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### ► To cite this version:

Lydiane Agier, Nadège Martiny, Oumy Thiongane, Judith E Mueller, Juliette Paireau, et al.. Towards understanding the epidemiology of *Neisseria meningitidis* in the African meningitis belt: a multi-disciplinary overview.. *International Journal of Infectious Diseases*, 2016, 54, pp.103-112. 10.1016/j.ijid.2016.10.032 . hal-01483563

**HAL Id: hal-01483563**

**<https://hal.science/hal-01483563>**

Submitted on 23 Mar 2021

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## Review

Towards understanding the epidemiology of *Neisseria meningitidis* in the African meningitis belt: a multi-disciplinary overview

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## ARTICLE INFO

## Article history:

Received 24 August 2016

Received in revised form 21 October 2016

Accepted 29 October 2016

**Corresponding Editor:** Eskild Petersen, Aarhus, Denmark

## Keywords:

Bacterial meningitis

Disease control

Research priorities

African belt

## SUMMARY

**Objectives:** *Neisseria meningitidis* is the major cause of seasonal meningitis epidemics in the African meningitis belt. In the changing context of a reduction in incidence of serogroup A and an increase in incidence of serogroups W and C and of *Streptococcus pneumoniae*, a better understanding of the determinants driving the disease transmission dynamics remains crucial to improving bacterial meningitis control.

**Methods:** The literature was searched to provide a multi-disciplinary overview of the determinants of meningitis transmission dynamics in the African meningitis belt.

**Results:** Seasonal hyperendemicity is likely predominantly caused by increased invasion rates, sporadic localized epidemics by increased transmission rates, and larger pluri-annual epidemic waves by changing population immunity. Carriage likely involves competition for colonization and cross-immunity. The duration of immunity likely depends on the acquisition type. Major risk factors include dust and low humidity, and presumably human contact rates and co-infections; social studies highlighted environmental and dietary factors, with supernatural explanations.

**Conclusions:** Efforts should focus on implementing multi-country, longitudinal seroprevalence and epidemiological studies, validating immune markers of protection, and improving surveillance, including more systematic molecular characterizations of the bacteria. Integrating climate and social factors into disease control strategies represents a high priority for optimizing the public health response and anticipating the geographic evolution of the African meningitis belt.

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## 1. Introduction

## 1.1. Epidemiological context

Meningococcal meningitis is an acute bacterial disease characterized by the sudden onset of fever, intense headache, nausea, stiff neck, and photophobia.<sup>1</sup> The meningococcus *Neisseria meningitidis* is found only in humans and is transmitted from person to person by airborne droplets of respiratory or throat

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secretions.<sup>2</sup> Most infections with *Nm* result in a period of asymptomatic pharyngeal carriage and only occasionally lead to severe invasive disease.<sup>3</sup> Meningococcal meningitis is a serious public health problem because of its high case fatality rate<sup>4</sup> and, in some regions, its propensity for epidemics.

The African meningitis belt is a region stretching from Senegal to Ethiopia with an estimated population exceeding 400 million people. A high seasonal incidence of meningitis has been recorded in the area for decades,<sup>5,6</sup> with epidemic waves occurring periodically but irregularly every 5–12 years.<sup>7</sup> Seasonal hyper-endemicity is observed every dry season between January and May, when weekly incidence rates rise up to 10/100 000 population throughout the African meningitis belt and can locally exceed 100/100 000 population.<sup>8,9</sup> Even with swift and appropriate treatment, case fatality fluctuates around 10%,<sup>10</sup> and 10–15% of survivors suffer long-term neurological sequelae.<sup>11</sup> While *Nm* serogroup A (NmA) has been the main cause of large meningitis epidemics in the African meningitis belt,<sup>12,13</sup> serogroups W (NmW), C (NmC), and X (NmX) have also been, and are still, responsible for localized epidemics and occasionally more widespread epidemic waves.<sup>13–17</sup> Other bacteria contribute to the seasonality of the disease, namely *Haemophilus influenzae* type b and *Streptococcus pneumoniae*, the latter having a high recorded incidence among adults and a particularly high burden from serotype 1.<sup>18</sup>

The massive introduction of a monovalent group A polysaccharide–tetanus toxoid conjugate vaccine, known as MenAfriVac,<sup>19</sup> was initiated in 2010 and has successfully reduced the incidence of NmA disease.<sup>13,20–23</sup> To date, an estimated 217 million population have been immunized through mass vaccination campaigns targeting the 1–29 years age group in 15 countries. MenAfriVac continues to be rolled out via these mass campaigns. In 2015, long-term strategies incorporating the vaccine into the routine Expanded Programme on Immunization schedule were recommended.<sup>24</sup> Concurrently, pneumococcal conjugate vaccines were recently included in this routine immunization programme. However the older age groups, representing the most susceptible population, may currently not be sufficiently protected to reduce the high disease burden.<sup>25</sup>

Global *Nm* incidence may increase again in the future as a result of (1) a possible serogroup replacement, for example if NmA was the main competitor in the nasopharyngeal ecological niche; (2) the spontaneous emergence of highly invasive and transmittable strains given the capacity of *Nm* for rapid genomic evolution; and (3) population-level immunity against NmA waning following vaccine introduction in the absence of a natural booster and with the arrival of unvaccinated birth cohorts. Until an effective multivalent meningococcal vaccine covering all relevant *Nm* serogroups is available to the populations and pneumococcal vaccination protects all age groups, control and prevention strategies need to be adapted to the changing disease epidemiology in the African meningitis belt.<sup>26,27</sup> A better understanding of the determinants of bacterial meningitis transmission dynamics in the African meningitis belt is thus needed.

### 1.2. Definition of the African meningitis belt

The definition of the African meningitis belt was triggered by the unique epidemiology of bacterial meningitis in the region; it set the stage for international efforts towards a specific prevention and public health response strategy. Lapeyssonnie first described the African meningitis belt in 1963 based on cerebrospinal meningitis cases reported over 23 years in the area, with several serogroups of *Nm* predominantly causing the epidemics.<sup>5</sup> Geographic boundaries were established from isohyets ranging between 300 mm and 1100 mm annual rainfall, coinciding with this 'endemo-epidemic' region, while sporadic or grouped cases of

bacterial meningitis occurred outside the area. The critical population size allowing epidemic outbreaks was considered not to be reached in regions with less than 300 mm of annual rainfall, due to difficult conditions for subsistence farming. The southern limit (1100 mm of annual rainfall) corresponds to the threshold of 50% of relative humidity.

In 1971, an extension of the African meningitis belt to the eastern and southern shores of Lake Victoria was suggested, particularly to cover Kenya and Uganda, countries that were regularly devastated by epidemics in 1923–1950.<sup>28</sup> In 1992, it was suggested that Egypt, Tanzania, and Uganda be included,<sup>29</sup> although the local epidemiology did not fully match Lapeyssonnie's description. In 1996, an extension of the African meningitis belt to the south was suggested after improvements in microbiological diagnostic tools allowed the detection of epidemic strains of NmA subgroup III in the Central African Republic, Uganda, Rwanda, Burundi, Tanzania, and Zambia.<sup>30</sup> These studies relied on clinically suspected rather than laboratory-confirmed meningitis cases (other diseases such as malaria and mumps may produce similar symptoms) and did not account for the mechanisms driving the disease transmission dynamics. There is a risk that global environmental change may accelerate the geographic distortion of the African meningitis belt in the near future.

### 1.3. Objectives of this review

The present review aimed to bring a multidisciplinary perspective on meningococcal meningitis disease in the African meningitis belt. Based on the literature, the main knowledge of the determinants of the disease epidemiology and the concepts that have emerged were synthesized, focusing on five main topics: disease transmission dynamics, asymptomatic carriage, pathogen ecology, host immunity, and extrinsic risk factors for the disease. In particular, the role of climate in driving meningitis transmission dynamics was investigated. Meningitis is clearly identified as one of the most climate-sensitive diseases in Africa,<sup>31</sup> with 25% of the incidence variability being explained by climatic factors.<sup>32</sup> It has been recommended in recently published reviews on meningitis that major climate indicators are identified for possible integration into operational decision-making.<sup>33</sup> Research questions to be addressed in the future are highlighted, with the aim of gaining a better understanding of transmission dynamics and developing appropriate long-term vaccination strategies to reduce the burden of this disease in Africa.

### 1.4. Literature search methodology

Various electronic databases were searched to identify relevant literature, independently for each topic. Details on the databases searched, keywords used, and inclusion/exclusion criteria applied are provided in the **Supplementary Material**. No limits were applied for language or publication date. The records retrieved were first screened by title and abstract and then by examination of the full text. Studies that clearly did not meet the inclusion criteria were discarded. The publications that were retained investigated meningitis in various locations and time periods, using variants of the case definition (suspected or confirmed cases, with different lists of serogroups being included), aggregated on different spatio-temporal scales.

## 2. Materials and methods

### 2.1. Meningococcal disease transmission dynamics and modelling

A set of statistical methods were investigated to analyze the spatio-temporal transmission dynamics of meningitis epidemics

and case emergence, spread, and outbreaks on different spatial and time scales, including simple epidemiological description,<sup>34,35</sup> and more advanced modelling techniques such as wavelet analysis,<sup>7</sup> cross-correlation between time series,<sup>36</sup> Kulldorff's spatial scan statistic,<sup>37,38</sup> principal component analysis, and cluster analysis.<sup>39</sup> Mechanistic susceptible–infected–recovered (SIR) transmission modelling was used to explore and test potential disease processes.<sup>40–42</sup>

## 2.2. Asymptomatic carriage

Most existing carriage studies were cross-sectional or series of cross-sectional surveys,<sup>43–51</sup> with only one published cohort approach.<sup>52</sup> All studies aimed to rely on representative population samples, and when reported, recommended nasopharyngeal swabbing via the mouth behind the uvula (with or without tonsils).<sup>53,54</sup> An evaluation of PCR analysis of enriched swab suspension compared to usual culture analysis found low sensitivity of conventional microbiology methods for carriage studies,<sup>55</sup> which had already been suggested in a study comparing swabbing with immunohistochemistry after tonsillectomy.<sup>56</sup> It is therefore likely that all existing meningococcal carriage studies have underestimated true carriage prevalence.

## 2.3. Pathogen ecology

Laboratory testing was not performed systematically in the African meningitis belt over the last 40 years. Approximately 10% of reported cases were laboratory tested,<sup>57</sup> and most large-scale retrospective studies relied on suspected cases defined by clinical criteria rather than laboratory-confirmed cases.<sup>58</sup> Phenotypic approaches to antigenic typing using serotyping and serosubtyping were most commonly used until the mid-2000s. These techniques were used to identify epidemic clones of *Nm* (e.g. Kwara et al.<sup>59</sup>, Ouedraogo-Traore et al.<sup>60</sup>). Nowadays, the identification techniques routinely used are sequence-based methods relying on cerebrospinal fluid obtained through lumbar puncture. They include standard microbiology with culture isolation and serological identification of serogroup, latex agglutination testing, and PCR testing.<sup>61</sup> Beyond bacterial isolation and identification of serogroups, there is now a wide range of molecular typing techniques available to genetically characterize meningococcal strains, from invasive cases to carriage. Among these, multi-locus sequence typing (MLST) and multi-locus enzyme electrophoresis (MLEE) have frequently been used to characterize strains in the African meningitis belt.<sup>62,63</sup> Sequence types are grouped into clonal complexes according to their similarity with a central genotype.

## 2.4. Host immunity

The immunological assays that are currently available for population-based serological studies of meningococcal disease (i.e., IgG concentration and serum bactericidal antibody assays) do not allow distinction between naturally acquired immunity following carriage or disease, and vaccine-induced immunity. This is currently limiting the interpretation of results, mostly for studies conducted in areas with both high endemicity and high vaccination coverage.<sup>45,64</sup> No serological correlate of protection is known for NmA disease or carriage in the African meningitis belt. The serum bactericidal assay is the accepted correlate of protection for meningococcal disease,<sup>65</sup> but thresholds of protection are only established for serogroup C meningococcal disease.<sup>45,66</sup> In addition, most *Nm* seroprevalence studies in the African meningitis belt have used cross-sectional study designs to quantify immunity at specific time points, and at best cohort studies to quantify changes during one meningitis season.<sup>50,52</sup>

## 2.5. Risk factors

Risk factor analyses were assessed both at the individual level (e.g., in case–control studies) and at an aggregated ecological level (e.g., in geographical correlation studies). The most frequently investigated factors for infection were environmental and climatic factors,<sup>32,67–73</sup> with a few studies including other risk factors such as population density,<sup>37,38,74</sup> household socio-demographic characteristics and lifestyle,<sup>47,75–77</sup> or other co-infections.<sup>78,79</sup> Although climate was long suspected to influence the transmission dynamics of meningococcal disease in Africa,<sup>5</sup> researchers only began to test these associations in the 2000s when long-term remote sensing data became available. Before this, climate and health associations were investigated on a local scale using in situ meteorological data (e.g., air temperature and humidity,<sup>68</sup> or rainfall<sup>69</sup>). The advances made in remote sensing enabled the effects to be investigated on a larger scale.

Regarding the specific role of desert dust in epidemics, a high diversity of existing dust products were investigated, from remote sensing products (generally indices that are proxies for the aerosol quantity over the whole atmospheric column, some of which need to be refined or corrected from various complex effects before being used for health impact studies, e.g. aerosol index<sup>80</sup>)<sup>69,80</sup> to in situ aerosol measurements (e.g., the PM<sub>10</sub> mass concentration, which is available from a limited number of meteorological stations across the African meningitis belt, or visibility, which is more widely available but gives a qualitative rather than quantitative estimate of the number of dusty days and the atmospheric turbidity in a given location).

Risk factors were primarily investigated using regression methods to estimate their association with the disease. The other approaches investigated included disease mapping,<sup>6,81</sup> hypothetical explanatory models,<sup>25,82</sup> and mathematical modeling.<sup>80</sup> The characteristics of the publications relating meningococcal meningitis to environmental and climatic risk factors are detailed in Table 1, including the list of factors investigated, the methods used for analysis, and a summary of the results.

Few studies have investigated the social science viewpoint on the disease and on vaccination. In the African meningitis belt, these studies relied on qualitative data collected through in-depth interviews and/or focused group discussions in several ethnic groups in Burkina Faso,<sup>83–85</sup> Niger,<sup>86,87</sup> and Benin.<sup>88</sup> They investigated the knowledge and perceptions of the disease and its risk factors.

## 3. Knowledge and concepts

### 3.1. Pathophysiology of meningitis in the African meningitis belt

Laboratory-based surveillance studies on meningococcal disease in the African meningitis belt usually rely on suspected cases of acute bacterial meningitis and the analysis of cerebrospinal fluid. Based on the usual pathophysiology requiring invasion of the blood stream before invasion of the central nervous system,<sup>89</sup> epidemics of meningococcal meningitis should come with high morbidity and mortality due to meningococcal septicaemia. For example, assuming that 28% of cases of invasive meningococcal disease are accompanied by clinical signs of septicaemia, as was observed in France,<sup>90</sup> one would have expected around 400 cases of septicaemia in Niger in 2015, when 1435 cases of *Nm* were confirmed in the laboratory.<sup>91</sup> However, the surveillance of febrile syndromes, which requires wide inclusion criteria and blood culture for evaluation, is rarely conducted in the African meningitis belt,<sup>92</sup> and no published data are available on the incidence of septicaemia in the region. A possibly high ratio of meningitis to septicaemia cases could be due

**Table 1**  
Characteristics of the publications relating meningococcal meningitis to environmental and climatic risk factors.

First author/year	Location	Period	Epidemiological data	Risk factors investigated	Methods of analysis	Space/time scale
Agier 2013 <sup>80</sup>	Niger	1986–2007	Suspected cases	Dust, wind direction and force, relative humidity, temperature	Wavelets	District/week
Agier 2013 <sup>39</sup>	Niger, Mali, and Burkina Faso	1986–2007	Suspected cases	( <i>Incidence only was investigated</i> )	Cluster analysis, principal component analysis	District/week
Besancenot 1997 <sup>68</sup>	Benin	1965–1992	Biologically confirmed cases and suspected cases of <i>Nm</i>	Temperature, relative humidity, vapour pressure, dust haze	Simple linear regression	Region/month
Bharti 2012 <sup>128</sup>	Niger	1995–2004	Suspected cases	Human density, daily rainfall	Cox proportional hazard regression model	District/year
Broutin 2007 <sup>7</sup>	Mali, Burkina Faso, Ghana, Togo, Benin, Niger, Nigeria, Chad, and Sudan	1939 – 1999	Suspected cases	( <i>Incidence only was investigated</i> )	Wavelet analysis	Country/year
Dukić 2012 <sup>79</sup>	Navrongo in Ghana	1998–2008	Biologically confirmed cases	Rainfall, temperature, relative humidity, wind speed, dusty days, carbon dioxide emissions from fires	Poisson generalized additive model, possibly with lagged risk factors	Month (no space scale)
Greenwood 1984 <sup>67</sup>	Zaria area in Northern Nigeria	1977–1979	Biologically confirmed cases of <i>Nm</i>	Temperature, absolute humidity, rainfall, Harmattan intensity	Pearson correlation	Two weeks (no space scale)
Hodgson 2001 <sup>75</sup>	Kassena-Nankana District in northern Ghana	1997	Suspected cases (case–control study)	Socio-economic factors, housing and household overcrowding, smoking and exposure to smoke, and close contact with a case	Computation of Mantel–Haenszel odds ratios	Odds ratio
Irving 2011 <sup>40</sup>	( <i>this simulation study did not require real data</i> )	( <i>this simulation study did not require real data</i> )	( <i>this simulation study did not require real data</i> )	Model parameters: (1) rate of progression from asymptomatic carriage to invasive disease is seasonally forced; (2) carriers and cases are infectious, same transmission rate; (3) no immunity, immunity due to disease and carriage	Deterministic compartmental model susceptible–carrier–ill– recovered	District–week
Jackou-Boulama 2005 <sup>69</sup>	Niger	1996–2002	Suspected cases	Rainfall: monthly cumulative rainfall from four meteorological stations	Pearson correlation	Country/month
Mainassara 2010 <sup>37</sup>	Niger	2002–2008	Biologically confirmed cases of <i>Nm</i>	( <i>Incidence only was investigated</i> )	Spatial scan statistics	Canton/year
	Niger	2002–2008	Biologically confirmed cases of <i>Nm</i>	Population density	Pearson correlation	Department/year
Martiny 2013 <sup>71</sup>	Niger and Mali	2004–2009	Suspected cases	Dust, absolute humidity	Comparisons between mean standardized annual regimes in dust, absolute humidity, and meningitis; Pearson correlation	Country/week
Molesworth 2003 <sup>74</sup>	Africa	1841–1999	Meningitis epidemics published (PubMed) and unpublished (institutional reports)	Absolute humidity, absorbing aerosols, rainfall, land-cover type, population density	Principal component analysis, clustering, logistic regression	District (no time scale)
Mueller 2008 <sup>76</sup>	Bobo-Dioulasso City in Burkina Faso	February to June 2003	Carriers of <i>Nm</i> during hyperendemic period (5 monthly visits: pharyngeal swabs)	Socio-demographic information (medical history, smoke exposure, crowding, etc.), meteorological data	Multivariate mixed Poisson regression	Individual scale
	Three rural villages in Burkina Faso	2006	Carriers of <i>Nm</i> during NmA epidemic period	Socio-demographic information (medical history, smoke exposure, crowding, etc.), meteorological data	Cox proportional hazard model Multivariate mixed logistic regression	Individual scale Individual scale

Table 1 (Continued)

First author/year	Location	Period	Epidemiological data	Risk factors investigated	Methods of analysis	Space/time scale
Mutonga 2009 <sup>77</sup>	West Pokot District in Kenya	December 2005–April 2006	Suspected cases (case–control study)	Characteristics of the household, lifestyle, recent travel, exposure to sick people, upper respiratory tract infection, socio-economic status, level of education	Conditional multivariate logistic regression	Individual scale
Paireau 2012 <sup>38</sup>	Niger	2003–2009	Biologically confirmed cases of <i>Nm</i>	(Incidence only was investigated)	Spatial scan statistics and local Moran's <i>I</i> test for spatial autocorrelation	Health area/year
	Niger	2003–2009	Biologically confirmed cases of <i>Nm</i>	Distance to road and population density	Pearson correlation	Health area/year
Philippon 2009 <sup>36</sup>	Mali	1992–2003	Suspected cases	(Incidence only was investigated)	Cross-correlation of times series of cases	Region/week, district/week, and village/week
Raghunathan 2006 <sup>47</sup>	Burkina Faso, two districts vaccinated against <i>NmA</i> and <i>NmC</i>	2002	5–25-year-olds, carriage and seroprevalence	Demographic information, household conditions, recent medical history, and self-reported previous meningococcal vaccination: exposure to meningitis in the household, travel to Mecca	Logistic regression	Individual scale
Sultan 2005 <sup>73</sup>	Mali	1994–2002	Suspected cases	Winter maximum	Linear regression	Country/week
Tall 2012 <sup>34</sup>	Six districts of Burkina Faso	2004–2008	Suspected cases	(Incidence only was investigated)	Pearson correlation	Health centre/week
Thomson 2006 <sup>70</sup>	Burkina Faso	1997–2001	Suspected cases	Dust, rainfall, normalized difference vegetation index, cold cloud duration	Multivariate linear regression	District/year
	Niger	1993–2001				
	Parts of Mali	1989–1998				
Yaka 2008 <sup>32</sup>	Togo	1990–1997				
	Niger and Burkina Faso	1966–2005	Suspected cases	Wind velocity, surface temperature, specific/relative humidity near the surface	Multivariate linear regression	Country/year

*Nm*, *Neisseria meningitidis*; *NmA*, *N. meningitidis* serogroup A; *NmC*, *N. meningitidis* serogroup C.

to the direct spread of bacteria from the nasopharynx to the central nervous system along the olfactory nerve, which is supported by a few animal studies.<sup>93,94</sup>

### 3.2. Meningitis transmission dynamics

In the African meningitis belt, seasonal meningitis outbreaks are localized both in time and space when monitored on a scale smaller than the district.<sup>34,37,38</sup> When data are aggregated on a country or broader scale, pluri-annual cycles of 5 to 12 years are observed.<sup>7,39,57</sup> No systematic spatial diffusion pattern was observed at the country,<sup>7</sup> region, district, village,<sup>36</sup> or health centre levels.<sup>38</sup> However, it was shown that large outbreaks were associated with early epidemic onset,<sup>32,39</sup> and with large numbers of localized epidemics within a district.<sup>34</sup>

It was hypothesized that the transition to seasonal hyperendemicity, localized epidemics, and larger pluri-annual epidemic waves are distinct phenomena with their own respective mechanisms, which could be explained by an increased risk of invasion given nasopharyngeal colonization (possibly due to a dry and dusty climate), epidemic co-factors increasing meningococcal transmission and colonization during short periods (such as viral respiratory infections), and changing population immunity (e.g., due to the evolution of the predominant circulating meningococcal strains), respectively.<sup>8</sup> The suggested roles of an increased risk of invasion in the seasonal hyperendemicity and of increased transmission in driving localized epidemics were reinforced by the findings of a systematic review on surveillance and carriage in the African meningitis belt.<sup>95</sup>

The transmission dynamics of infectious diseases are primarily explained by vaccine or disease-induced immunity. For epidemic meningitis in the African meningitis belt, vaccination coverage data were not systematically reported before the introduction of MenAfriVac, and few seroprevalence estimates were available, such that the effect of vaccination on the disease transmission dynamics could not be investigated before 2010.

### 3.3. Asymptomatic carriage

The estimated prevalence of *Nm* carriage varies between 5% and 30%,<sup>96,97</sup> and was shown to be low in young children and higher in adolescents and young adults.<sup>97–99</sup> There is growing evidence that carriage of the epidemic strain is substantially increased during an epidemic.<sup>44,48,95</sup> The season and immunization with polysaccharide vaccine appear to have little effect on carriage, but being in contact with a case has.<sup>97,100</sup>

In industrialized countries, hyperinvasive *Nm* clones are rarely identified in carriers, and carriage populations are highly genetically diverse.<sup>96</sup> In the African meningitis belt, a low carriage rate of *Nm* and extensive genetic diversity of carriage strains was also found,<sup>101–103</sup> except in one study.<sup>43</sup> The carriage of less virulent clones may help to prevent hypervirulent clones spreading through induced immunity (indirect competition),<sup>104</sup> or the physical presence of a clone in the nasopharyngeal niche may hamper colonization by other strains (direct interaction). Carriage of meningococci with a capsular null locus or *FetA* null locus, which cannot produce a capsule, was also reported frequently in the African meningitis belt.<sup>101,102,105</sup> While these

unencapsulated strains may establish long-term carriage relationships with the host,<sup>43</sup> sporadic cases of meningitis due to these meningococci have been reported.<sup>105</sup>

Little is known about the duration of carriage episodes in the African meningitis belt. Carriage can be transient or can last up to several months before being cleared naturally,<sup>99</sup> and this duration is likely to vary by strain<sup>107</sup> and by age of the host. One study estimated a half-life of 3 months,<sup>51</sup> and another estimated a carriage episode duration of 30 days on average.<sup>102</sup>

It is unclear what triggers the transition from asymptomatic carrier status to disease development, and what the impact is of the duration of carriage on the process. Hypothetical models have suggested that a systematic and widespread increase in the carriage rate during the dry season is not likely, although it is required locally for an epidemic to occur.<sup>8</sup> The first point contradicts Greenwood's hypothetical model<sup>67</sup> and the conclusion of the first SIR simulation models, which stated that a seasonal increase in transmission was necessary to obtain uneven annual incidences.<sup>40</sup>

### 3.4. Pathogen ecology

Many of the observed genotypes in the African meningitis belt are escape variants (in terms of antigenic typing or in other outer membrane antigens<sup>108–111</sup>) resulting from positive selection, which may be attributed to herd immunity. Competition between fit genotypes results in dramatic changes in population composition over short time periods. Most often, clonal complexes comprise a dominant genotype and closely related variants. Most escape variants are less fit than their parents and are lost because of competition and bottlenecks during spread from country to country. Yet, new variants with heightened fitness may arise, allowing antigenic escape and spread when the antigenic characteristics are partially distinct from the parents. Although this is unlikely to happen in the presence of cross-immunity, it may occasionally result in the emergence of a novel epidemic strain.<sup>108</sup> Epidemics are usually triggered by concomitant short-term changes in the pathogen's genetics, host immunity, and the environment.<sup>112</sup>

Little is known regarding the strains that caused the disease in the first part of the twentieth century in Africa. However, from the 1950s and prior to the introduction of MenAfriVac, the majority of meningitis cases were caused by *Nm*,<sup>113,114</sup> mainly serogroup A.<sup>12,13</sup> NmA outbreaks were caused by the sequence type ST-1, ST-4, and ST-5 clonal complexes.<sup>57,62,115</sup> In particular, ST-5 was linked to three successive pandemic waves in the African meningitis belt; the latest occurred in 1996–1997 and resulted in more than 250 000 cases and 50 000 deaths. The ST-5 complex persisted in Africa until MenAfriVac was introduced. Serogroup W strains were circulating at low levels in the African meningitis belt (mostly in Chad, Cameroon, Niger, Togo, and Senegal) before 2000, until clone ST-11 caused epidemics in Burkina Faso and Niger.<sup>57,116,117</sup> The NmW ST-2881 clone was occasionally reported. No NmC epidemic was reported in the region for over 30 years, until epidemics occurred in 2013–2015 in Nigeria<sup>16</sup> and in Niger, due to a previously unknown NmC strain ST with unique antigenic properties.<sup>16</sup> The incidence of serogroup X has increased in recent years; this represents a major concern, as there is currently no available vaccine.<sup>15,118</sup> The surveillance of these non-A serogroups is important due to their epidemic potential in the context of the wide-scale introduction of MenAfriVac, which has eliminated epidemics due to NmA so far. Since *Nm* shows a great capacity to change its genome, the emergence of a new and possibly highly virulent serogroup cannot be excluded.<sup>119</sup> Recent studies of the post-vaccination epidemiology of meningitis have all found that NmA cases have disappeared from vaccinated countries and that the global number of meningitis suspected cases has decreased,

but they have reported an increase in other serogroups and/or pathogen incidence, mainly NmW, NmC, and *S. pneumoniae*.<sup>16,20,23,120–122</sup> A few years of additional data are needed to evaluate the long-term effectiveness of the MenAfriVac vaccine.

### 3.5. Host immunity

Disease and vaccination both induce immunity; however carriage can promote bactericidal activity as well, and repeated carriage episodes may offer some immunity against future carriage and disease,<sup>123,124</sup> including cross-strain immunity.<sup>44,66,125</sup> Some evidence has been given for such serogroup-specific relationships,<sup>44,47,50</sup> but not systematically.<sup>50</sup> It is, however, coherent with studies that have found antibody concentrations to increase with age,<sup>125</sup> and that living in a district with emerging serogroup W disease is a predictor of higher immunity antibody levels.<sup>47</sup> The duration of immunity is unknown, but likely depends on the route of acquisition (through vaccination, asymptomatic carriage, or by developing the disease).

Some studies have found an inverse relationship between immunity and incidence (low NmW immunity during a hyperendemic season and high NmA immunity with no detectable circulation of the bacteria<sup>52</sup>), but others have not. A positive association was found between age-specific NmA immunity and meningitis incidence,<sup>44,45</sup> and higher antibody titres were recorded (1) in Sudan (even in unvaccinated populations) compared to other regions outside the African meningitis belt, although this did not prevent epidemics from occurring;<sup>104,126</sup> (2) for NmW in endemic areas of Burkina Faso compared to non-endemic areas (even when an epidemic had just occurred).<sup>47</sup> Immunity possibly does not have a direct effect, but rather an interaction effect with another risk factor affecting the disease transmission dynamics (a climatic factor for instance), so that no clear relationship can be found with incidence.

One major limitation in serological studies is the absence of a correlate of protection for most relevant serogroups in the African meningitis belt.<sup>45</sup> The high prevalence of putatively protective serogroup A serum bactericidal antibody (SBA) titres >1:8 or >1:128 in the population even before the introduction of the MenAfriVac<sup>®</sup> suggests that the standard SBA either does not measure functional antibody, or that these antibodies are not functional in this region.<sup>45</sup>

Overall, our knowledge of the relationship between immunity, carriage, and disease is limited, especially as immunity and carriage are likely to change greatly over time. Yet, long-term and repetitive carriage episodes may bring some immunity to the host.

### 3.6. Risk factors

The first suspicion of climate largely impacting *Nm* transmission dynamics was inspired by the finding that the seasonal profile for meningitis coincided with the core of the dry season, when the Harmattan regime is well settled, and ended with the arrival of the African monsoon.<sup>5,6,71,82</sup>

At spatially aggregated levels, evidence suggested that humidity/rainfall was negatively associated with incidence,<sup>59,70,74</sup> while temperature showed a positive association.<sup>79</sup> Low humidity appeared to prevent acquisition and increase clearance of the non-groupable bacteria,<sup>76</sup> and to be a necessary but not sufficient condition for meningitis outbreaks to occur.<sup>71</sup> Carbon monoxide emission<sup>79</sup> and land cover type<sup>74</sup> were also found to be associated with the magnitude of the epidemics; yet no hypothetical causal effect was suggested. Despite a negative association between dust and meningitis in one study,<sup>70</sup> more recent studies have shown a positive correlation between dust and meningitis incidence,<sup>72,79</sup> with a 1- to 2-week delay between dust and meningitis seasonal

components.<sup>71,80,127</sup> This time-lag is consistent with the biologically plausible hypothesis that dust particles and dry air favour bacterial invasion into the blood stream by damaging the host's mucosal barrier or by inhibiting mucosal immune defenses,<sup>82</sup> with an incubation period of <14 days.<sup>123</sup> Wind was also found to impact meningitis incidence,<sup>32,73</sup> but it may rather be a correlate of a true risk factor, such as dust or humidity.

Regarding non-climatic risk factors, the reoccurrence rate of epidemics was higher in highly populated districts,<sup>36,128</sup> but the association between annual incidence and population density was not proven significant.<sup>37,74</sup> Human contact associated with primary roads might largely contribute to local spatial transmission dynamics and spread of the disease.<sup>128</sup>

At the individual level, symptoms of upper respiratory tract infection appeared to favour NmA and NmW carriage during localized epidemics,<sup>47,76</sup> while this and previous symptoms of flu were found to be associated with subsequent meningococcal meningitis during localized epidemics.<sup>44,77</sup> This may relate to immune depression following viral infections, as is known for influenza virus and pneumococci.<sup>129</sup> Similarly, the monthly incidence of meningitis was shown to be associated with the incidence of pneumonia in Ghana,<sup>79</sup> yet the 2-month delay was likely too long to be biologically relevant. Smoking was shown to be a risk factor for NmW disease<sup>47</sup> and NmY carriage,<sup>76</sup> but not for NmA carriage or disease.<sup>44,75,77</sup> Different measures of proximity with asymptomatic carriers or meningitis cases were found to increase the risk of both carriage<sup>47,76</sup> (except for one contradictory result) and infection.<sup>75,77</sup> Being a student lowers the risk of contracting the disease.<sup>75</sup> Exposure to kitchen fire smoke was found to inflate the risk of meningitis during epidemics,<sup>44,75</sup> but the evidence is not conclusive.<sup>77</sup>

None of the studies investigating quantitative socio-economic factors found significant associations with carriage or with developing the disease.

The social perceptions of the aetiological risk factors of meningitis were examined and highlighted environmental factors with supernatural explanations in all West African societies. One sort of wind in particular is believed to be pathological, i.e., to be a sorcery entity purportedly bringing disease.<sup>86</sup> In Niger, this entity is expected to be met in the bush and cause agitations and delirium during the disease phase.<sup>87</sup> Meningitis is also viewed as an airborne disease in Burkina Faso,<sup>130</sup> in northern Benin where it is believed to be caused by winds carrying waste, and in the Mosse groups where it is considered the 'disease of the sun' or 'disease of the wind'.<sup>84,88</sup> In both Benin and Burkina Faso, staying under the sun during the hot season is believed to increase the risk of developing the illness, particularly among children.<sup>83</sup>

Meningitis is also believed to have dietary causes, such as malnutrition in the Hausa groups, or green foods in Burkina Faso, e.g. green mangoes mostly when consumed by children, during the hot season, or when ingested with dust.<sup>83</sup> People with a predisposition for meningitis in Burkina Faso activate the disease by eating prohibited green mangoes and green food,<sup>83</sup> and those with a predisposition for meningitis in Niger have weak souls and develop the disease by looking at a sick person.<sup>87</sup>

These West African representations of the aetiology of meningitis display similarities with the risk factors identified in epidemiological studies, mostly with environmental factors. Yet, different mechanistic assumptions are described in these two viewpoints, which deserve further exploration, as this may be crucial to integrate more social science into operational tools.

#### 4. Perspectives on research to date and the way forward

Despite research efforts over the last decades, gaps in the understanding of several key aspects of meningococcal disease

epidemiology and ecology in the African meningitis belt have prevented better control of the occurrence of seasonal outbreaks and optimization of the public health response. Specifically, these gaps include (1) clarifying the role of climatic risk factors, carriage, and immunity in driving meningitis transmission dynamics; (2) understanding why large-scale meningitis epidemics occur only in a few Sahelian countries, and the possible role of behavioural and socio-cultural factors; (2) elucidating how insights into the molecular epidemiology of meningococcus may help prevent epidemics; and (4) defining populations at risk and better characterizing the boundaries of the African meningitis belt and its potential evolution in the future in a context of climate change.

In order to advance the field of meningococcal meningitis epidemiology in the African meningitis belt, efforts should focus on developing the infrastructure, methods, and approaches to systematically collect high-quality, population-representative longitudinal data on carriage, immunity, disease incidence, social factors, and key molecular characteristics in countries of the African meningitis belt. Mathematical and statistical models that draw upon these aspects, along with climatic and sociological factors, should be further adapted and developed so as to better explain the patterns of the disease observed, anticipate future outbreaks and vaccine impact, and help characterize the changing boundaries of the African meningitis belt. Ultimately, this would allow better adaptation of prevention and control strategies and a more efficient response to localized outbreaks.<sup>27</sup> Several important considerations and limiting factors that need to be addressed are discussed below.

##### 4.1. Meningococcal meningitis risk factors in the African meningitis belt

Population-level changes in natural and vaccine-induced immunity over time have not been investigated systematically in the African meningitis belt. Innovative seroprevalence studies with repeated immunogenic samples, ensuring more extensive geographic and temporal coverage, are needed. Such studies would require immune markers to be fully validated as surrogates of protection against the most commonly reported serogroups in the African meningitis belt. They would also benefit from comparing clones at the whole genome level using novel molecular techniques so as to identify differences in virulence, transmissibility, or antigenicity.<sup>109,131–133</sup> A better understanding of the genetic evolution of meningococcal strains would help to determine and foresee the emergence and spread of new strains and the succession of invasive strains in the African meningitis belt. Ecological factors within the nasopharyngeal environment and strain competition are not well understood at present, but likely play an important role in the epidemic wave phenomenon. Competition can be indirect (mediated through immunity) or direct (through interactions in the nasopharynx, via either exploitative or interference mechanisms). Both immunological and direct competitive interactions have been suggested to be potentially important in high-income countries,<sup>134,135</sup> but no observation has been made in the context of the African meningitis belt. The nasopharyngeal microbiome should indicate the pathogen interactions and their role in epidemic waves in a context of multi-vaccine implementation (i.e., MenAfriVac and pneumococcal conjugate vaccines), including the role of *S. pneumoniae*, which is also responsible for local meningitis epidemics.

In addition to the biological factors, further investigations, possibly combined, into climatic factors (especially humidity and dust in the dry season) and social factors (especially resource inequalities, migration, and seasonal population movements) and their relationships with meningococcal disease would be valuable



in developing plans to prevent and mitigate the spread of this disease.

#### 4.2. Mathematical and statistical modelling of meningococcal disease in Africa

In terms of statistical and mechanistic models, more precise data would allow (1) narrow spatial heterogeneities in disease transmission dynamics to be detected; (2) risk factors to be better detected and their impact to be estimated; (3) this knowledge to be built on to obtain a clearer idea of the mechanisms underlying the disease. In this regard, mathematical mechanistic SIR models have great potential, but need to be developed further, with reliable parameter estimates being plugged in. Scaling down the spatial resolution of analyses to the health centre level would require that the ministries of health of the countries of interest report cases at the health centre level and keep up-to-date records of the evolution of the health centres' spatial definition. More timely reporting of meningitis incidence would reduce the time for decisions and allow reactive vaccination strategies to be optimized, which remain crucial for global meningitis control. In contrast, the current delay in the dissemination of information and aggregation of data at the district level reduces the vaccination campaign efficacy in preventing cases.<sup>27</sup> Finally, as the epidemiology of bacterial meningitis is currently changing in the African meningitis belt following the introduction of MenAfriVac, the national surveillance systems could subsequently be adapted if all stakeholders and partners prioritize this undertaking.

In conclusion, the priorities identified here for future research ultimately aim at understanding the observed patterns of the disease, anticipating meningitis epidemic outbreaks, forecasting the effects of possible public health policies, and determining the geographical evolution of the African meningitis belt. Despite the imminent introduction of a multivalent meningococcal vaccine and the use of pneumococcal vaccine in routine childhood immunization, no time should be wasted and efforts should be made towards better understanding bacterial meningitis in the African meningitis belt and in particular the links between climate, pathogens, and hosts, so as to be prepared for suboptimal disease elimination following vaccine introduction.

#### Acknowledgements

This review was conducted by members of the international consortium MAMEMA (Multidisciplinary Approach for Meningitis Epidemiology and Modeling in Africa). MAMEMA was initiated in 2011 as part of the MERIT (Meningitis Environmental Risk Information Technologies) activities, a multidisciplinary group focusing on understanding the epidemiology and transmission dynamics of meningococcal disease in the African meningitis belt. We thank all MERIT and MAMEMA participants for the thorough discussions on the topic.

**Funding:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Conflict of interest:** None.

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