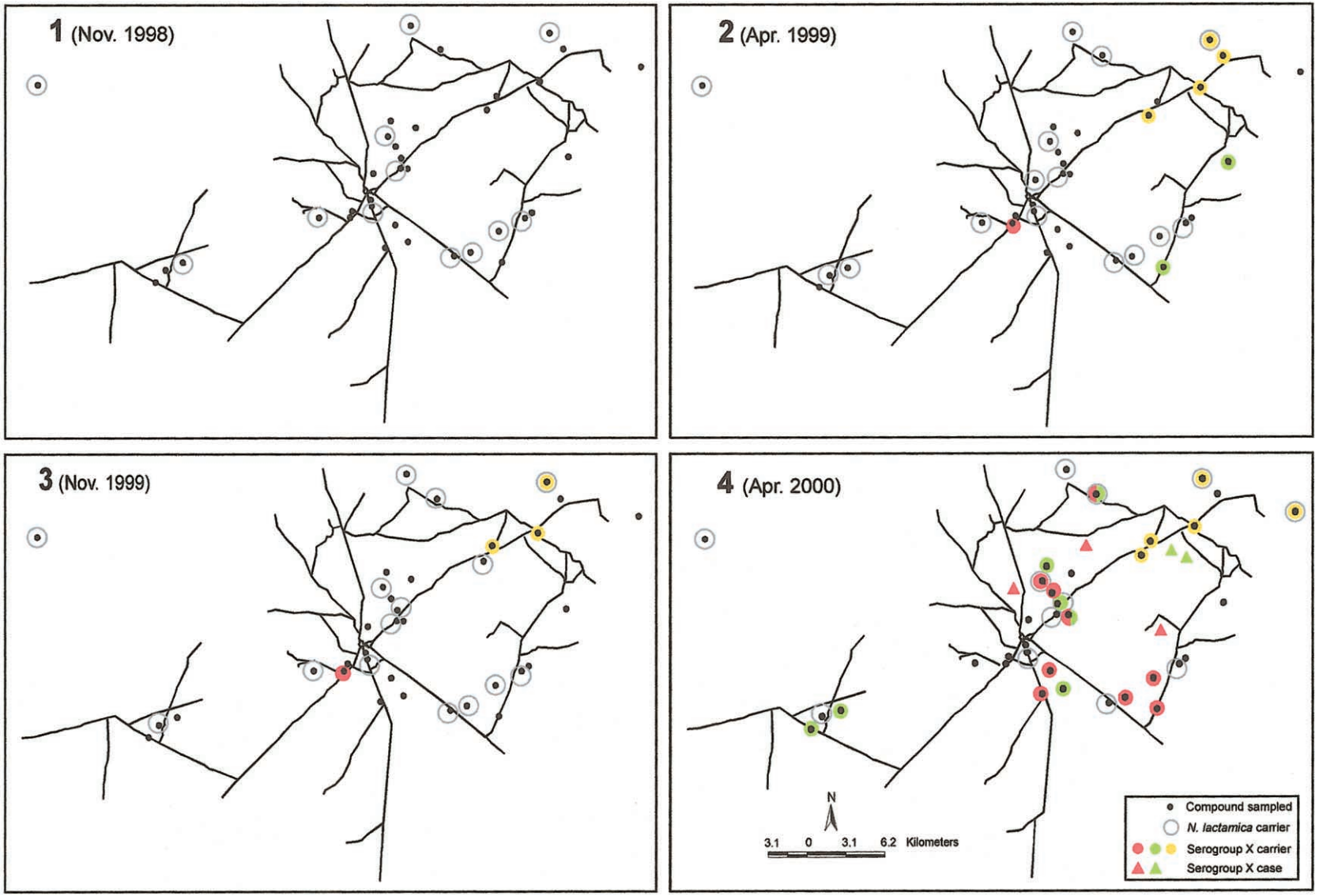

Figure 4. Spatial distribution of housing compounds with carriers of serogroup X *Neisseria meningitidis* and *Neisseria lactamica* at different time points. Black dots indicate compounds sampled. Red, yellow, and green dots indicate compounds in which serogroup X *N. meningitidis* carriers were identified. The colors correspond to the 3 clusters identified by phylogenetic analysis (figure 3). *Colored triangles,* compounds in which meningitis cases were identified; *gray circles,* compounds with *N. lactamica* carriers.

son to person within compounds and that recolonization probably is frequent.

The serogroup X meningococci that colonized the KND population have been isolated in West Africa for ⩾3 decades (authors' unpublished data). Bacteria belonging to the same clonal grouping caused a meningitis outbreak with >60 cases in Niger in 1997, although, during that period, most of the meningococcal meningitis cases were caused by serogroup A [21] (authors' unpublished data). Some microheterogeneity was found among the Ghanaian serogroup X isolates. The different PFGE types identified clustered in 3 phylogenetic clusters that did not differ in virulence but exhibited very distinct patterns of dispersal. Cluster 1 spread extensively without genetic diversification. Cluster 2, which was more diverse than cluster 1, colonized only a few compounds and did not spread further. Cluster 3 spread and diversified during the process.

Although serogroups A, B, and C are responsible for >90% of meningococcal disease worldwide, recent outbreaks of serogroup X and W-135 meningococci illustrate that these serogroups also have considerable pathogenic potential [20, 21, 48]. In *Streptococcus pneumoniae,* the introduction of polyvalent capsule polysaccharide conjugate vaccines seems to have induced changes in bacterial population structure of carrier isolates [49, 50]. The effects of widespread immunization with conjugate polysaccharide vaccines on the population structure of meningococci is also under discussion [51]. Selection can lead to frequent isolation of escape variants [28, 39]. It is possible that the mass vaccination with A/C polysaccharide in 1997 and 1998 in northern Ghana might have contributed to the colonization and disease by serogroup X. Although serogroup X usually causes only a small proportion of meningococcal disease, repeated vaccination against serogroups A and C in many African countries has the potential to select meningococci of other serogroups (e.g., serogroup X) and might result in a changed profile of meningococcal disease. This possibility should be considered when conjugate vaccines carrying limited ranges of serogroups are introduced. It is important that more comprehensive conjugate vaccines that include X polysaccharide be developed as soon as possible.

Acknowledgments

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