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Review

A hypothetical explanatory model for meningococcal meningitis in the African meningitis belt☆

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SUMMARY

Despite much progress in surveillance and biological research, no explanation exists to date for the epidemic pattern of meningitis in the African meningitis belt, which is required to mathematically model the impact of vaccine strategies or to predict epidemics. This paper presents a hypothetical explanatory model for epidemic meningococcal meningitis. Four incidence patterns are defined as model states, including endemic incidence during the rainy season, ubiquitous hyperendemicity during the dry season, occasional localized epidemics, and–at the regional level–regular epidemic waves spanning over communities or years. While the transition from endemic to hyperendemic situation in a community is caused by an increase in risk of meningitis given colonization by a virulent meningococcus (due to damage of the pharyngeal mucosa by dry climate), the transition from hyperendemic to epidemic situation involves increased pharyngeal colonization and transmission (possibly caused by viral respiratory infection epidemics). The described mechanisms are sufficient to explain the 10- to 100-fold incidence increase that both transitions usually imply. Epidemic waves occur if new meningococcal strains which escape pre-existing immunity, enter the population. Future research should include the impact of viral co-infection on bacterial colonization and invasion.

Introduction

Epidemic meningococcal disease in sub-Saharan Africa probably occurred first in the late 19th century.[1] A few decades later, Lapeyssonnie described the particular epidemiological pattern of meningococcal meningitis in an area spanning from Mali to Sudan, which he named the 'meningitis belt'.[2] He described an 'endemo-sporadic' incidence beyond that observed on other continents, with 'seasonal re-enforcement' and regular epidemic waves. Further particularities of meningococcal disease in the meningitis belt, which today is defined by a larger area, spanning from Senegal to Ethiopia,[3] include a preponderance for meningitis as the primary clinical syndrome rather than septicemia[4] (although surveillance may underestimate the latter due to poor access to health care), and the predominance of serogroup A over other serogroups for sporadic and epidemic disease.[5,6]

The recent development of a serogroup A conjugate meningococcal vaccine specifically for preventive use in African countries (Meningitis Vaccine Project, www.meningvax.org) promises a substantial decrease in meningococcal serogroup A epidemic disease over the coming decade. Mathematical models will be useful to evaluate different vaccination schedules with this vaccine with regard to their impact, similar to research conducted around the group C conjugate vaccine in the UK.[7] These transmission dynamic models, however, require assumptions about the meningococcal transmission pattern in relation to seasons and epidemics, which have not yet been identified. In addition, because serogroups other than group A also have epidemic potential, attempts are being made to mathematically predict epidemics based on meteorological data.[8–11] These projects usually model district-level epidemic data as a function of variables such as rainfall, wind speed, dust load, and air humidity. Finally, understanding the mechanisms that lead to the unique epidemiological patterns would also be of interest for prevention and control of other infectious diseases with epidemic potential.

Several years ago, Moore[12] and Griffiss[13] proposed explanatory models for epidemic meningitis. However, neither model allows combining the relevant factors (strain biology, immunity, and climate/environment) to explain the observed disease incidence and carriage patterns. This paper presents a hypothetical explanatory model for the epidemiology of meningococcal meningitis in the African meningitis belt, which may guide further research and the development of mathematical models and preventive interventions. We review herein the typical incidence and carriage patterns before assembling them into a hypothetical model.

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The incidence pattern

The following description of incidence patterns is based on a variety of data sources, including: (1) national routine surveillance data for the last decade available from the ministries of health in Burkina Faso, Mali and Niger, which represent weekly or annual numbers of suspected meningitis cases per district or country as reported by health care agents; (2) routine surveillance data for the last five years, which were obtained from selected sanitary district authorities in western Burkina Faso and Mali and which represent weekly numbers of suspected meningitis cases per health center as reported by health care agents; (3) published data on etiology- and age-specific incidence rates over time from surveillance studies at study sites (one or several districts) in Burkina Faso, Niger and northern Ghana.

Endemic period

During the rainy season, approximately June through November, the incidence of meningococcal disease in the meningitis belt is low, with weekly incidence rates in most districts of 0–0.5 per 100 000 (data: ministries of health, Burkina Faso, Mali and Niger). Figure 1a illustrates this using the example of three sanitary districts in western Burkina Faso during 1997–2008. This 'endemic' incidence is comparable to that observed in Europe.[14] For example, in France, annual incidence rates of meningococcal disease (all serogroups combined, 77% as meningeal syndrome) vary between <1 and 5 per 100 000 across regions and years. This corresponds to an average weekly incidence rate of <0.001 to 0.1 per 100 000, where the peak in late winter implies a doubling of incidence compared to the lowest incidences during the summer and autumn.[15–17] Incidence estimates from Africa may be biased in one direction by limited access to health care and in the other by case definitions based on clinical syndromes rather than laboratory confirmation (which also means that a substantial part of the non-epidemic morbidity is due to pneumococcus, not only meningococcus[18]). Taken together, endemic meningococcal disease incidence during the rainy season in the meningitis belt seems to be roughly comparable to that observed in Europe and other continents.

By contrast, during the dry season, three features distinguish its pattern: hyperendemicity, localized epidemics, and epidemic waves.

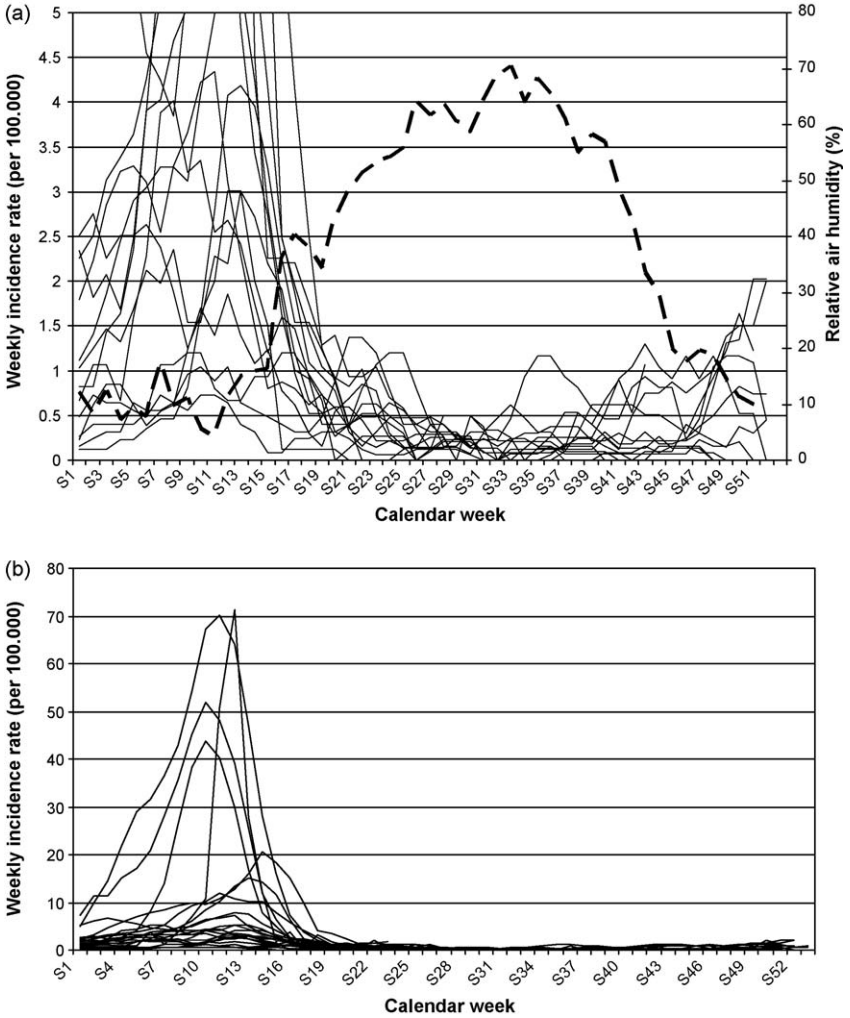

Figure 1. Example of weekly incidence rates (per 100 000, 4-week moving average) of notified suspected meningitis cases and air humidity in the meningitis belt. Sanitary districts Secteur 15 (400 000 inhabitants) and Houndé (250 000 inhabitants) in western Burkina Faso, 1997–2008. Data: Direction Régionale de Santé des Hauts-Bassins, Burkina Faso. (a) Scale of *y*-axis up to 5 per 100 000; hatched line, relative air humidity measured at the Bobo-Dioulasso airport during 2006. All districts experience hyperendemic incidences of about 1 per 100 000 during all years. (b) Scale of *y*-axis up to 80 per 100 000. Epidemics were declared at the district level only during some years (here during 1996, 2002, and 2006).

Hyperendemicity

During each dry season, most districts in the meningitis belt experience an increase in meningitis incidence, a period usually described as meningitis season (data: ministries of health, Burkina Faso, Mali and Niger). During this hyperendemic situation, which is only observed during the dry season, district level weekly incidence rates (of reported suspected cases) usually rise to 1 per 100 000 and well above, as illustrated in Figure 1a. For example, in Burkina Faso during January through May 2008, 96% and 79%, respectively, of the 63 sanitary districts reported a weekly incidence rate above 1 or 2 during at least 4 weeks, and 89% and 63%, respectively, reported a rate above 1 or 2 during at least 8 weeks (data: Ministry of Health, Burkina Faso). This hyperendemic increase is also seen in laboratory-confirmed meningococcal cases.[6,19–22] As shown by bacterial meningitis surveillance studies in northern Ghana and Burkina Faso, pneumococcal meningitis incidence in the meningitis belt also increases during the dry season and therefore contributes to a certain extent to this hyperendemic meningitis situation during the dry season.[18,22] Overall, compared to the endemic situation, meningococcal meningitis incidence during the hyperendemic period seems to be multiplied by a factor of about 10–100.

Localized epidemics

Exclusively during the dry season and in addition to hyperendemic incidence, epidemics may occur in some communities of the meningitis belt in given years (Figure 1b). On the district level, weekly incidence rates of ≥10 per 100 000 are considered epidemic. In Burkina Faso during January through May 2008, 27% of districts showed such weekly incidence rates of ≥10 during at least one week. Although useful for planning of reactive vaccination, district level incidence rates likely hide the true force and localization of epidemics, and the weekly incidence threshold of 10 for distinguishing hyperendemic from epidemic situations may be too low at the community-level. Typically, if entire sanitary districts are in an epidemic situation as defined, the majority of health centers report weekly incidence rates below 20, while rates of 20–100 and ≥100 are observed in only a few health centers and only during a few weeks. Furthermore, incidence rates seem to increase suddenly within two or three weeks. This pattern can consistently be observed over the years in health center-level national surveillance data of meningitis belt countries, while the number and extent of such localized epidemics in a given region vary over the years (data: ministries of health, Burkina Faso and Mali). In addition, among the population served by a given health center, only a few villages may experience the epidemic, as shown by several reports of such highly localized epidemics.[23–25] Two surveillance studies conducted during localized epidemics in Burkina Faso reported a peak weekly incidence rate of 247 per 100 000 for confirmed meningococcal meningitis cases[23] and a peak attack proportion (for the total duration of the epidemic) of suspected cases of 2.8%.[25] However, to date, there is no formal threshold definition of localized epidemics on the community level, which would require a large-scale systematic analysis of health center-level data in the meningitis belt. A weekly incidence rate of 50 or 100 per 100 000 may be considered a preliminary threshold definition.

In conclusion, if hyperendemic disease incidence found in most communities during the meningitis season was defined as weekly incidence rates of 1–20 per 100 000 on the community level, and weekly incidence rates during localized epidemics range from 50 to 1000 per 100 000, it can be estimated that incidence during localized epidemics compared to hyperendemic incidence is multiplied by a factor of about 10–100, and this over several weeks. This epidemic increase in incidence is most likely unique for meningococcus, as no

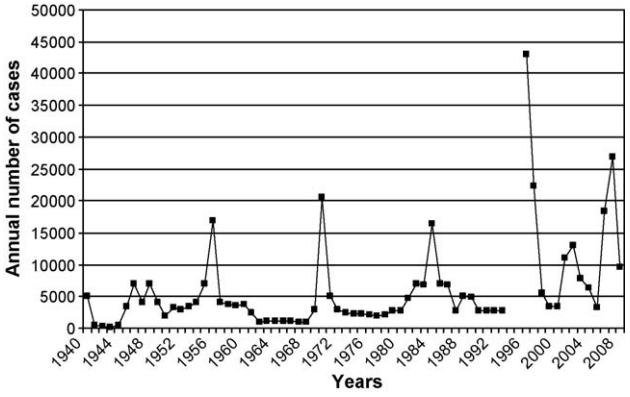

Figure 2. Annual total number of reported suspected meningitis cases, Burkina Faso, 1940–2008. Data: Ministry of Health, Burkina Faso.

such localized meningitis epidemics, only seasonal hyperendemicity, have been reported for other common bacterial meningitis agents involving all age groups, such as pneumococcus.[20,22]

Epidemic waves

If the communities of a given country had an independent and constant risk of localized epidemics, the total annual number of notified meningitis cases in the country should be fairly constant. However, this number is subject to great yearly variation, as shown in several meningitis belt countries.[19,26] For example, among the approximately 15 million inhabitants of Burkina Faso, a minimum of 1000–5000 cases has been reported each year since 1940, but spikes of 10 000–30 000 annual cases occur approximately every 7 to 10 years (Figure 2). Improvements in surveillance have occurred over the last decade; however, this pattern has remained. In a given decade, annual case counts during epidemic waves appear to be 3- to 10-fold higher than outside epidemic waves. Even during epidemic waves that last for several years (e.g., the 2001–3 and 2006–8 waves in Burkina Faso), meningitis incidence always returns to endemic levels during the rainy and early dry season (data: ministries of health, Burkina Faso, Mali and Niger). These major incidence variations are most likely unique for meningococcus, although minor annual variations may exist for pneumococcus.[22]

The carriage pattern

While invasion and invasive disease can probably occur after a short period of adhesion of the meningococci to the pharyngeal mucosal epithelium, meningococci can also form persistent colonies on the mucosal surface. Whether adhesion leads to colonization, or whether adhesion or colonization lead to invasion, depends on the host's mucosal and systemic immune status,[27] bacterial factors,[28] and probably the integrity of the mucosa.[29]

Prevalence

According to a recent systematic review, there does not seem to be a systematic variation in the carriage prevalence of virulent meningococcal strains (serogroups A, W135, X, Y) by season in the meningitis belt.[30] Rather, long-term variations in meningococcal ecology, including clonal waves of colonization, occur over time.[31] In most studies done during the endemic or hyperendemic periods, virulent strains are carried at a relatively low prevalence of between <1% and 5%.[30–38] By contrast, in populations that were experiencing an epidemic at the time of evaluation, carriage prevalence of the outbreak strain (at least for serogroups A and W135) was found to be high at 10–30% in most instances, while

Table 1
Estimates of risk of serogroup A meningococcal meningitis given serogroup A colonization, across endemic, hyperendemic, and epidemic situations. Data: KKD district, northern Ghana as published in Leimkugel et al.,[31] and Bobo-Dioulasso region, western Burkina Faso[20,23,32]

	Epidemiologic situation	Month	Risk as published[a]	Peak weekly incidence (per 100 000)[b]	Carriage prevalence (per 100)[c]	Risk calculated as weekly cases/ carriers (×100)	Increase in risk between situations (-fold)
KKD district							Endemic to hyperendemic situation:
	Hyperendemic	April 2002	42.3	7.17	3	0.238	67 (following[d])
	Endemic	November 2002	1.1	0.18	5	0.004	
	Hyperendemic	April 2003	0.4	4.46	6	0.074	21 (preceding[d])
							13 (following[d])
	Endemic	November 2003	18.7	0.18	3	0.006	
	Hyperendemic or epidemic	April 2004	16.8	7.14	11	0.065	11 (preceding[d])
							7 (following[d])
	Endemic	November 2004	1.5	0.18	2	0.009	
Bobo-Dioulasso region							Hyperendemic to epidemic situation:
	Hyperendemic	March 2003	–	0.44	0.01–0.10[e]	0.4–4.4	
	Epidemic	March 2006	–	250	16	1.6	0.36–3.56

[a] Calculated as total of confirmed cases during the surrounding 6-month period/1000 carriers.[33]
[b] Laboratory-confirmed meningococcal serogroup A cases; incidence rates for KKD were estimated from graphs shown in Leimkugel et al.[31]
[c] Carriage prevalences for KKD were estimated from graphs shown in Leimkugel et al.[31]
[d] Hyperendemic compared to the preceding or following endemic period.
[e] Assumption, as no *Neisseria meningitidis* serogroup A carriers were found among 488 participants at five repeat exams during February through June,[40] consistent with other studies.[25,33,34]

non-outbreak virulent strains in each respective situation showed prevalence between <1% (serogroups A, W135) and 6% (serogroup Y).[23,25,33] In conclusion, it can be estimated that carriage prevalence of a virulent strain varies between the non-epidemic and epidemic situation by a factor of 10 or higher.

Risk of invasive disease (meningitis) given colonization

The risk of invasive disease following meningococcal colonization can be approximated by calculating the ratio of the number of disease cases over the number of carriers during a certain period, or of disease incidence over carriage prevalence at a given time point. Unfortunately, little evidence exists on changes of this parameter by season or epidemic situation. However, a series of carriage surveys combined with exhaustive meningitis surveillance in northern Ghana allowed calculating the disease-to-carrier ratio specifically for serogroup A over several rainy and dry seasons.[31] Across study years, this ratio was reported as 0.4–1.5 during the rainy season and 17–42 during the dry season, suggesting that risk of meningitis given colonization changed by a factor of 7 to 67 between the endemic and the hyperendemic period (Table 1). In the Bobo-Dioulasso area of western Burkina Faso, carriage studies and exhaustive meningitis surveillance were conducted during the hyperendemic period in 2003 and during a serogroup A epidemic in 2006.[20,23,32] The disease-to-carrier ratio estimated from these data was 1.6 in the epidemic situation and 0.4–4.4 (depending on assumptions) during the hyperendemic period, suggesting that the risk of meningitis given colonization changed by a factor of at maximum 4 between hyperendemic and epidemic situations (Table 1). In conclusion, the risk of meningitis given colonization with a virulent meningococcus seems to increase from the endemic to hyperendemic period by a factor of 10–100, while it remains relatively constant between the hyperendemic and epidemic situation.

The model

Model structure

In our hypothetical model (Figure 3), the endemic, hyperendemic and localized epidemic situations are considered as a series of three states at the community level, which can change, only in this order, from one to another. The term community has broad application here and can refer to a rural village or urban neighborhood of 1000 inhabitants, or a dense urban population of 100 000 inhabitants. At the regional level, two states are defined: during a given year or meningitis season, regional disease incidence can be 'regular' with some localized epidemics occurring among the communities, or part of an epidemic wave, if more localized epidemics than usual occur in the region or country or they occur with a higher attack ratio. Region is considered a larger group of communities, e.g., all villages and towns of Burkina Faso. The transition from one state to the other implies a multiplication of the meningococcal meningitis incidence rate in the community or the region. Each state is associated with a specific order of magnitude of carriage prevalence and risk of meningitis given colonization. Specifically, the transition from endemic to hyperendemic situation (10- to 100-fold) is associated with a change from low to high risk of meningitis given colonization (10- to 100-fold); and the transition from hyperendemic to epidemic situation (10- to 100-fold) with an increase from low carriage prevalence to high prevalence (10-fold or higher). Because changes in incidence are of the same order of magnitude as the respective changes in carriage prevalence or risk of invasion, the latter may be sufficient to cause the increase in incidence. In consequence, hyperendemic incidence during the dry season could be explained by a greater risk of invasion by colonizing meningococci, while the occurrence of a localized epidemic during the dry season could largely be explained by a transient increase in meningococcal transmission and colonization. The latter implies that a surge in carriage prevalence, not a specific carriage prevalence level per se, is associated with epidemic risk.

Factors causing transitions

Climate likely plays the decisive role for the changes in risk of invasion given colonization between endemic and hyperendemic periods. The association between various meteorological parameters, including low air humidity, wind speed, and dust load, and seasonal variations in meningitis incidence, has been well documented.[9–11] However, these climatic factors as measured during the dry season do not vary substantially between years or

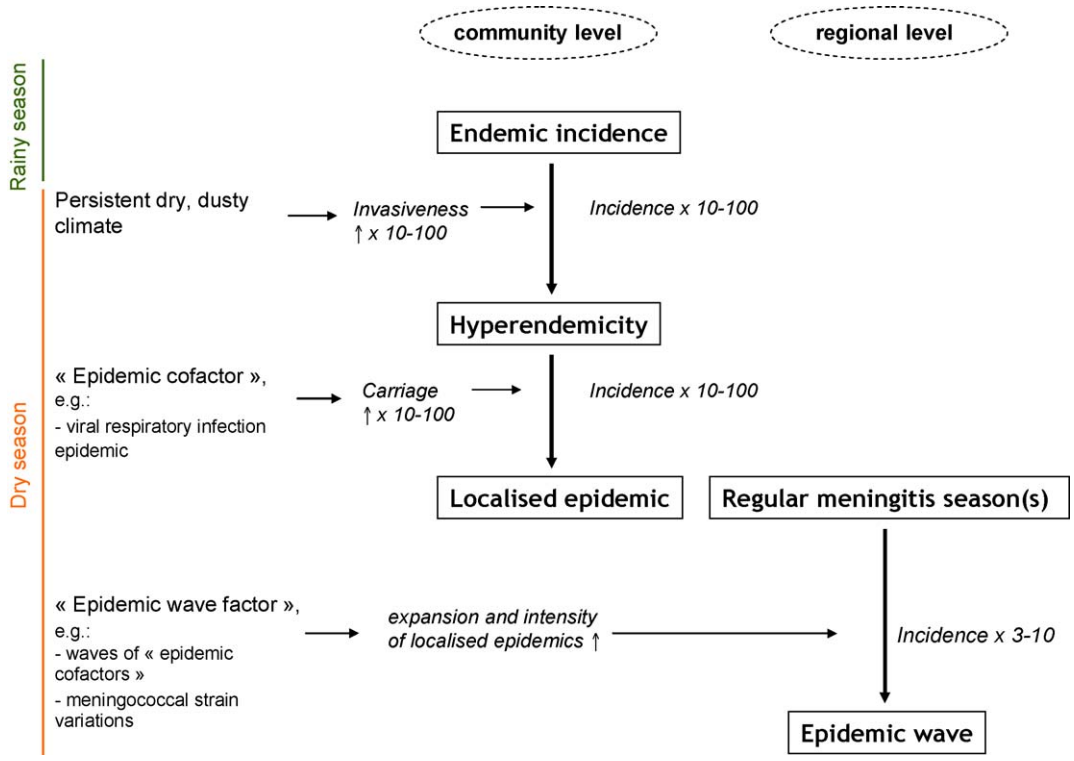

Figure 3. Hypothetical explanatory model for meningococcal meningitis in the African meningitis belt.

communities in a given region and given year; therefore, they are unlikely to be responsible for the occurrence of localized epidemics, and their role may be limited to the hyperendemic increase during the dry season.[9] Hyperendemicity is more pronounced during the second half of the dry season (Figure 1). This suggests that some accumulation of noxious effect may be responsible. For example, extremely low air humidity or high dust load that persists over many weeks may increasingly damage the pharyngeal mucosa, to the point where colonizing meningococci are more likely to invade the epithelium.[1] In the model presented, this mechanism does not imply any change in the frequency of meningococcal transmission or colonization, but rather that transmitted meningococci of any serogroup can cause disease more frequently during hyperendemic than endemic periods. This is consistent with the regular finding of sporadic cases of various serogroups (A, W135, X, Y, and previously C) during the meningitis season.[21,31,39] Meningococcal strains that are transmitted but rarely colonize, such as serogroup A,[34,40] may, however, carry an accrued risk for disease if less efficient natural immunity exists in the host in the absence of regular colonization.

In the previous paragraph, we hypothesized that the transition from hyperendemic to epidemic disease requires an increase in carriage prevalence, and thus in frequency of individual colonization. Little is known about factors that can facilitate strain-specific meningococcal colonization within a short time. A hypothesis that is compatible with the highly localized and sporadic occurrence of meningococcal epidemics is that some infectious agents act as co-factors. Some studies during meningitis epidemics have found an association between outbreak strain carriage and current or previous respiratory pathogen infection or symptoms.[23,33,41,42] Viral pharyngeal infections are known to promote transmission and adhesion of bacteria to the pharyngeal mucosa or respiratory epithelium by coughing and sneezing, or by changes of the mucosa, of bacterial surface structure or of the immune response in the host.[43–48] If current or preceding respiratory infections favor meningococcal colonization and transmission on the individual level, respiratory infection epidemics could lead to a surge in carriage prevalence in the population. Other serogroups than A, such as W135, exhibit the same pattern of carriage surge and association with respiratory infection.[33] Serogroup A, though, may be particularly fit at substantially increasing colonization during pharyngeal viral infection. In addition, reduced immune defense during or after viral infections may contribute to an increased risk of invasive disease given colonization. Micro-epidemics of enteric pathogens, as proposed by Griffiss,[13] may play a similar role, but are less apt to explain the observed surge in pharyngeal carriage. In specific situations, sudden crowding and population movement may play a role, such as in refugee or military camps.[49] Such factors are usually not observed in localized epidemics occurring in rural populations during the dry season and thus are not obligatory factors, but they may contribute to the risk of micro-epidemics of co-infections.

Epidemic waves on the regional level may be due to a combination of two events. First, wider geographic spread of the discussed epidemic co-factors, for example a viral epidemic, may occur during these years than usual. More importantly, changes in meningococcal strain biology most likely play a role, such as the arrival and propagation of new strains that escape pre-existing immunity or feature higher virulence or transmissibility.[28] Such emergence has been repeatedly described, most recently with W135:2a:1.5,2 of sequence type (ST) 11 and serogroup A of ST-5, ST-7 and ST-2859.[50,51] Co-factor epidemics or changes in strain biology by itself cannot cause epidemic waves, as incidence always returns to endemic levels during the rainy season, and new strains may be found in endemic or hyperendemic disease while it is involved in an epidemic wave elsewhere.

Discussion

The presented model is novel in that it combines previously discussed factors such as climate, viral infections, and strain biology[12,13] with observed meningococcal incidence and carriage

patterns. It is in line with Lapeyssonnie's observation of endemic disease with seasonal increase and epidemic waves,[2] but adds the feature of localized epidemics as an obligatory element that is caused by different and specific mechanisms. Additional factors known to contribute to the disease pattern, such as crowding in refugee camps (increase in transmission) or waning pre-existing immunity in the population (increased risk of invasion given carriage), can be integrated in specific steps of the model.

The explanatory model has several applications. First, is may help our understanding of specific observations or events, for example, the emergence of serogroup W135 in Burkina Faso during 2001–2003.[21] During the dry season of 2002, all districts observed at least hyperendemic meningitis, and about half reported epidemics.[52] According to the presented model, the occurrence of epidemics in specific districts or communities did not depend on the arrival of a new strain, but on the discussed co-factors that precipitate epidemics. The extension from some localized epidemics to an epidemic wave, however, was probably associated with the (re–)introduction and circulation of a highly virulent strain variant (W135:2a:1.5,2 of ST-11)[53] that escaped pre-existing immunity and that possibly was capable of quickly increasing colonization under certain conditions.

A second application of this explanatory model is in mathematical modeling. Our model suggests that attempts to predict epidemics based solely on meteorological and district-level data are not likely to succeed. After validation with surveillance data, mathematical models that aim to evaluate vaccine impact on meningitis incidence may need to take into account vaccine impact on transition probabilities between the four incidence states we described (endemic, hyperendemic, epidemic, epidemic wave). The model also suggests that the direct vaccine effects will protect against both hyperendemic and epidemic disease, while the indirect effect of conjugate vaccines, which prevent transmission, will play a particular role against epidemic disease.

Lastly, this explanatory model suggests that in the absence of preventive vaccine strategies against serogroups like X or W135 in meningitis belt countries, it may be possible to reduce the burden of disease using interventions that limit the harmful link between climatic conditions during the dry season and the seasonal increase of disease (e.g., by indoor air humidification) and between epidemic co-factors and localized epidemics (e.g., influenza vaccines, if influenza was found to be a co-factor).

This hypothetical model requires validation in various settings and areas of the meningitis belt. Health center-level incidence data should be systematically evaluated over expanded periods and regions. Further evidence on the serogroup-specific variation of case-to-carrier ratio and carriage prevalence over seasons and epidemiological situations is needed, especially from Mali, Burkina Faso and Niger, which are the core countries of the meningitis belt. Although difficult to perform, ecological comparison studies of communities in epidemic versus hyperendemic situations will be useful to evaluate the role of viral epidemics and other epidemic co-factors. Knowledge about seasonality of viral respiratory and systemic infections in the meningitis belt and their impact on serogroup-specific meningococcal colonization, transmission and invasion should be improved. Finally, exhaustive population-based surveillance that yields information on incidence rates and serogroup and genotype distribution is an essential background for this research agenda.

Conflict of interest

JEM and BDG work for AMP, which receives substantial financial support from Sanofi Pasteur, a meningococcal vaccines manufacturer.

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