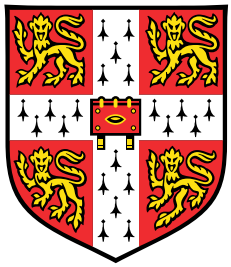
Reducing the Burden of Bacterial Meningitis in the African Meningitis Belt After MenAfriVac



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Declaration

This thesis is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text. It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my thesis has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. It does not exceed the prescribed word limit for the Department of Veterinary Medicine Degree Committee.

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Laura V. Cooper

The African meningitis belt - a semi-arid region stretching from Senegal to Ethiopia - experiences the highest incidence of bacterial meningitis in the world, characterised by seasonal fluctuations in endemic disease, localized outbreaks, and multiennial epidemics. MenAfriVac, a serogroup A meningococcal conjugate vaccine, was introduced in mass campaigns in 2010 and has significantly reduced carriage and incidence of group A disease across the meningitis belt.

However, other meningococcal serogroups and *Streptococcus pneumoniae* continue to cause outbreaks of meningitis in the region. A new pentavalent meningococcal conjugate vaccine protecting against serogroups A, C, W, Y, and X is in development and promises to help eliminate outbreaks of meningococcal meningitis by 2030. However, questions remain as to how best to respond to outbreaks of pneumococcal meningitis and non-A meningococcal meningitis and how to use the pentavalent meningococcal conjugate vaccine when it becomes available. This thesis aims to evaluate the remaining challenges to control of bacterial meningitis in the African meningitis belt and assess the relative effectiveness and efficiency of various responses.

The first research chapter describes patterns in bacterial meningitis incidence before and after the introduction of MenAfriVac and compares outbreaks where *Nm*A, *Nm*C, *Nm*W, and *S. pneumoniae* are predominant. The second chapter describes in detail an outbreak of pneumococcal meningitis in Ghana and models the potential impact of reactive vaccination using pneumococcal conjugate vaccine. In the third chapter I present a systematic review and meta-analysis of meningococcal carriage patterns by age and season in the African meningitis belt and propose ways in which it might inform the use of the pentavalent meningococcal conjugate vaccine. In the fourth chapter, I analyse the results of a longitudinal household study to identify behavioural and environmental risk factors for meningococcal carriage acquisition. The final chapter examines the spatio-temporal spread of the novel *Nm*C strain which emerged in Nigeria in 2013, estimates the impact of reactive vaccination campaigns that occurred in the region between 2015 and 2017, and models the effects of alternative outbreak response strategies, including targeting neighbouring districts.

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List of abbreviations

cnl	Capsule-null
Nm	*Neisseria meningitidis*
CFR	Case-fatality ratio
CI	Confidence interval
CMAP	Climate Prediction Center Merged Analysis of Precipitation
CSF	Cerebrospinal fluid
DRC	Democratic Republic of the Congo
Gavi	Gavi, the Vaccine Alliance, previously the GAVI Alliance, previously the Global Alliance for Vaccines and Immunization
Hib	*Haemophilus influenzae* b
ICG	International Coordinating Group on Vaccine Provision for Epidemic Meningitis
IHME	Institute for Health Metrics and Evaluation
MenAfriCar	African Meningococcal Carriage Consortium
MenAfriVac	Group A meningococcal conjugate vaccine
MOOSE	Meta-analysis of observational studies in epidemiology
MVP	Meningitis Vaccine Project
NCAR	National Center for Atmospheric Research
NCEP	National Centers for Environmental Prediction
NmCV-5	Pentavalent (groups ACWYX) meningococcal conjugate vaccine
NNV	Number needed to vaccinate to prevent a case

NNVD	Number needed to vaccine to prevent a death
NOAA	National Oceanic and Atmospheric Administration
NPV	Negative predictive value
OPA	Opsonic pneumococcal activity
OR	Odds ratio
PATH	Program for Appropriate Technology in Health
PCV	Pneumococcal conjugate vaccine
PCV10	10-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PPV	Positive predictive value
PREC/L	Number needed to vaccine to prevent a death
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
Spn	*Streptococcus pneumoniae*
ST	Serotype
UN	United Nations
VIMC	Vaccine Impact Modelling Consortium
VIS	Vaccine investment strategy
WHO	World Health Organization
WHO-IST	WHO Inter-country Support Team

Chapter 1

Aims and rationale

The African meningitis belt is a semi-arid region of sub-Saharan Africa stretching from Senegal in the west to Ethiopia in east and falling between 4 and 16 degrees north latitude, characterized by high incidence and recurrent epidemics of bacterial meningitis.[1] For decades, group A *Neisseria meningitidis* (or meningococci) were the predominant cause of meningitis in the African meningitis belt. The introduction of a group A meningococcal conjugate vaccine, MenAfriVac, in mass vaccination campaigns in countries across the meningitis belt has almost eliminated the burden of group A meningococcal meningitis and reduced all-cause meningitis by 57%.[2] Many countries are planning to introduce or have already introduced the vaccine into their routine infant vaccination programs. With adequate coverage, routine infant vaccination can ensure long-term reductions in group A meningococcal meningitis incidence.[3] However, the years following the introduction of MenAfriVac have seen significant increases in the incidence of non-group-A meningococcal meningitis.[2] Of particular note are the re-emergence of group C, which caused the largest group C epidemic ever observed in 2017, and the persistence of groups W and X. Outbreaks of meningitis caused by *Streptococcus pneumoniae* (or pneumococci) are also of concern.

A thermostable pentavalent vaccine protecting against meningococcal serogroups A, C, W, Y, and X is currently in development by the Serum Institute of India, which hopes to submit the vaccine to the World Health Organization (WHO) for pre-qualification by 2023.[4] Gavi, the Vaccine Alliance has approved, in principle, some degree of financial support for this new vaccine. If delivered widely enough, this multivalent vaccine has the potential to nearly eliminate epidemics of meningococcal meningitis. A variety of scenarios including restricting use of the pentavalent vaccine to higher-risk countries and introducing the pentavalent only in routine infant immunisation are being considered to limit the extent of Gavi's investment.

In 2017, experts from governments, global health organisations, academia, and the private sector gathered to draft a global roadmap to defeat meningitis by 2030.[5] The resulting plan focused on the four organisms responsible for most bacterial meningitis - *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *Streptococcus agalacticae* - with three broad aims to be achieved by 2030: eliminate meningitis epidemics, substantially reduce

overall cases and deaths from vaccine-preventable meningitis, and provide high quality care for survivors with sequelae.[6] In the African meningitis belt in particular, achieving this goal requires the use of distinct short- and long-term strategies. Meningococcal meningitis outbreaks will continue to occur at least until the pentavalent meningococcal conjugate vaccine (NmCV-5) is available for use, and possibly for longer if widespread use is unaffordable. Use of *H. influenzae* b (Hib) conjugate vaccine in infants has reduced Hib meningitis dramatically[7,8] and in European countries with high ($\geq$ 90%) infant coverage, pneumococcal conjugate vaccine (PCV) has had significant direct and indirect effects on invasive pneumococcal disease in as little as five years.[9] The introduction of group C meningococcal conjugate vaccine in Spain, the United Kingdom, and Canada demonstrated significant indirect effects within just one year, but all of these countries used catch-up campaigns for older children in addition to routine infant immunisation.[10–12] It is likely that routine infant PCV and NmCV-5 will eventually have the same effects in the African meningitis belt - but how long it will take to establish herd immunity for these bacteria remains unclear. Epidemiological research can inform choices about short-term responses to meningitis outbreaks and long-term strategies for establishing and maintaining protection.

This thesis addresses both short- and long-term issues. In the short-term, the focus is on responding to outbreaks of meningococcal and pneumococcal meningitis, including testing alternative warning systems, use of conjugate vaccines in reactive responses, and informing stockpile management. The long-term aims contribute to the use of and understanding the impact of MenAfriVac and NmCV-5. These issues are addressed over five research chapters. Chapter 3 describes patterns in bacterial meningitis before and after the introduction of MenAfriVac and compares outbreaks in which *Nm*A, *Nm*C, *Nm*W, and *S. pneumoniae* are predominant. Chapter 4 describes an outbreak of pneumococcal meningitis in Ghana and models the impact of reactive vaccination using a pneumococcal conjugate vaccine. In Chapter 5 I present a systematic review and meta-analysis of meningococcal carriage patterns by age and season in the African meningitis belt and propose ways in which it might inform the use of the pentavalent meningococcal conjugate vaccine. In Chapter 6, I analyse the results of a longitudinal household study of meningococcal carriage acquisition and identify behavioural and environmental risk factors for acquisition. Chapter 7 examines the spatio-temporal spread of the novel *Nm*C strain which emerged in Nigeria in 2013, estimates the impact of reactive vaccination campaigns that occurred in the region between 2015 and 2017, and compares new strategies for outbreak response. In Chapter 8 I review my findings and discuss how this research can be used to inform bacterial meningitis control in the African meningitis belt.

Chapter 2

Introduction

2.1 Human and microbe

Meningitis refers to the inflammation of the meninges, the membranes surrounding the brain and central nervous system. One of the most serious causes of this inflammation is bacterial infection. Two of the most common causes of bacterial meningitis today are *Neisseria meningitidis* and *Streptococcus pneumoniae*, with *Haemophilus influenzae* type b making up a sizeable burden in the pre-vaccine era.[7] All three of these species are human commensals that primarily inhabit the nasopharynx and are transmitted between hosts via respiratory secretions. An individual may host the bacteria in his or her nasopharynx transiently or over sustained periods, a phenomenon known as carriage. The duration of carriage varies from days to months, and depends on the characteristics of the colonising strain, the host's mucosal immune environment, and the presence of other bacteria in the nasopharynx. The limited data available on meningococcal carriage in Africa indicate an average duration of carriage for group A meningococci of about one month and other meningococci about three months.[13–16] A more comprehensive study of pneumococcal carriage in children in Kenya estimates average durations ranging from 28 to 124 days, varying by serotype.[17] There is considerable diversity in carriage duration across settings and individuals, and in reality carriage may be chronic, intermittent, or transient.[15,18]

S. pneumoniae belongs to the phylum Firmicutes and is Gram-positive. *H. influenzae* and *N. meningitidis* belong to the phylum Proteobacteria and are Gram-negative. In the absence of resistance, penicillin, ampicillin, and chloramphenicol are effective antibiotic treatments for meningitis caused by *S. pneumoniae*, *H. influenzae* and *N. meningitidis*. A systematic review of studies of antibacterial resistance in West Africa found low levels ($< 20\%$) of penicillin and chloramphenicol resistance in *S. pneumoniae*, *H. influenzae* and *N. meningitidis* isolates.[19]

Because the bacteria are susceptible to drying and cannot survive for long periods outside of the nasopharynx, transmission between hosts requires close contact for the exchange of saliva or upper respiratory secretions. Many meningococci and pneumococci are encased in protective outer capsules that help to slow drying and aid in transmission. Meningococci are classified

into serogroups depending on the biochemical makeup of the polysaccharides embedded in these capsules. There are twelve serogroups, but only six regularly cause invasive disease: A, B, C, W, Y, and X. Pneumococci are similarly classified into serotypes, of which there are more than 90, and *H. influenzae* are classified into six serotypes, with type b most commonly causing disease. The capsule is the main virulence factor and the most immunogenic part of these bacteria, and may be lost permanently or temporarily by deletion or down-regulation of the capsule locus - thus helping to evade the host's immune system. Meningococci which have lost the capsule locus entirely are referred to as capsule-null and very rarely cause invasive disease.

Although they are primarily commensals, these species of bacteria may also be characterised as accidental or opportunistic pathogens. In rare cases, the bacteria may penetrate the mucosal lining of the nasopharynx and pass into the cerebrospinal fluid (CSF), resulting in meningitis, or into the blood, resulting in sepsis. When invasive disease does occur, it is thought to occur soon after acquisition.[20] *S. pneumoniae* and *H. influenzae* are also important causes of pneumonia. Instances of invasion of normally sterile sites of the body, called invasive disease, do not aid in the transmission of bacteria between hosts and as such are not thought to be evolutionarily beneficial. Nonetheless, strains may acquire virulence traits through mutation or horizontal transfer and relatively hypervirulent strains have been shown to persist and cause outbreaks for years.[21,22]

2.2 Epidemiology

Meningococcal carriage prevalence in the African meningitis belt is highly variable, with observations ranging from 0 to 35%.[23] The age distribution of meningococcal carriers in high-income countries peaks around 19 years of age.[24] Chapter 5 describes in detail patterns of meningococcal carriage by age in the meningitis belt. Pneumococcal carriage is most prevalent in children under five, and common across all age groups, with 63% of under five year olds and 28% of over fifteen year olds in sub-Saharan Africa estimated to be carriers.[25] The duration of carriage for both meningococci and pneumococci appears to decrease with age.[14,17] For *S. pneumoniae*, this has been shown to be linked to the development of both serotype-specific and serotype-independent natural immunity.[26,27]

Meningococcal disease incidence and serogroup distribution vary widely from region to region.[28,29] The African meningitis belt has the highest incidence of bacterial meningitis of any region and is the only place where irregular and recurrent epidemics of meningococcal disease are still observed.[1,30,31] Meningitis in this region is highly seasonal, with the majority of cases occurring during the dry season, predominantly in the first five months of the year.[32–34] Epidemics tend to start in the middle of the dry season, which lasts from October to April, and end with the onset of the rainy season, which usually starts in May.[35,36] One proposed explanation for this striking seasonality is an increased risk of invasive disease in the dry season, due to mucosal damage from environmental factors such as low absolute humidity and

dust.[31,37,38] This risk is sometimes measured as the ratio of meningitis cases to carriers in the same population. An alternative hypothesis suggested by mathematical modelling is that higher rates of carriage transmission during the dry season contribute to regular seasonality, and combine with longer-term fluctuations in population immunity to produce irregular interannual epidemics.[39] Although a review of carriage in the meningitis belt published in 2007 found no evidence to support a seasonal effect on carriage,[23] more recent studies have found a higher prevalence of carriage in the dry season.[40,41] I will return to this question in Chapter 5.

Meningococcal meningitis, which is the most epidemic-prone of the three major causes, is also characterised by unique long-term trends.[42] Mueller and Gessner propose an explanatory model for meningitis with three distinct dry-season patterns: hyperendemicity, localised epidemics, and epidemic waves.[43] During the rainy season, a weekly incidence of less than 1 case per 100 000 persons is usual - a rate comparable to that observed in most other regions globally.[43] In the hyperendemic pattern, incidence increases by a factor of about 10 to 100, driven, according to Mueller and Gessner, by an increase in invasiveness caused by the dusty, dry weather. This occurs in most districts during the dry season. In some communities, incidence may be further increased 10- to 100-fold – an increase the authors attribute to an increase in carriage prevalence. Localised epidemics may form a wave affecting multiple regions, with incidence 3- to 10-fold higher than during seasons with only localised epidemics.[43] These epidemic waves occur with irregular periodicity, resulting in peaks at the national level every 7 to 12 years.[44] These epidemic waves may last for multiple years, but incidence always returns to endemic levels during the intervening rainy seasons.[43]

It seems likely that the meningococcus was brought to Africa by European colonisers, with the earliest documented outbreak among soldiers in Algiers in 1840. From here, it may have spread via the Egyptian army to Sudan, and from Sudan to West and Central Africa via the Hajj.[31] The first proven meningococcal outbreak in the general population, confirmed by the observation of diplococci in the CSF of cases, occurred in northern Nigeria in 1905 and caused thousands of deaths.[31] Since at least the 1940s and up until the introduction of a conjugate polysaccharide vaccine in 2010, serogroup A has been the predominant cause of bacterial meningitis in the African meningitis belt, causing major epidemics most recently in 1996-1997 and 2009.[28] Meningococcal serogroups C, W, and X have also demonstrated their potential for causing epidemics. In the 1970s and 1980s there were reports of epidemic serogroup C meningococcal disease in Guinea, Nigeria, and Burkina Faso.[45] Sporadic cases of serogroup W and X occurred in the 1990s in Niger, Mali, the Gambia, Cameroon, and Chad.[28] A large outbreak of serogroup X followed an epidemic and subsequent decline of serogroup A disease in northern Ghana in 2000, and another occurred in 2006 in Niger.[28,46] A serogroup W epidemic occurred in Burkina Faso in 2002 and 2003, and in 2012.[28] Epidemics of group Y or B have not been observed in the African meningitis belt, although sporadic cases do occur.[30] A novel strain of serogroup C caused an outbreak in Northern Nigeria in 2013, the first since 1979.[47] This strain continues to circulate, and has caused outbreaks in Nigeria, Niger, Burkina Faso, and

Mali as of 2019. *S. pneumoniae* has not caused documented widespread epidemics of meningitis, but accounts for about one fourth of confirmed cases of bacterial meningitis reported to the World Health Organization (WHO) meningitis belt surveillance system since 2003.[34]

Since the 1980s, the reference method for categorising strains of *N. meningitidis* was multilocus enzyme electrophoresis, which identifies clusters of closely related strains by indirectly assigning alleles based on their electrophoretic mobility. The application of multilocus enzyme electrophoresis (MLEE) revealed greater genetic diversity in *N. meningitis* than other bacterial species.[48] It also revealed that successive epidemics waves of serogroup A meningitis in the African meningitis belt between 1960 and 2000 were caused by three distinct clonal complexes, named subgroups I, IV-1, and III.[49] In the late 1990s a new method for classifying meningococcal strains was developed called multi-locus sequence typing, which grouped strains based on the alleles identified by sequencing seven important housekeeping genes.[50] Application of this method to a set of 357 isolates from patients with invasive disease from countries in the meningitis belt between 1988 and 2003 identified three sequence types (STs) that caused the majority (92%) of outbreaks and endemic disease: serogroup A ST-5 and the closely related ST-7 and serogroup W ST-11.[51] Serogroup A ST-5 was previously identified by MLEE as subgroup III; subgroups I and IV-1 (now ST-1 and ST4, respectively) are rarely identified since 1988.[51] More recently, researchers have identified a novel serogroup A sequence type, ST-2859, which is closely related to ST-5 and ST-7 and caused the 2006 epidemic in Burkina Faso.[49] By 2010, ST-7 and ST-2859 appeared to have completely replaced ST-5.[52,53] In 2014, Funk and colleagues identified a novel sequence type 10217 associated with the *Nm*C outbreaks in Northern Nigeria.[47] Brynildsrud and colleagues hypothesise that a related unencapsulated strain horizontally acquired a group C capsule and other virulence genes at some time between 2007 and 2011, becoming invasive and causing the *Nm*C outbreaks beginning in 2013.[54] The authors identify a strain isolated from a carrier in Burkina Faso in 2012 as the closest carriage relative of the outbreak strain present in the publicly available *N. meningitidis* genome library, but this analysis is limited by the low number of carriage isolates available in the library. Whole-genome sequencing of invasive *Nm*C isolates from Nigeria, Niger, Burkina Faso, and Mali 2013-2016 revealed a new sequence type closely related to ST-10217, ST-12446, circulating in Mali in 2016.[55] In general, molecular studies of *N. meningitidis* have focused on isolates from invasive disease, as these are readily available. Molecular studies of carriage isolates have generally found a high level of non-groupable meningococci in carriers, with very low or no carriage of known virulent types.[56,57]

Bacterial meningitis has a fast onset: as many as 84% of deaths occur within the first 24 hours of illness.[58] The case-fatality ratio (CFR) reported for meningococcal meningitis is usually around 10% in the African meningitis belt, a rate not different from that found in industrialised countries.[31] However, detailed community studies suggest that the true CFR may be significantly higher because individuals may die before reaching a health care facility.[58] Pneumococcal meningitis has a higher CFR, with observations ranging from 17% to 53%.[21,32,59–65] Recent data from the Burkinabe case-based surveillance system shows a crude CFR of 9.7% for

meningococcal meningitis (95% CI 8.3-11%) and 23% for pneumococcal meningitis (95% CI 22-25%).[33]

Meningococcal disease in the African meningitis belt tends to be more evenly distributed across age groups than in high-income, temperate countries, but higher incidence is still observed in individuals under 20 years of age, while disease is uncommon in adults over 30 years.[30] Recent surveillance data from Burkina Faso show about one-third of confirmed meningococcal meningitis in children under 5 and about one-half in 5- to 14-year-olds, with few cases in older children and adults (see Table 2.1).[33] By contrast, nearly one-third of pneumococcal meningitis cases occurred in individuals 15 years and older, roughly equal to the share in under fives. The large majority of *H. influenzae* meningitis cases occur in children under five.

Table 2.1 Confirmed bacterial meningitis cases by age and etiology in Burkina Faso, 2011 – 2015.[33]

	Confirmed meningitis cases			
Cause	Under 5 years	5-14 years	15 plus years	Total
H. influenzae b	77 (69%)	31 (28%)	3 (3%)	111
N. meningitidis	621 (34%)	889 (49%)	298 (16%)	1808
S. pneumoniae	690 (27%)	1090 (42%)	801 (31%)	2581

In the years 1990 to 2017, the Institute for Health Metrics and Evaluation (IHME) estimates that meningococcal, pneumococcal and *H. influenzae* b meningitis caused on average 73 000 deaths and 600 000 cases per year across the African meningitis belt, accounting for about 1.6% of total deaths and 0.4% of years lived with disability.[66] It should be noted that *S. pneumoniae* causes pneumonia more frequently than meningitis, with on average 260 000 deaths due to pneumococcal pneumonia annually in the region over the same time period (1990-2017). In recent years (2013-2017), the burden of bacterial meningitis has decreased somewhat, with 55 000 deaths and 560 000 cases estimated annually. Nonetheless, these estimates place meningitis among the top ten causes of years of life lost and death in sub-Saharan Africa.[66]

The IHME estimates that *N. meningitidis*, *S. pneumoniae*, and *H. influenzae*b cause a roughly equal share of cases, with a somewhat larger share of deaths due to *S. pneumoniae*. However, these estimates are dubious when compared to data on confirmed cases reported by national ministries of health: of more than 15 000 confirmed cases reported between 2004 and 2013, roughly 4% were *H. influenzae*b, 26% were *S. pneumoniae*, and 67% were *N. meningitidis*.[34] The IHME model relied heavily on verbal autopsy data for the African meningitis belt region, which would not give information on the etiology of meningitis. It is possible that their estimates of the breakdown of meningitis deaths by etiology are reliant on data from other regions, where *N. meningitidis* does not predominate.

2.3 Control and policy

Twenty-six countries have some territory in the meningitis belt: Benin, Burkina Faso, Burundi, Cameroon, the Central African Republic, Chad, Cote d'Ivoire, the Democratic Republic of the

Congo, Eritrea, Ethiopia, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Mali, Mauritania, Niger, Nigeria, Rwanda, Senegal, South Sudan, Sudan, Togo, Uganda, and Tanzania. PCV has been introduced in infant immunisation in 23 of these 26 countries.[67] Guinea and South Sudan have not yet introduced PCV and Chad plans to introduce the vaccine in 2021. Hib conjugate vaccine has been in use in all countries since 2014.

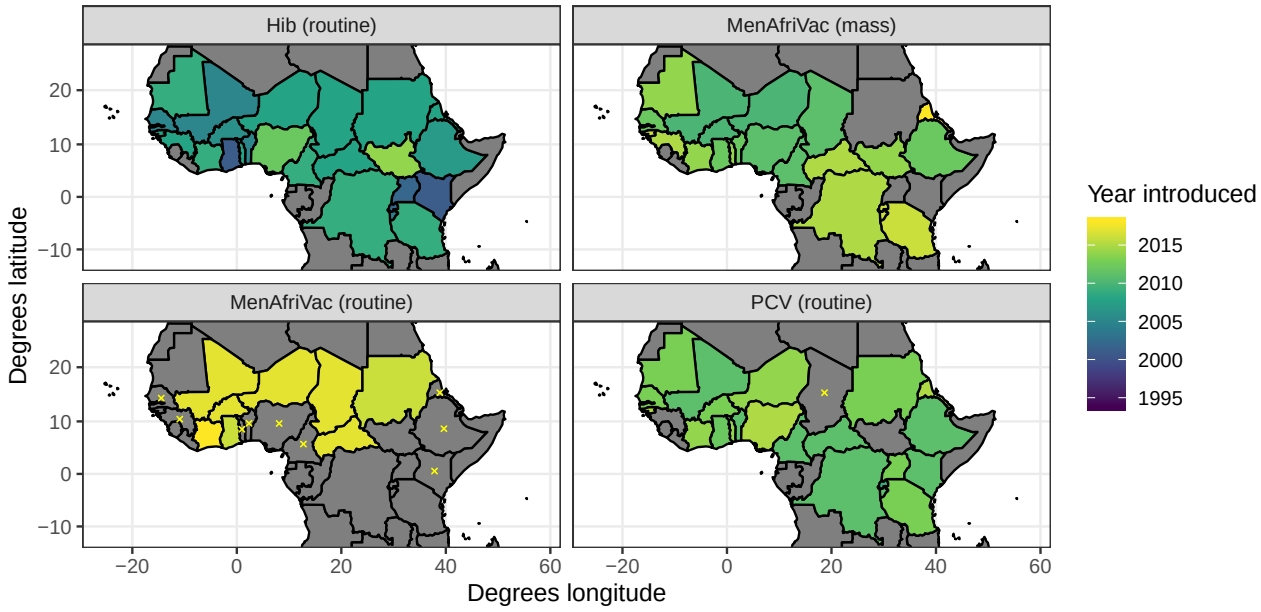


Fig. 2.1 Map showing the timing of actual and planned (post-2018, shown as crosses) introduction of conjugate vaccines to prevent bacterial meningitis. Source: WHO Immunization, Vaccines and Biologicals website.[67]

For years, the approach to reducing morbidity and mortality due to meningococcal meningitis has been reactive mass administration of meningococcal polysaccharide vaccines in districts experiencing epidemics. Because polysaccharide vaccination has low immunogenicity in infants, induces only short-lived immunity, and does not protect against carriage, it is not a lasting control measure. In response to group A epidemics in the meningitis belt, the Meningitis Vaccine Project (MVP), a partnership between the WHO and the Program for Appropriate Technology in Health (PATH), was established in 2001 with the aim of eliminating epidemic group A meningitis through the development, testing, licensure, and introduction of a group A meningococcal conjugate vaccine that would be affordable in Africa.[68]

The vaccine, MenAfriVac, uses group A meningococcal polysaccharide with tetanus toxoid protein as a carrier. Protein-polysaccharide conjugate vaccines induce T-cell dependent immune response, allowing for memory response priming, antibody maturation, inducement of protective antibodies in young children and infants, and reduction of nasopharyngeal carriage.[69] The

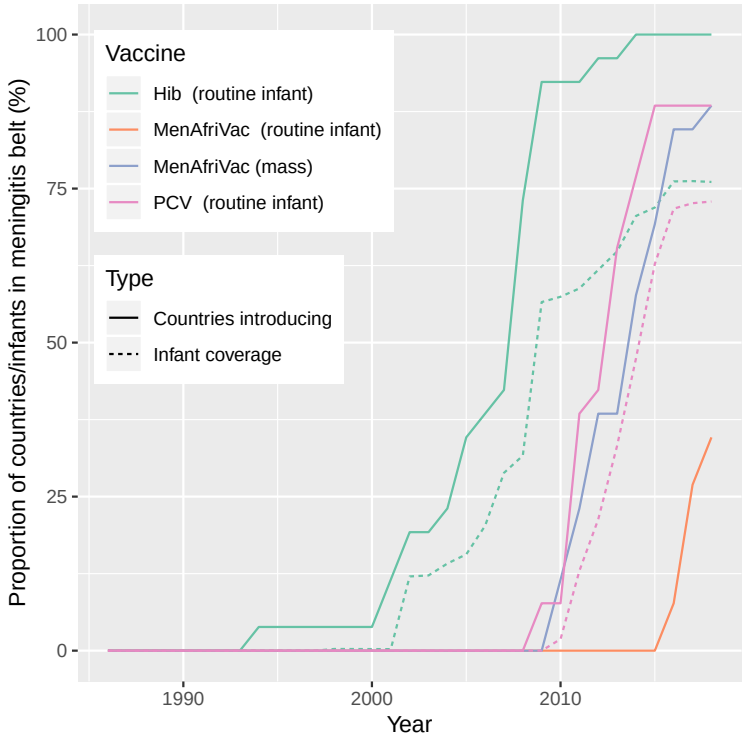


Fig. 2.2 Timing of introduction of conjugate vaccines to prevent bacterial meningitis (proportion of 26 meningitis belt countries), and third-dose coverage estimates for PCV and Hib vaccine for infant cohorts. Source: WHO Immunization, Vaccines and Biologicals website.[67]

reduction of carriage reduces transmission of the bacteria and allows for the development of herd immunity, whereby unvaccinated individuals are protected by reduced transmission. Herd immunity is largely responsible for the high impact of the meningococcal group C conjugate vaccine in the United Kingdom and may also be key to MenAfriVac's success in the meningitis belt.[70]

MenAfriVac was pre-qualified by the WHO and first introduced in mass vaccination campaigns for individuals between the ages of 1 and 29 years across the meningitis belt starting in 2010. As of 2018, 23 countries had introduced MenAfriVac in mass campaigns (Kenya, Sudan, and Uganda did not undertake mass campaigns).[67] MenAfriVac is now included in the WHO Extended Programme of Immunisation for infants between 9 and 18 months and 9 countries have introduced MenAfriVac in routine infant immunisation (Burkina Faso, Central African Republic, Cote d'Ivoire, Ghana, Gambia, Mali, Niger, Sudan, Chad) (see Figures 2.2 and 2.1). A further nine countries plan to introduce MenAfriVac into infant schedules in the coming years (Benin, Cameroon, Eritrea, Ethiopia, Guinea, Kenya, Nigeria, Senegal, Togo).

Vaccination has significantly reduced the prevalence of serogroup A nasopharyngeal carriage and incidence of group A meningitis in short-term studies.[71,72] In Burkina Faso, this reduction in carriage has persisted for at least two years following vaccination.[73] A study of surveillance data between 2010 and 2015 found that mass MenAfriVac campaigns have decreased the incidence of suspected cases of meningitis by 57% and confirmed cases of *Nm*A meningitis by 99%.[2] The

vaccine has continued to be effective, with only 19 confirmed cases of group A meningitis across Benin, Burkina Faso, Chad, Cote d'Ivoire, Ghana, the Gambia, Mali, Niger, Nigeria and Togo since vaccination was implemented (as of November 2019).[72,74]

However, other meningococcal serogroups continue to circulate and cause disease in the region, in particular serogroups W, X, and C. Although previously an infrequent cause of disease in the African meningitis belt, a new serogroup C strain emerged in Nigeria in 2013, spread to Niger in 2015, and in 2017 caused the largest serogroup C outbreak ever observed in the African meningitis belt.[75] The strain has now spread to Burkina Faso, where it caused outbreaks in 2019. Group W has continued to cause outbreaks, most significantly in Ghana in 2016, in Togo in 2016, 2017, and 2019, and in Chad in 2019.

Vaccine for outbreak response is often either unaffordable or in short supply, as pharmaceutical companies phase out production of polysaccharide vaccines and transition towards increased production of conjugate vaccines for the Western market. In 2018, the International Coordinating Group (ICG) on Vaccine Provision for Epidemic Meningitis, which coordinates the provision of vaccines for reactive vaccination campaigns in response to meningococcal outbreaks, held 3.5 million doses of C-containing meningococcal vaccine, 1.5 million doses short of the 5 million required to respond adequately in 5 of 6 epidemic years, and 7.1 million doses short of the 10.6 million needed to respond in most worst-case scenarios.[76,77]

In 2008, the United Kingdom Department for International Development partnered with PATH and the Serum Institute of India to develop an affordable and thermostable pentavalent meningococcal conjugate vaccine for Africa, protecting against serogroups A, C, W, Y, and X. The vaccine is currently in stage III trials in Mali and the Gambia for use in 2- to 29-year-olds.[78,79] The partners hope to submit the vaccine to the WHO for pre-approval by 2023.[4] The 2018 Gavi Vaccine Investment Strategy approved, in principle, financial support for this vaccine.[80] If delivered widely enough, this multivalent vaccine has the potential to nearly eliminate epidemics of meningococcal meningitis. Modelling work is ongoing in assessing the cost-effectiveness of routine infant pentavalent vaccination in combination with reactive or preventative vaccination campaigns in the wider population.[81,82] A variety of scenarios including restricting use of the pentavalent vaccine to higher-risk countries and introducing the pentavalent only in routine infant immunisation are being considered to limit the size of Gavi's investment.[83]

In 2017, experts from governments, global health organisations, public health bodies, academia, private sector and civil society gathered to create a roadmap with the aim of eliminating meningitis epidemics, reducing cases and deaths from vaccine-preventable meningitis, and providing high quality care for survivors with sequelae by 2030, focusing on the four organisms responsible for most bacterial meningitis - *N. meningitidis*, *S. pneumoniae*, *H. influenzae*b, and *S. agalacticae*.[5,6] Specific gaps and research priorities identified in the roadmap process include optimising strategies for outbreak prevention and response, including a better understanding of pneumococcal outbreaks, and finding an optimum schedule for the *N. meningitidis* pentavalent vaccine NmCV-5.This thesis focuses primarily on meningitis caused by

N. meningitidis and *S. pneumoniae*, with very brief mention of *H. influenzae*. It is useful to consider them together because all three of these organisms occupy similar ecological niches, but important to recognise that they have different potential to cause meningitis in individuals and to cause epidemics.

The following sections address some more technical aspects of relevance to this thesis. I begin with an overview of different types of models for meningococcal transmission which are used in Chapters 4 and 7. I then review the epidemiology of pneumococcal meningitis in the African meningitis belt, with relevance to Chapter 4, and summarise the findings of studies of climactic and environmental risk factors for meningococcal meningitis outbreaks in Africa, which serve as a starting point for the analyses in Chapter 3 and 7 and underpin investigations of the seasonality of carriage in Chapters 6 and 5.

2.4 Modelling meningococcal meningitis in the African meningitis belt

Mathematical models describe systems using mathematical concepts. Models provide a means of experimentation where it would be unethical or unfeasible to do so in reality. As such, they are useful both for informing decisions about public health and disease control - for example, the best age to give a vaccine in a national immunisation scheme - and for testing scientific hypotheses about processes that may be difficult to observe - for example, the role of seasonality in disease transmission.[84] It is generally accepted that a model should be as simple as possible while still accurately answering the question at hand and the information available.[85] As the aim of this thesis is primarily to test hypotheses relevant to the control of bacterial meningitis in resource-poor settings where information may be limited, the models used are fairly simple.

2.4.1 Models of reactive vaccination for meningococcal meningitis outbreaks

Reactive vaccination policy in the African meningitis belt has evolved in response to changes in disease burden and continuing insights from research. The first epidemic definition for meningococcal meningitis was recommended by the WHO in 1995 on the basis of analysis by Moore and colleagues of surveillance data from Burkina Faso.[86] Under these guidelines, an epidemic threshold was triggered where a district recorded 15 suspected cases of meningitis per 100 000 population per week average over two consecutive weeks. In districts neighbouring a district which had already triggered the epidemic threshold, the threshold was lowered to 5 cases per 100 000 per week.[87] This was updated in 2000 to recommend a lower threshold of 10 suspected cases per 100 000 per week for high risk districts and to emphasise the importance of surveillance at a district level, as outbreaks of meningitis tend to occur at a fine spatial scale and can be missed when surveillance is carried out more coarsely.[88] A recommendation was

also made for vaccination of districts in alert (exceeding incidence of 5 suspected cases per 100 000 per week) and neighbouring an epidemic district. With the introduction of group A meningococcal conjugate vaccine in the meningitis belt in 2010 and subsequent reduction in the burden of group A meningococcal meningitis, these thresholds were re-evaluated, focusing on *Nm*W outbreaks.[89] This research informed the next iteration of WHO guidelines, which maintained the epidemic threshold of 10 suspected cases per 100 000 per week but emphasised the importance of surveillance in populations smaller than 100 000 persons, shortening the delay between triggering of the incidence threshold and intervention, lowered the alert threshold to 3 suspected cases per 100 000 per week, and relaxed the recommendation for vaccination in neighbouring districts to allow for more flexibility.[90]

The principle behind the policy is the use of weekly incidence thresholds to predict high cumulative seasonal incidence. The weekly threshold is triggered as the outbreak grows, giving an early warning sign and allowing local health authorities to carry out preventative measures, including mass vaccination. If the weekly incidence threshold is set low, it will give earlier warnings, but also will warn more often in cases where an outbreak does not actually occur. If the threshold is set high, it will warn later, giving less time to respond, but is more predictive of an outbreak. The optimal threshold is generally determined on the basis of its sensitivity and specificity, or by maximising the potential cases averted per dose of vaccine used.

An early method developed by Pinner and colleagues to estimate the cases averted by a vaccination campaign treated a localised outbreak of meningitis as a temporally varying environmental exposure, defining the observed incidence, I, in a partially-vaccinated population as

$$I_t = I_{V,t}p_t + I_{N,t}(1 - p_t)$$

where $I_{V,t}$ is the incidence in the vaccinated population, $I_{N,t}$ is the incidence in the non-vaccinated population, and p_t is the proportion of individuals vaccinated at time t.[91] Making the assumption

$$I_V = (1 - \sigma)I_N$$

where σ is the individual vaccine efficacy, allows us to solve for incidence in the non-vaccinated population by substitution:

$$I_{N,t} = \frac{I_t}{1 - \sigma p_t}$$

thus giving an estimate of incidence in the absence of vaccination. This method ignores transmission during the outbreak and assumes that all cases are the result of carriers progressing to invasive disease.

Parent-du-Chatelet extended this model with age-specific attack rates and vaccine efficacy, such that

$$I_{N,t,a} = \frac{I_{t,a}}{1 - \sigma p_{t,a}}$$

for each age class, a, and each week, t.[92] Woods and Kaninda also added to the Pinner model, taking into account time for the vaccine to take effect with a delay of l weeks,[93,94] such that

$$I_{N,t,a} = \frac{I_{t,a}}{1 - \sigma p_{t-l,a}}$$

It is important to note that σ must be individual vaccine efficacy against all causes of meningitis, such that in a district with an epidemic in which half the cases are caused by *Nm*A and half by *Nm*W, modelling a reactive campaign using *Nm*W vaccine, the usual vaccine efficacy must be reduced by one half. In practice, many early studies assume that all suspected cases are due to the focal pathogen (usually *Nm*A).

Ferrari and colleagues added an upper bound to their estimates of vaccine impact by fitting a dynamic time-series SIR model to the observed incidence.[95] Under this model, no cases in the epidemic are the result of asymptomatic carriers progressing to invasive disease and vaccination prevents onward transmission. By contrast, under the Pinner-type model all cases are the result of asymptomatic carriers progressing to invasive disease and vaccination has no effect on transmission (under the assumption that transmission does not occur during the epidemic). It is not clear how much increased transmission during the epidemic contributes to incidence of invasive disease and to what extent cases are simply triggered by environmental effects like increased temperature and dust that increase the risk of invasive disease in existing carriers. These two models represent two extremes in potential models of the outbreak process.

Estimates of the proportion of cases averted by reactive vaccination campaigns varies widely, in part because of differing assumptions of vaccine efficacy and in part because meningitis outbreaks are variable (see Table 2.2 for a summary of studies of reactive vaccination). Those that progress slowly after triggering the epidemic threshold allow more time for the vaccine to take effect; in contrast, some epidemics have all but finished by the time the vaccine is delivered.

Table 2.2 Studies modelling the impact of reactive vaccination for meningitis outbreaks. All the studies use a variant of the static Pinner model. The study by Ferrari and colleagues compares this to the dynamic time-series SIR model.

Study	Setting	Serogroup	Coverage	Vaccine efficacy	Delay	Impact findings
Pinner 1992[91]	Nairobi, Kenya 1989	A	Variable by ward	87%	None	Cases reduced by "at least" 20%
Kaninda 2000[93]	Togo 1990-1997	A	85%	85%	1 week seroconversion, 2 weeks operational	65% of cases in epidemic districts prevented
Woods 2000[94]	One district in Ghana 1997	A	72%	85%	2 weeks	23% of cases prevented
Parent du Chatelet 2001[92]	One district in Senegal 1997	A	77%	85%	Until weekly incidence of 60 per 100 000	49% of cases prevented
Leake 2002[96]	One district in Burkina Faso 1997	A	86%	85%	2 weeks seroconversion, 3 weeks operational	59% of cases prevented
Ferrari 2014[95]	Katsina State, Nigeria 2009	A	Variable by ward	85%	Variable by ward	4-12% of cases in state prevented
Trotter 2015[89]	136 district-years across belt	W	Effective coverage of 75%		2 weeks seroconversion, 4 weeks operational	75% of cases during epidemic period prevented
Mainassara 2015[97]	3 regions of Niger 2002-2011	A	80%	80%	3 weeks	4% of all cases in 3 regions prevented
Mainassara 2017[98]	Dosso Region, Niger 2015	C	80%	80%	3 weeks	2% of all cases in region prevented (only 1 district vaccinated)

A study using a Pinner-type model to simulate reactive vaccination in three regions of Niger between 2002 and 2012 found that reactive vaccination was most effective (most cases prevented) when surveillance was performed at the subdistrict level and vaccination at the district level and most efficient (most cases prevented per dose) when surveillance and vaccination were performed at the subdistrict level.[97] While reducing the delay between triggering epidemic threshold and vaccination from four to one week roughly doubled efficiency and effectiveness, these gains were not equal in magnitude to those associated with switching from district-level to subdistrict-level surveillance.

Another study using the same methods examined vaccine response strategies against group C meningitis in Dosso, a region of Niger with high group C meningitis incidence in 2015.[98] Efficiency was again highest for subdistrict-level surveillance and vaccination and effectiveness highest for subdistrict-level surveillance and district-level vaccination. Reducing delay from four weeks to one again improved efficiency and effectiveness of district-level vaccination, but not as much as switching to subdistrict-level surveillance. Weekly incidence thresholds of 9 and 10 suspected cases per 100 000 at the district level were optimal for detection of annual incidence greater than the 95th and 97th percentiles, respectively. This finding reinforced the current threshold of 10 cases per 100 000 per week.

Trotter and colleagues assessed reactive vaccination for group W epidemics across the meningitis belt using a data set of weekly suspected case counts by district linked to requests to the ICG for group W polysaccharide vaccine to identify likely group W outbreaks.[89] As with Mainassara's assessment, shortening response time is more effective than lowering the epidemic threshold.

Trotter and colleagues found much higher efficacy overall for reactive vaccination for group W (27 cases per 100 000 doses with a threshold of 10 cases per 100 000 per week and delay of four weeks) than Mainassara's findings for group C (fewer than 2 cases per 100 000 doses with equivalent assumptions) and simulating group A elimination (no cases prevented). However the group C and simulated post-group A elimination datasets were small (three epidemic signals compared to 49 for the group W dataset), encompassing only parts of Niger and only the year 2015 for group C.

Unfortunately, it is difficult to directly compare the findings of these various studies because they do not use a standardised set of values for coverage, efficacy, and delays. However, the internal comparisons drawn within a given framework are sound - for example, the findings by Mainassara regarding optimal spatial scale. Modelling consistently indicates that timeliness is crucial to maximising the impact of an outbreak response. The studies by Trotter and Kaninda reflect the largest datasets of the group and indicate that a high proportion of cases in epidemic districts are prevented by reactive vaccination.

2.4.2 Dynamic models of meningitis

A variety of model structures have been used to study the dynamics of meningococcal disease and vaccination, but most are compartmental SIR models in which the "infected" compartment tracks individuals who are carrying the bacteria.[99] To distinguish from invasive disease, these compartments are sometimes labeled "C" for carriage, and compartments for individuals with meningitis labeled "I". However, because of the very low prevalence of invasive disease relative to carriage, the role of the "I" compartment in transmission dynamics can often be ignored. The remaining underlying dynamics of carriage transmission follow the same fundamental dynamics of any disease system that can be approximated by an SIR model, allowing for parallels with other systems for which more sophisticated models have already been developed.

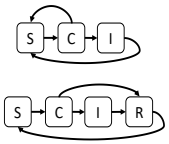
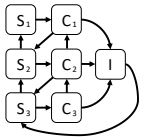
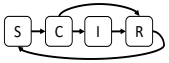
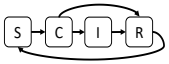
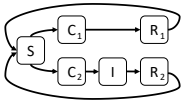
Some meningitis models include invasive disease explicitly as a state whereas others model incidence of disease solely as a function of carriage prevalence. Both systems have advantages. Including invasive disease as a state represents the infectious and the susceptible populations more accurately. However, as the duration of invasive disease is short relative to the duration of carriage (typically one week compared to one to three months) and the intensity of the illness is such that individuals are often confined to bed during this time, the contribution of diseased individuals to the force of infection may be negligible. Excluding compartments for invasive disease reduces the number of states in the model, allowing for faster and easier computation and simulation.

Natural immunity induced by carriage is another prominent source of diversity and uncertainty in modelling approaches. Some models assume no natural immunity from carriage[100] whereas others assume durations as long as 11 years.[3] Some studies have even used two tiers of immunity, each increasing in duration with age, essentially proposing that the first instance of carriage induces some modest protection against reacquisition, which can then be further boosted to a higher level if an individual is reinfected before protection wanes.[101] This structure is drawn in Table 2.3, with S_1 indicating immunologically naive persons, C_1 indicating carriage by naive persons, S_2 indicating persons with moderate immunity, C_2 indicating carriage by moderately immune persons, S_3 indicating persons with high immunity, and C_3 indicating carriage by highly immune persons. Individuals in S_3 are less likely to acquire carriage than individuals in S_2 and individuals in S_2 are less likely to acquire carriage than individuals in S_1. Carriers in C_3 are less likely to experience invasive disease (progress to I) than carriers in C_2, and likewise for C_2 compared to C_1. Another model structure assumes a shorter duration of immunity from carriage (individuals moving from C_1 to R_1) than invasive disease (individuals moving from C_2 to I to R_2) .[81]

One modelling study that attempted to infer the average duration of natural immunity by maximum likelihood using an SCIRS model and surveillance data from Burkina Faso found an inter-quartile range of 0.87 to 5 years.[102] Such a wide range does not inspire confidence, less so when considering that the plausible range explored was 0.13 to 5 years. There is no

known serological correlate of immunological protection against carriage acquisition, which makes it difficult to critically evaluate.[103] It is generally believed that some degree of natural mucosal immunity develops over the course of an individual's lifetime through exposure to *N. meningitidis* and other commensal *Neisseria* species, including *Neisseria lactamica*. There is strong evidence that *N. lactamica* may out-compete and exclude *N. meningitidis* from the nasopharynx. Considering the high prevalence of carriage of *N. lactamica* in infants, this may explain the low prevalence of meningococcal carriage in infants.[104] However, few authors have included *N. lactamica* co-infection in their modelling frameworks as it is generally more expedient to assume low transmission among infants.

Table 2.3 Dynamic models for meningococcal meningitis transmission in the African meningitis belt.

Paper	Aim	Structure	Model type	Age structure	Population	Seasonality
Irving 2011[105] Irving 2012[39]	Characteristic periodicity and magnitude with regular seasonal forcing		Deterministic, extended to stochastic	None	National, extended to gridded metapopulation	Regular sinusoidal forcing of transmission and/or invasion
Tartof 2013[101] Jackson 2018[106]	Evaluate MenAfriVac vaccination strategies		Deterministic compartmental	Demography Transmission Invasion Immunity	National	Two seasonal transmission matrices plus annual stochasticity
Karachaliou 2015[3]	Evaluate MenAfriVac vaccination strategies		Deterministic	Demography Transmission Invasion	National	Irregular sinusoidal forcing of transmission and invasion (annual stochasticity)
Koutangni 2018[102]	Compare seasonal forcing of carriage and invasive disease		Deterministic	None	District	Sinusoidal forcing of transmission and/or invasion (single year)
Yaesoubi 2018[81] Niaz Arifin 2019[82]	Evaluate strategies for polyvalent conjugate vaccine		Stochastic, extended to agent-based	Demography Transmission Invasion	National, subdivided into districts	Irregular sinusoidal forcing of transmission and invasion (annual stochasticity)

Most published models of meningococcal meningitis, including all those designed for the meningitis belt, have considered transmission of a single strain, though in reality a variety of serogroups coexist in a community. The primary target for immunity is the polysaccharide capsule which determines the serogroup classification, but some limited cross-immunity may arise from common sub-capsular antigens. Aggregation of strains in models may bias predictions about vaccine effects: a study of two stochastic models of meningococcal conjugate vaccination, one with two strains (C and other *Neisseria* species) and one with four strains (C, B, *N. lactamica* and other) found that the two-strain model tended to predict faster reductions in vaccine-type disease and little to no strain replacement compared to the four-strain model.[107] The four-strain model also displayed evidence of multiple attractors, resulting in sustained oscillations in serogroup prevalence even in the absence of vaccination pressure. The authors speculate that this is because prevalence is spread more thinly across four serogroups than two, so competitive effects are enhanced. Despite the important epidemiological consequences of antigenic diversity, the lack of strain- or serogroup-specific data has been a significant obstacle to the development of more accurate multi-strain models.

Most models of meningitis in the African meningitis belt make use of a sinusoidal function to introduce seasonality in transmission and progression to invasive disease, with a number including a further stochastic term drawn from a uniform distribution to force greater inter-annual variability in the size of epidemics.[3,101] This annual term is often likened to the impact of climactic drivers on incidence. While it is true that large-scale inter-annual variation in meningitis incidence is likely driven by climactic variation, national- and district-level variation must necessarily further depend on differences in the serogroups present and levels of immunity, neither of which are captured by single-population single-strain models.

Two models have attempted to capture spatial heterogeneity in meningitis by using a meta-population structure. Irving made use of a lattice framework approximating the population of Burkina Faso of around 3 500 homogeneously mixing patches of 5 arc-minutes square, showing that a relatively simple model with constant seasonal forcing could reproduce the complex behaviour observed in the meningitis belt - localised outbreaks occurring in different populations every year and sometimes extending to become widespread epidemic waves.[105] Yaesoubi and colleagues developed a 55-patch model in which each patch represented one homogeneously-mixing district of Burkina Faso, using a gravity model to describe the rate of contact between individuals in different districts.[81]

Although this thesis makes limited direct use of dynamic modelling, it is important to discuss the key findings and limitations of earlier studies as these guide later chapters. Dynamic models of meningitis in Africa have been limited by a lack of age- and serogroup-specific data. I attempt to address this gap with respect to disease incidence in Chapter 3 and carriage prevalence in Chapter 5. Chapters 3 and 7 capture some aspects of spatial heterogeneity in meningitis incidence. These data could be used to inform mixing assumptions in spatial dynamic models.

2.5 Pneumococcal meningitis

Since 1999, 14 studies studies have been published reporting on passive surveillance (individuals attending health facilities) of pneumococcal meningitis in countries of the African meningitis belt: two studies in Niger, one in Nigeria, one in Mali, five in Burkina Faso, two in Ghana, four in Togo, and one in Ethiopia. Study dates range from 1981 to 2016, many spanning multiple years and in populations of various sizes.[21,32,59–65,108–112] In two studies, 10- or 13-valent pneumococcal conjugate vaccine (PCV) had been recently introduced into national routine infant immunisation programs (see Table 2.4).

Eight studies reported the serotype distribution of isolates, seven in populations with no PCV use (Table B.3, Figure 2.3). PCV13 covers the majority of strains that have historically caused pneumococcal meningitis in the African meningitis belt and a high proportion of meningitis is caused by a single serotype, ST1. Seventy percent of isolates were PCV13 vaccine-types; 45% were serotype 1. Kwambana-Adams *et al.* 2016 reports a higher proportion of isolates belonging to serotype 1 (67% overall) than other studies.[21]

Unlike for meningococcal meningitis, there is no consistent definition for an outbreak or epidemic of pneumococcal meningitis. Only three studies specifically report outbreaks or non-endemic patterns of disease: Kwambana-Adams and colleagues report a single outbreak over one dry season in a single region of Ghana.[21] Data from this outbreak are used to model the impact of reactive vaccination in Chapter 4. Leimkugel *et al.* report an outbreak continuing over three years, 2000 to 2003, in a single region in Ghana.[61] The authors cite seasonality, broad host age range, and clonality of the strains isolated as evidence of a single outbreak rather than seasonal changes in endemic disease. Traore and colleagues describe an "epidemic pattern similar to that of *N. meningitidis* meningitis" in a region including three districts in Burkina Faso and three districts in Togo over a four-year period.[62]

Across all 14 studies, the confirmation rate of suspected bacterial meningitis cases ranged from 24-48%, with *S. pneumoniae* isolated from between 10 and 77% of confirmed cases. There is no consistent difference between studies characterising pneumococcal meningitis incidence as "outbreak" or "epidemic" behaviour and those reporting on endemic incidence.

All but three studies find seasonal trends in pneumococcal meningitis, most reporting that incidence peaks between February and March.[32,59–63,65,108,110–112] Leimkugel notes that the peak in pneumococcal meningitis cases appears to precede the peak in meningococcal meningitis cases each year by 1-2 months.[61] A wavelet analysis by Paireau and colleagues shows a consistent trend, with pneumococcal meningitis incidence peaking in mid-February and meningococcal meningitis incidence peaking in mid-March.[113]

Table 2.4 Studies of pneumococcal meningitis in the African meningitis belt, published 1999 to 2017. ¶ Proportion (and number) of bacterial cases confirmed *S. pneumoniae*. *Proportion of suspected cases confirmed for any bacteria. **Average cumulative annual incidence of confirmed pneumococcal meningitis per 100 000 population.

Publication	Setting	Years	Proportion *S. pneumoniae*¶	Proportion confirmed*	Annual incidence**
Campagne 1999[59]	National Hospital of Niamey, Niger (nearly all suspected meningitis cases in Niamey)	1981-1996	10% (n=613) §	42%	14
Emele 2000[112]	Usman Danfodio University Teaching Hospital in Sokoto, Nigeria	1987-1992	18% (n=53)	26%	<1
Campbell 2004[60]	Hopital Gabriel Toure, (nearly all pediatric admissions in) Bamako, Mali	2002-2003	(n=47)		7
Leimkugel 2005[61]	Kassena Nankana, Bongo, and Builsa Districts, and Bolgatanga Regional Hospital, Ghana	1998-2003	43% (n=117)		17
Traore 2009[62] †	Regional Hospital of Bobo-Dioulasso, Burkina Faso; three hospitals in Dapaong, Sokode, and Soutouboua in Togo	2002-2006	42% (n=463)	41%	14
Mueller 2012[63]	Four health districts in and around Bobo-Dioulasso, Burkina Faso	2007-2009	35% (n=159)	47%	9
Karou 2012[110]	Regional Hospital of Dapaong, Tone District, Togo	2007-2010	27% (n=68)	48%	8
Gessner 2012[111]	Regional Hospital of Bobo-Dioulasso, Burkina Faso; four referral hospitals in Dapaong, Kara, Sokode, and Soutouboua in Togo	2007-2009	(n=282)		8
Collard 2013[109]	Niger, principally Niamey, Tillabery and Dosso	2003-2011	13% (n=1010)	42%	2
Chaibou 2014[108]	Ouagadougou Yalgado Ouedragogo Teaching Hospital, Burkina Faso	2007-2011	(n=455)		<1
Mihret 2016[64] ‡	Three referral hospitals in Ethiopia	2012-2013	39% (n=18)	33%	-
Kambire 2016[32]	Burkina Faso, nationwide bacterial meningitis surveillance system	2011-2013	53% (n=1528)	24%	6
Kwambana-Adams 2016[21] #	All hospitals in Brong-Ahafo Region, Ghana	2015-2016	77% (n=104)	24%	9
Moisi 2017[65]	All six health facilities in Tone and Cinkasse Districts, Togo	2010-2013	59% (n=78)	34%	7

§Also presents data from 11 non-epidemic years, where *S. pneumoniae* responsible for 21% of confirmed cases. †Links to Yaro 2006. ‡PCV10 in routine immunisation since 2011. # PCV13 in routine immunisation since 2012.

Six studies reported age-specific annual incidence of confirmed pneumococcal meningitis, all in populations where PCV was not in use at the time (Table B.4, Figure 2.3). In all of the studies, incidence is greatest in infants. Many studies show an additional peak in older children and adults, but the precise age and magnitude of this peak is variable. Variation in incidence could come from difficulties in estimating the catchment area of the health facilities where these studies are being carried out or in differences in the frequency of taking and testing CSF samples, in addition to variability in the intensity of and age groups affected by pneumococcal meningitis.

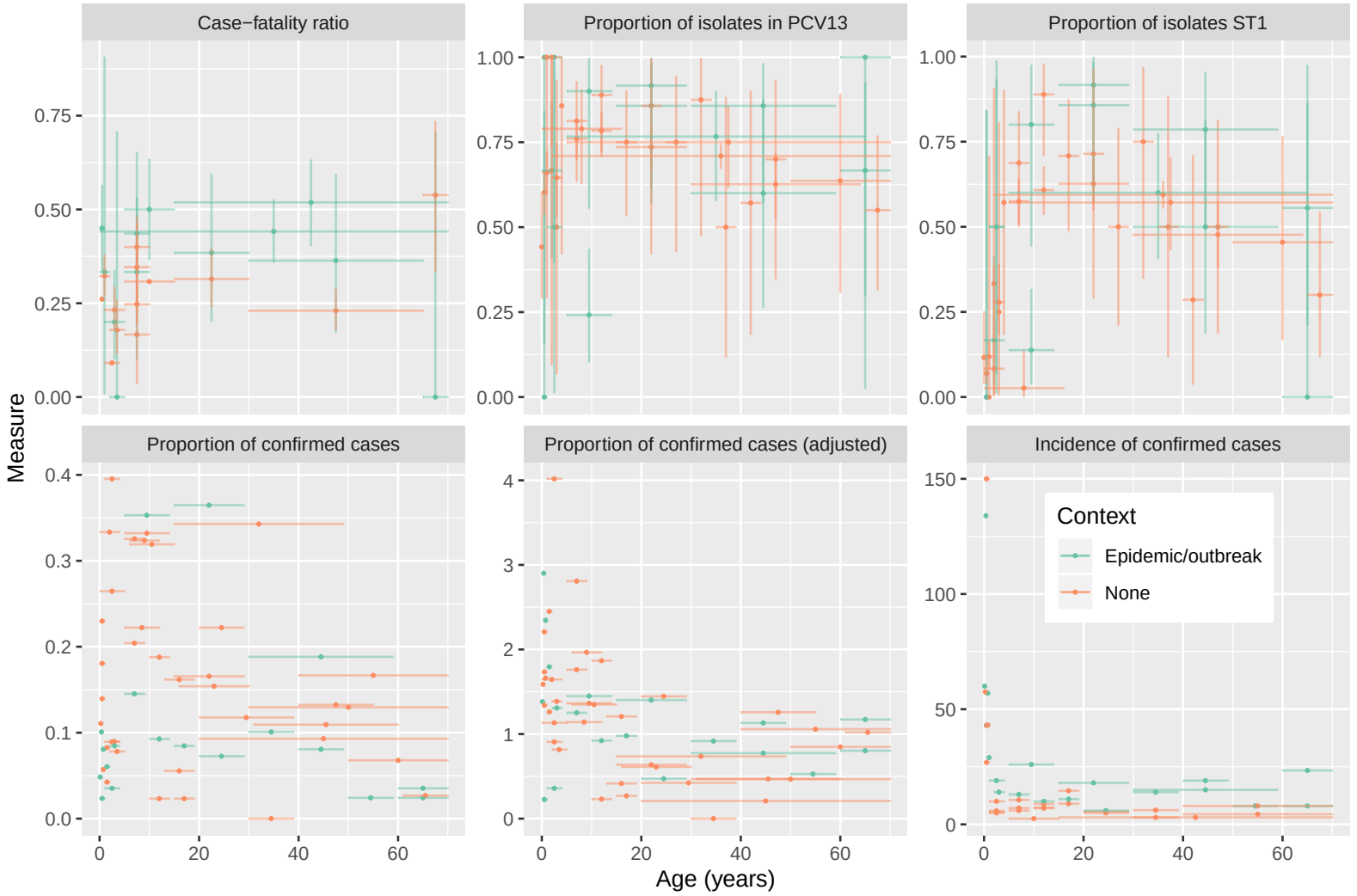


Fig. 2.3 Case-fatality ratio, proportion of pneumococcal meningitis cases caused by serotype 1 and PCV13 vaccine-type serotypes, proportion of all pneumococcal meningitis cases (adjusted by proportion of population in age group), and incidence of pneumococcal meningitis by age group and study. Vertical error bars indicate binomial 95% confidence intervals for case-fatality ratio and proportion of cases due to ST1 and PCV13 types; horizontal error bars indicate minimum and maximum age of reported age group. Studies describing outbreaks or epidemic patterns shown in blue.

Eight studies reported the age distribution of confirmed cases of pneumococcal meningitis (Table B.1, Figure 2.3). Although case distribution varies significantly from study to study, seven of eight report more than 60% of confirmed cases in individuals 5 years and older and more than 25% of confirmed cases in individuals 15 years and older. The data from the recent Brong-Ahafo outbreak shows a particularly strong peak in older age groups, however it is not markedly different from other distributions from situations not described as outbreaks. By contrast, the distribution of cases by age reported in Traore *et al.* 2009 is uniform despite a description in the discussion of "epidemic" patterns.[62]

Nine studies reported case-fatality ratios (CFR) or provided necessary data for the calculation of CFR for confirmed pneumococcal meningitis (Table B.2, Figure 2.3). Reported age-specific CFRs range from 9% to 62%, with no obvious variation by age. Overall CFRs ranged from 17% to 53%. More recent studies generally show lower overall CFR; the highest CFRs were reported in association with the data from 1981 to 1996.

Overall, there is no clear distinction between epidemic and endemic patterns of pneumococcal meningitis in the African meningitis belt. PCV13 covers the most serotypes that cause pneumococcal meningitis in the African meningitis belt, in particular ST1. A substantial burden of disease falls on older children and adults, and CFRs appear higher than those for meningococcal meningitis, with no clear variation in fatality by age.

2.6 Environmental correlates and risk factors for meningitis outbreaks

The climate in the African meningitis belt is primarily bimodal and tropical, characterised by a dry season from October to April, and a wet season from May to September. In the middle of the dry season, January to March, dry, hot winds called the Harmattan blow from the northeast to the southwest, carrying dust from the Sahara desert. In the wet season, monsoon winds bring rain (mostly between July and September) and high humidity from the Gulf of Guinea.[36] Meningitis incidence in the region is strongly seasonal, and the influence of climate on meningitis dynamics has been studied extensively. Quantitative studies generally fall into two categories: explanatory studies which use all available data and attempt to explain or describe the normal seasonal behaviour of meningitis,[114–116] and predictive studies which restrict predictor variables to those measured in the time before an outbreak and try to explain what characterises particularly high-incidence years or district-years.[117,118] Table 2.5 provides a brief summary of quantitative studies of risk factors for meningitis outbreaks and their findings. Elevated incidence of meningitis has been linked with high temperatures,[38,115,116,119] low humidity,[38,115,116,119–121] dust,[36,38,115,116,119,120,122–124] low rainfall,[37,114,116,119–122] land cover,[120] population density,[120] wind speed and direction,[116,118,123,125] and sunshine hours.[119] Many studies are set in Niger and Burkina Faso, as both have most of their territory inside the meningitis belt and experience the highest incidence of meningitis. Because climate variables describe

large-scale trends, climate-based models tend to be more successful at higher spatial aggregation and less good at explaining variation at the district and subdistrict level.[126] Only one study has examined the relationship between carriage and climate explicitly, although some other studies have examined seasonal trends in carriage.[127] Non-climactic risk factors, including outbreaks in neighbouring communities, connectivity, and population density, are less well studied, with early cases (October through December), population density, presence of primary roads, and cases in neighbouring communities sometimes being associated with increased risk.[121,123,124,128] The next chapter examines patterns of suspected cases of meningitis and tests for associations between the occurrence of early cases, cases in neighbouring communities, and district-level outbreaks in a broad range of countries across the meningitis belt.

Table 2.5 Studies of risk factors for meningitis outbreaks.

Study	Location	Years	Resolution	Outcome	Risk factors	Analysis	Key findings
Greenwood 1984[115]	Zaria, Nigeria	1977-1979	Fortnight	Suspected cases	Dust (visibility), humidity, temperature	Correlation	Positive correlation with temperature (0.63) & dust (0.48); negative correlation with humidity (-0.34)
Molesworth 2002[37]	All Africa	1980-1989	Mostly district	Outbreak in literature 1980-1999	Rainfall	Mapping	Outbreaks coincide with mean annual rainfall 300-1100 mm
Molesworth 2003[120]	All Africa	1841-1999	Mostly district	Outbreak in literature pre-2000	Dust, humidity, land cover, population density, rainfall	Logistic regression	All risk factors independently associated with outbreaks; humidity profile & land-cover type gave the best predictive model (sensitivity 83%, specificity 67%)
Jackou-Boulama 2005[114]	Niger	1996-2002	National, month	Confirmed cases	Rainfall	Correlation	Significant negative correlation between cases & rainfall ($R = -0.27$)
Sultan 2005[125]	Mali	1994-2002	National, week	Week of epidemic onset	Week of winter wind maximum	Linear regression	Harmattan winds peak at onset of meningitis season ($R^2 = 0.95$)
Thomson 2006[122]	Burkina Faso, Mali, Niger, Togo	1990-2001	District, month	Suspected cases	Cloud cover, dust, land cover, rainfall, vegetation	Log-linear regression on anomalies	Increased rainfall in January & August & dust in April linked to fewer cases, increased dust in October linked to more cases ($R^2 = 0.38$)
Mueller 2008[127]	Bobo-Dioulasso, Burkina Faso	2003	Single site	Carriage	Humidity, temperature, & wind speed	Logistic regression	Higher humidity linked to acquisition of non-groupable meningococcus (OR 2.1), no significant relationship for *Nm*A, W, Y, X
Yaka 2008[118]	Niger & Burkina Faso	1968-2005	National, month	Suspected cases	Humidity, pressure, temperature, wind speed & direction	Log-linear regression	Northerly wind in October (Burkina), November & December (Niger) correlated with incidence; predicts roughly 50 cases per 100 000 annual with 74-83% sensitivity, 50-53% specificity
Paireau 2012[128]	Niger	2002-2009	Subdistrict	Confirmed cases	Distance to primary roads, population density	Pearson correlation coefficient	No association with population density or distance to roads
Agier 2013[36]	Niger	1986-2007	District, week	Suspected cases	Dust, humidity, temperature, wind speed & direction	Fourier wavelet	Meningitis in closest phase with aerosol index (dust measure)
Abdussalam 2014[119]	Northwest Nigeria	1990-2011	Month	Suspected cases	Dust, humidity, rain, sunshine, temperature, wind speed in current month or month before only, previous month cases	Generalised additive & generalised linear models	All found to be significant, with temperature (+) & humidity (-) contributing the most; rain (-) & previous cases (+) the least (Kendall's correlation 0.64)

Continued on next page

Table 2.5 – *Continued from previous page*

Study	Location	Years	Resolution	Outcome	Risk factors	Analysis	Key findings
Garcia-Pando 2014[123]	Niger	1986-2006	District & national, month	Suspected cases	Dust, early cases, humidity, latitude , longitude, temperature, wind speed & direction, urbanicity	Negative binomial regression	Both national- & district-level incidence predicted using November-December wind speed & early cases; October-December dust also predictive at district level; predicts 100 cases per 100 000 annual with 68 % sensitivity, 72% specificity
Paireau 2014[121]	Niger	2004-2010	Subdistrict	Confirmed *Nm*A cases	Dust, early cases, humidity, neighbouring cases, primary roads, rainfall, temperature, wind speed & direction	Logistic regression	High relative humidity in November-June & early rains (March) protective; neighbour having at least one case (OR 2.4), primary road crossing the area (OR 1.7), & cases between 1 October & 31 December increased risk (OR 6.8)
Stanton 2014[117]	Niger	1986-2007	District, week	Suspected cases	Spatio-temporal autocorrelation	Dynamic linear models & three-state Markov chain model	Models can predict exceeding epidemic threshold with specificity 71-80% & sensitivity 48-66% three weeks in advance
Jusot 2017[38]	Niamey, Niger	2003-2010	Day	Confirmed cases	Dust (visibility), humidity, rainfall, temperature, wind speed	Generalised additive model	Increased risk of meningitis linked to high temperatures, decrease in cases follows increase in visibility & relative humidity
Nakazawa 2017[116]	Burkina Faso	2006-2014	National, day	Suspected cases	Dust, humidity, rainfall, temperature, wind speed & direction	Log-linear regression	Wind speed & direction is the best predictor on its own, a model with wind speed, relative humidity, & dust correlated almost as well as model using all variables ($R^2 = 0.79$)
Woringer 2018[124]	Burkina Faso	2004-2014	Subdistrict, week	Suspected cases	Dust, early cases	Logistic regression	Weak association between early cases & elevated incidence (OR 1.1); high dust associated with elevated incidence (OR 6.8) but not after controlling for calendar week

Chapter 3

Trends in bacterial meningitis in the African meningitis belt 2005-2017

3.1 Introduction

This chapter brings together three data sources – district-level administrative maps, weekly district-level syndromic surveillance, and national laboratory confirmation – to provide a broad overview of bacterial meningitis in the African meningitis over the last decade. The weekly district-level surveillance data set was made available to me through collaboration with Katya Fernandez and Olivier Ronveaux at WHO Geneva and the data set is collated and maintained by Clement Lingani at the WHO Inter-country Support Team for West Africa.

In the 2013 MenAfriVac investment case, the 26 African meningitis belt countries were classified as follows:

- Core countries (n=7): Burkina Faso, Chad, Ethiopia, Mali, Niger, Sudan, and 26 northern states of Nigeria;
- Bordering countries with hyperendemic zones (n=12): Benin, Cameroon, Central African Republic, Cote d'Ivoire, Democratic Republic of the Congo, The Gambia, Ghana, Kenya, Togo, Senegal, Uganda and the remaining states of Nigeria;
- Other at-risk countries without hyperendemic zones (n=7): Burundi, Eritrea, Guinea, Guinea-Bissau, Mauritania, Rwanda, and Tanzania.

These categories have helped national ministries of health and international organizations to prioritize the most at-risk populations to receive MenAfriVac earlier. However, they are mostly based on geography, and do not necessarily reflect the burden of disease. To allow for the development of country-specific models for *Nm*A vaccination, Karachaliou and Trotter proposed an updated classification based on historical reports reviewed by Molesworth[120] and surveillance data presented by Lingani and colleagues:[34,129]

- High incidence countries, with average annual incidence of 45-50/100,000 and outbreaks every 5-6 years (n=2): Burkina Faso and Niger;

- Medium incidence countries, with average annual incidence of 15-20/100,000 and outbreaks every 10-15 years (n=9): Mali, Nigeria, Chad, Sudan, Ethiopia, Cameroon, Gambia, Ghana, and Togo;
- Low incidence countries, with average annual incidence of less than 5/100,000 (n=15): Senegal, Mauritania, Cote d'Ivoire, Benin, CAR, Eritrea, South Sudan, Guinea, Guinea-Bissau, DRC, Burundi, Kenya, Rwanda, Uganda, and Tanzania.

These categories are primarily used to estimate the cases and deaths averted by MenAfriVac as part of the Vaccine Impact Modelling Consortium (VIMC). The investment case presented to Gavi in 2018 for the pentavalent meningococcal conjugate vaccine proposed using the multivalent vaccine in high and medium incidence countries only.[83]

The aims of this chapter are: i) to use the data described above to examine the frequency of alert and epidemic signals, the frequency and magnitude of outbreaks, and the proportion of suspected cases which are laboratory tested and confirmed; ii) to characterise how the former vary across countries, over time, and by predominant etiology; iii) to validate or propose new risk categories for non-*Nm*A meningitis.

3.2 Methods

I use surveillance data from 2004 to 2017 on suspected cases of meningitis from the enhanced district-level surveillance system.[34] A suspected case is defined as any person with sudden onset of fever (>38.5°C rectal or 38.0°C axillary) and any one of the following: neck stiffness, flaccid neck (infants), bulging fontanelle (infants), convulsion, or other meningeal signs. Weekly district-level counts of suspected cases are collated nationally and then reported to the WHO Inter-country Support Team (WHO-IST) for West Africa. I use the district-level population sizes reported by each country to WHO-IST, which are updated annually. I compare the country-wide sum of these population sizes to the total population estimated in the United Nations (UN) 2017 Revision of World Population Prospects, available online at https://population.un.org/wpp/, to give an estimate of national surveillance coverage, a measure of the proportion of the population under surveillance for suspected bacterial meningitis.

Epidemic and alert incidence thresholds are consistent with current WHO guidelines, with alert defined as more than 3 suspected cases per 100,000 population per week or more than 2 cases total per week for districts with less than 30,000 population, and epidemic defined as more than 10 suspected cases per 100,000 population per week or more than 5 cases total per week or a doubling of cases in a two-week period for districts with less than 30,000 population.[90] Cumulative district incidence of 100 cases per 100,000 population annually (roughly the 97.5th percentile of cumulative annual incidence in the data set) is defined as a local outbreak (Table 3.1). Early cases are defined as any suspected case reported in the final 12 weeks of the preceding year, roughly October to December, as consistent with previous studies.[124]

Table 3.1 Incidence thresholds used to define alert and epidemic signals and localised outbreaks. *For districts with population less than 30,000.

Event	Definition
Alert signal	More than 3 suspected cases per 100,000 population per week
	*More than 3 suspected cases per week
Epidemic signal	More than 10 suspected cases per 100,000 population per week
	*More than 5 suspected cases per week or a doubling of cases in a two-week period
Local outbreak	More than 100 suspected cases per 100,000 population annually

I use national-level annual data on confirmed cases of bacterial meningitis. Cerebrospinal fluid (CSF) samples are tested by national reference laboratories using PCR, culture, or latex agglutination and these results are collated by WHO-IST.[130] From 2005 to 2009, the meningitis bulletin reported the overall number of CSF samples taken, the number of samples contaminated and negative (no bacteria), and the number of isolates of *Nm*A, *Nm*W, other *Nm*, *S. pneumoniae*, *H. influenzae* b, and "other pathogens". In 2010, the bulletin began reporting isolates of *Nm*B, *Nm*C, *Nm*X, and *Nm*Y separately.

Because fine-grained data on etiology is lacking, to identify characteristic outbreaks of particular etiology I use incidence data from only those country-years in which I can be reasonably confident that all outbreaks are caused by a single agent. I select country-years where a particular agent represents significantly more than 50% of bacterial cases (as determined by binomial test). I also show the country-years where a particular agent represents significantly more than 75% of bacterial cases. I make an exception for the years 2013, 2016, and 2017 in Nigeria, where little data is reported to WHO but evidence from the literature suggests that *Nm*C is predominant.[47,54,131]

As meningococcal immunity is thought to be largely serogroup-specific, I then also use these classifications to characterise pairs of country-years as "concordant" or "non-condordant" to identify years where the predominant cause of meningitis is the same or different from that in the previous year.

The data are generally described, noting differences by predominant etiology, year, and country. Trends by country are compared to data from Molesworth and colleagues' review and to the classifications proposed by Karachaliou and colleagues and used in the Gavi 2018 investment strategy.[129]

I then perform a series of mixed-effects logistic regressions, modelling the probability of crossing the epidemic threshold and the probability of a local outbreak (as defined by cumulative annual incidence threshold given in Table 3.1) as a function of the following risk factors: occurrence of cases early in the hyperendemic season, incidence exceeding the alert or epidemic threshold in the district in the previous year (focal status), and incidence exceeding alert or epidemic threshold in neighbouring districts in the previous year (neighbour status), adjusting for country as a fixed effect and district as a random effect. These analyses are performed on the full data set, in effect treating all suspected cases as equivalent, and then repeated for *Nm*A-

and *Nm*C-predominant and concordant district-years. There were insufficient data to consider *Nm*W circulation.

Linking the surveillance data and the map data presented two challenges: first, district names change in spelling from year to year and between data sources, and second, new administrative divisions are sometimes established. This causes difficulties in tracking individual districts' epidemiological history and in situating districts in space. I deal with these challenges first by correcting errors related to Unicode parsing, common abbreviations, and differences in punctuation, spacing, and capitalisation. Then, in order to capture as many variations in location name as possible, I use maps from five different data sources for primary (i.e. province), secondary (i.e. district), and tertiary (i.e. subdistrict) administrative boundaries: the Database of Global Administrative Areas, the United Nations Office for the Coordination of Humanitarian Affairs (accessed via the Humanitarian Data Exchange at https://data.humdata.org/), MenAfriNet, and two WHO maps, one of the full meningitis belt and an alternative version of the Nigerian administrative boundaries. I match districts by name between the surveillance data set and the maps, first by exact matching, and then by hand to identify districts with alternative spellings or names.

Finally, I preserve original geographies where they can be identified. For example, Niger's capital Niamey was originally divided into three districts, Niamey I, II, and III. As the population grew, it became necessary to further divide Niamey I and II in half, resulting in five districts, Niamey I through V. I maintain the original divisions in order to track the epidemiological history of these populations accurately.

3.3 Results

3.3.1 Coverage and linkage

Most country-years had surveillance coverage above 90% (see Figure 3.1). A few notable exceptions included Uganda in 2016, and Ethiopia in 2012, 2013, and 2015, where only one or two districts reported suspected cases. Surveillance coverage in the Democratic Republic of the Congo (DRC) declined sharply from 2015. Guinea in 2015, 2016, and 2017, and Ghana in 2006 reported much larger populations surveilled than the UN-estimated national population counts. As of 2017, surveillance coverage was above 90% in all countries but Mauritania, Uganda, and DRC.

There were 26,764 unique district-years of suspected case data representing meningitis incidence in 23 countries of the African meningitis belt from 2004 to 2017 to be geolocated. Before cleaning, 10,080 of these (38%) could be matched by name to the shapefile (see Figure 3.2). After cleaning and hand-matching, 25,477 (95%) could be matched by name to the shapefile. The majority of district-years which could not be located were in the DRC (502) and Sudan (328).

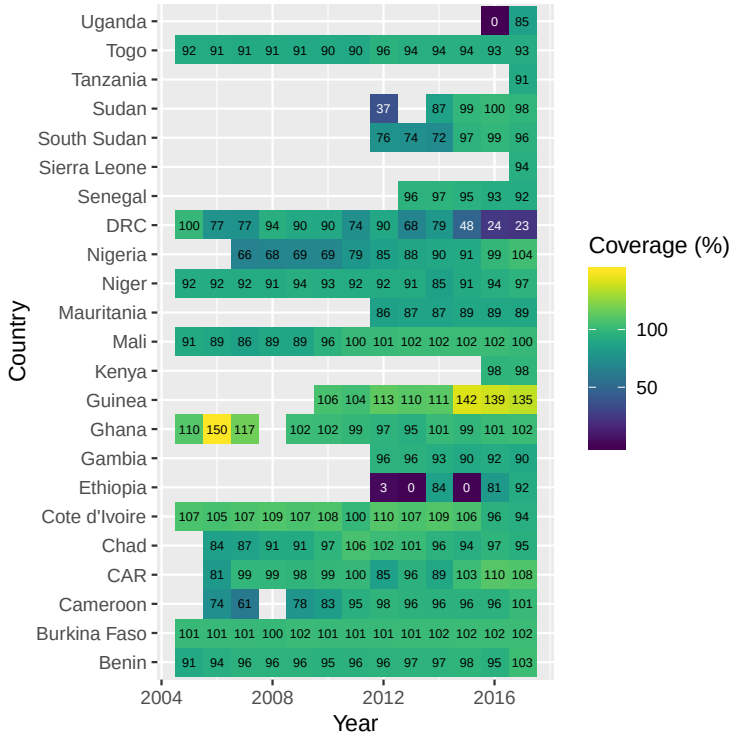


Fig. 3.1 Population reported in surveillance data set compared to UN national population estimates by year. Coverage higher than 100% is possible because the numerator comes from country estimates and the denominator from UN estimates.

The merged shapefile initially contained district data from five different map sources, giving 13,284 geographic shapes with unique names from 23 countries to which to link the surveillance data. 3,672 of these were linked to an entry in the surveillance data set.

3.3.2 Trends by predominant etiology

There was no clear majority etiology for meningitis in most country-years (see Table 3.2). I identified 16 country-years where *Nm*A was predominant, 8 where *Nm*C was predominant, 7 where *Nm*W was predominant, and 22 where *S. pneumoniae* was predominant (see Figure 3.3). In 2009 in DRC, other *Nm* was the predominant category of isolates, but because of reporting practices described above, these isolates could have been *Nm*B, *Nm*C, *Nm*X, or *Nm*Y. Bacteria other than *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* b were predominant in four district-years. There is, on average, a lower proportion of cases lab tested in country-years where *Nm*A is predominant, most likely because the quality of laboratory surveillance has improved over time. For country-years where *Nm*C, *Nm*W, and Spn are predominant, more than 50% of cases were lab tested. Bacteria were isolated from between 26% and 41% of tested cases, and more than 67% of positive isolates belonged to the majority group for each etiology.

Fig. 3.2 Proportion of geolocated district-years before and after data cleaning and hand-matching.

Table 3.2 Summary of surveillance data by predominant etiology (95% CI $\geq$ 50% of all bacterial isolates). Tested refers to the proportion of suspected cases that were tested; confirmed refers to the proportion of tested cases that were confirmed bacterial meningitis, and majority etiology group refers to the proportion of confirmed cases that were from the predominant group (i.e. *Nm*A, *Nm*C).

Etiology	Country-years	District-years	Proportion of cases		
			Tested	Confirmed	In majority etiology group
*Nm*A	16	1 282	8%	41%	87%
*Nm*C	8	3 654	58%	34%	71%
*Nm*W	7	359	72%	33%	67%
Other *Nm*	1	382	1%	33%	100%
Spn	22	1 253	55%	33%	68%
Other bacteria	4	471	44%	26%	85%
No majority	103	13 838	18%	26%	...
No lab data	38	5 136	...	...	...

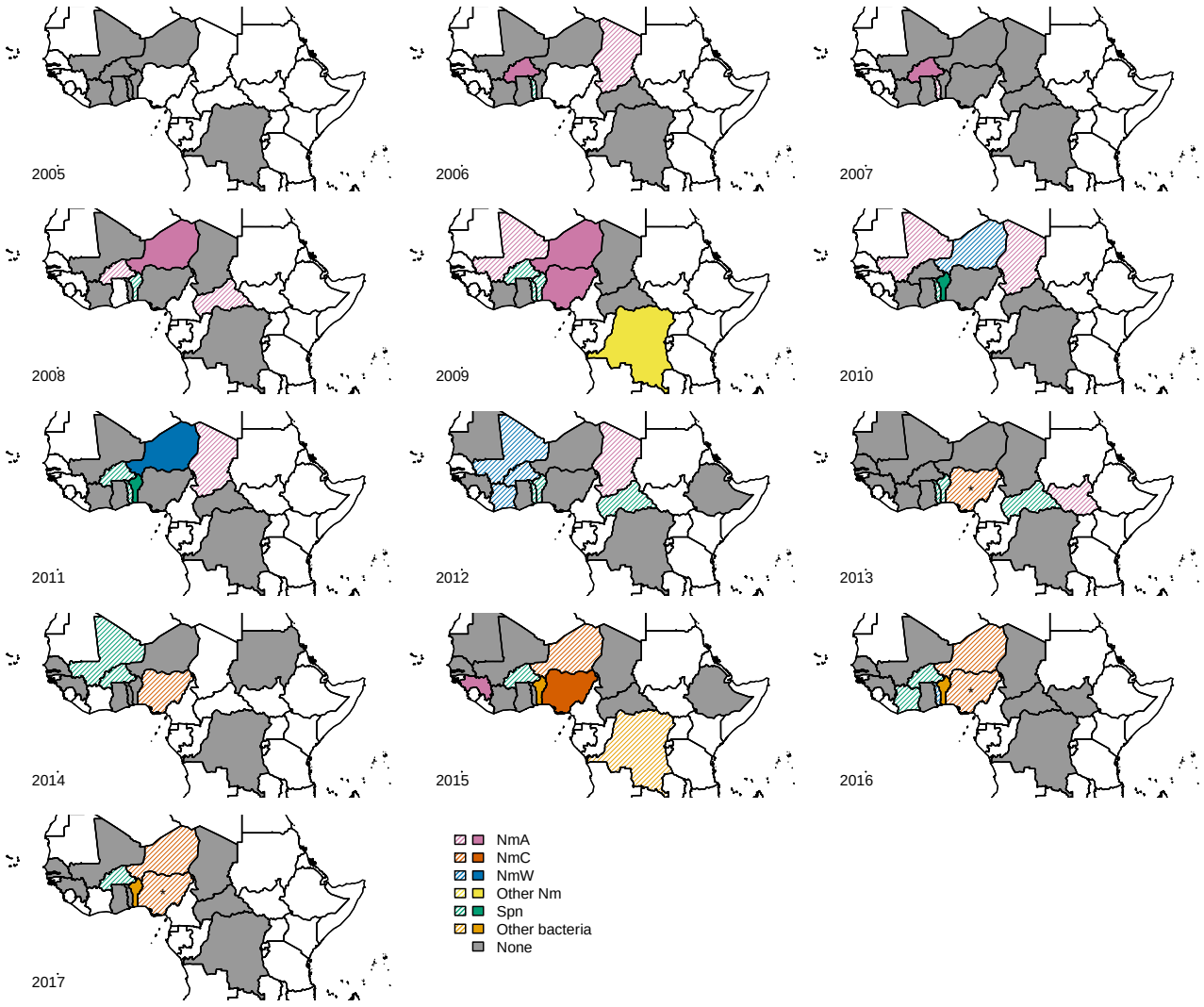


Fig. 3.3 Predominant cause of bacterial meningitis by country and year. Deeper tones indicate 95% CI $\geq$ 75% of all bacterial isolates; lighter tones indicate 95% CI $\geq$ 50% of all bacterial isolates. Asterisk shows exception for Nigeria 2013, 2016, 2017, see section 3.2.

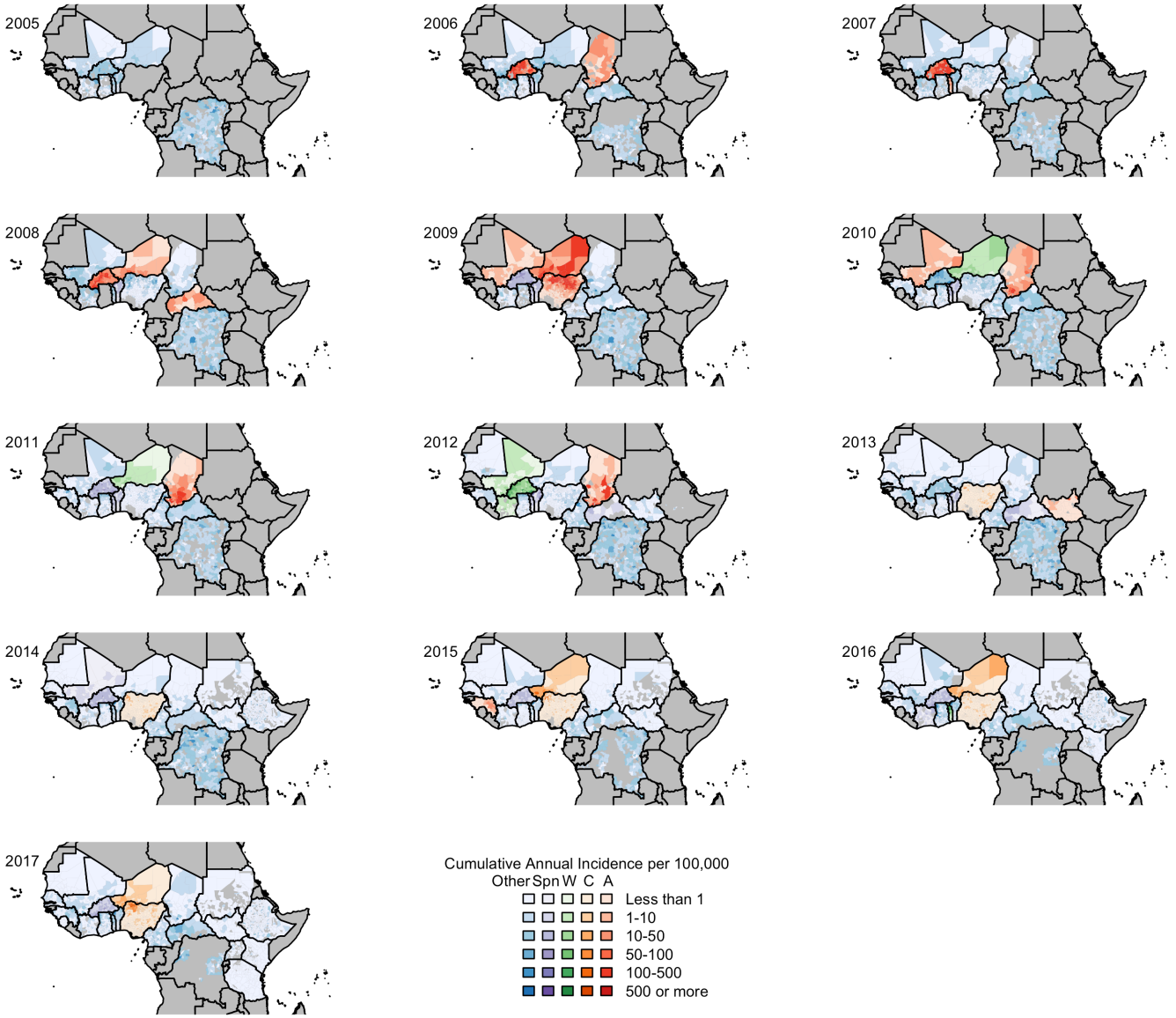


Fig. 3.4 Cumulative annual district-level incidence of suspected meningitis cases by dominant etiology.

There was a high rate of localised outbreaks during the periods identified where *Nm*A was predominant. Incidence exceeded the alert threshold in nearly half of all district-years where *Nm*A was predominant, and exceeded the epidemic threshold in more than one quarter (see Figure 3.5). By contrast, incidence exceeded the epidemic threshold in less than 10% of district-years for any other etiology. However, when comparing district-years in which incidence exceeded the epidemic threshold, the distributions of cumulative annual incidence are similar, with medians ranging from 74 to 127 cases per 100,000 for *Nm*A, *Nm*C, *Nm*W, and Spn. All distributions are left skewed, and there are more data for *Nm*A than for other groups, as shown in Figure 3.6.

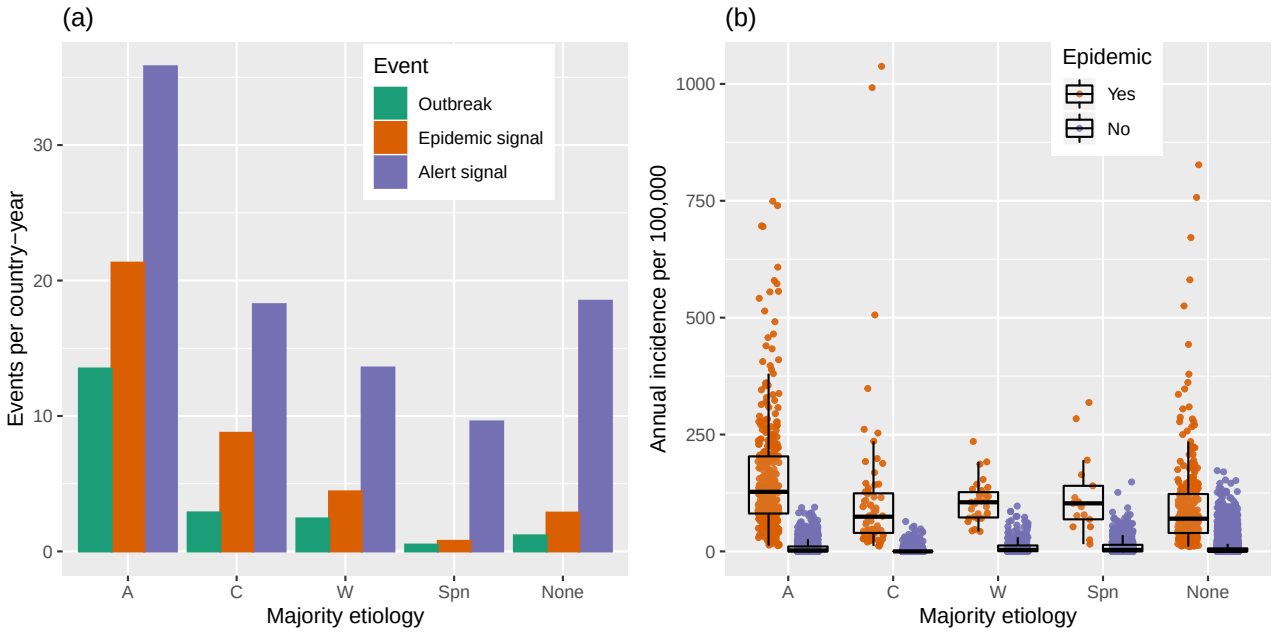


Fig. 3.5 (a) Number of districts per country-year triggering alert signal, epidemic signal, and outbreak thresholds, stratified by predominant etiology. (b) Cumulative annual incidence of suspected meningitis per 100,000 population in districts exceeding (blue) and not exceeding (orange) epidemic threshold. Box plot shows median and inter-quartile range.

3.3.3 Trends by country

District-level annual incidence of suspected cases of meningitis varied widely between countries, with the highest median annual incidence in Burkina Faso, CAR, DRC, Niger, and Togo, and median of less than one suspected case reported per 100,000 population per year in Benin, Cote d'Ivoire, Ethiopia, the Gambia, Ghana, Guinea, Kenya, Mauritania, Nigeria, South Sudan, Sudan, Tanzania, and Uganda (see Table 3.3). Incidence in districts triggering the epidemic threshold is less skewed but still variable, ranging from median 43 to 171 cases per 100,000. Burkina Faso, Niger, and Chad have the greatest proportion of district-years exceeding the epidemic and outbreak thresholds.

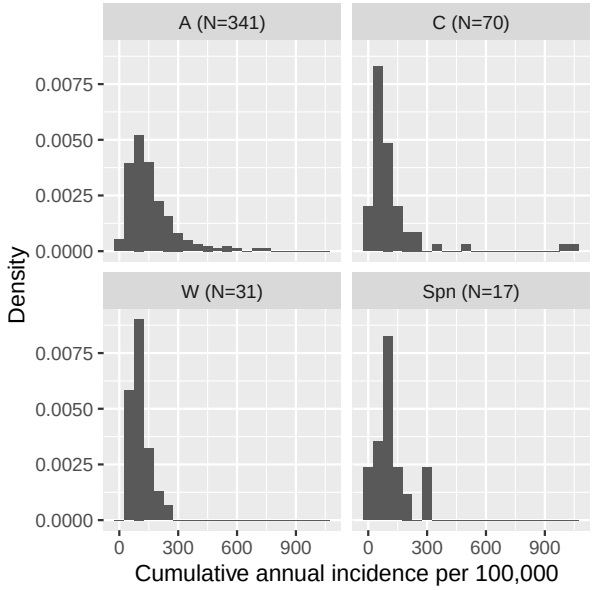


Fig. 3.6 Cumulative annual incidence in districts triggering epidemic signal by etiology.

Nigeria and Ethiopia report the highest rate of confirmation among cases that were tested, but also the lowest rate of lab testing, with just 1% of cases being tested between 2005 and 2017. Senegal and Sudan report testing more CSF than suspected cases overall. After these two countries, the highest rate of lab testing is in Togo, the Gambia, and Mali, with 89%, 76%, and 61%, respectively. Although DRC reports relatively high incidence of suspected cases, rates of testing and confirmation are low, with 2% of cases tested and 11% of tested cases confirmed. No lab confirmation data are shared for Kenya, Tanzania, and Uganda.

In recent years (2015-2017), all reporting countries tested more than 50% of suspected cases except for DRC, Ethiopia, Nigeria, Cameroon, South Sudan, and the Gambia. Benin, CAR, Senegal, and Togo reported more CSF samples tested at a national level than suspected cases occurring at district level. The reason for this is unclear. More than half of all countries confirmed 11 to 35% of cases, with the highest confirmation rates in Niger and Burkina Faso (38 and 36% respectively). Fewer than 10% of tested cases were confirmed in South Sudan, Senegal, DRC, the Gambia, and Cameroon.

Table 3.3 Summary of surveillance data by country. Outbreak defined as exceeding annual epidemic cumulative incidence threshold (100 cases per 100,000). Confirmed cases include all samples where bacterial pathogens are isolated. Annual incidence given in suspected cases per 100,000 population.

Country	Years	Cases	Proportion of district-years			Median annual incidence		Proportion of cases	
			Outbreak	Epidemic signal	Alert signal	Overall	Epidemic signal	Confirmed	Tested
Benin	13	7 710	2%	2%	11%	0	171	36%	56%
Burkina Faso	13	85 600	11%	16%	49%	25	120	35%	22%
Cameroon	11	11 300	1%	2%	14%	1	62	21%	14%
CAR	12	4 070	0%	2%	18%	5	45	23%	47%
Chad	12	19 400	4%	6%	20%	1	122	39%	9%
Cote d'Ivoire	13	4 590	<0.5%	1%	5%	0	74	12%	58%
DRC	13	82 500	2%	4%	32%	7	89	11%	2%
Ethiopia	6	4 120	0%	<0.5%	3%	0	43	81%	1%
Gambia	6	840	0%	2%	12%	0	54	10%	76%
Ghana	12	8 980	1%	2%	10%	0	75	29%	54%
Guinea	8	2 630	0%	0%	4%	0	...	19%	40%
Kenya	2	318	0%	0%	2%	0	...	...	...
Mali	13	8 160	0%	1%	6%	1	57	19%	61%
Mauritania	6	58	0%	0%	2%	0	...	31%	45%
Niger	13	42 500	6%	10%	27%	5	109	39%	57%
Nigeria	11	88 300	2%	4%	9%	0	81	58%	1%
Senegal	5	1 220	0%	<0.5%	1%	1	13	6%	115%
South Sudan	6	590	0%	<0.5%	2%	0	77	39%	5%
Sudan	4	324	0%	0%	<0.5%	0	...	10%	112%
Tanzania	1	3	0%	0%	0%	0	...	...	...
Togo	13	6 950	2%	3%	18%	3	120	21%	89%
Uganda	2	129	0%	0%	0%	0	...	...	...

3.3.4 Comparison to other data sources

The data from the Molesworth review are given in the form of median, minimum, and maximum cumulative annual incidence per 100,000 population. In Figure 3.7, these data are compared to those from the data analysed here. It is important to note that these sources represent different time periods (2005-2017 versus 1980-1999). The range between minimum and maximum incidence is generally very wide. These overlap in almost every case except for DRC (median 16, range 11-18 versus median 2, range 0-6 cases per 100,000), where the WHO-AFRO database reports consistently higher incidence than Molesworth. The ranges are also non-overlapping for Sudan (median 0.3, range 0.1-0.5 versus median 3, range 1-140 cases per 100,000) but this can be explained by the separate reporting of South Sudan in the more recent WHO-AFRO database (median 0.8, range 0.3-3). Median national-level incidence estimates are correlated (Pearson's correlation 0.71, p-value < 0.001). The median incidence values tend to be higher in Molesworth than in this analysis, with a linear relationship between the WHO-AFRO measures and the Molesworth measures of 1.7 ($R^2 = 0.67$).

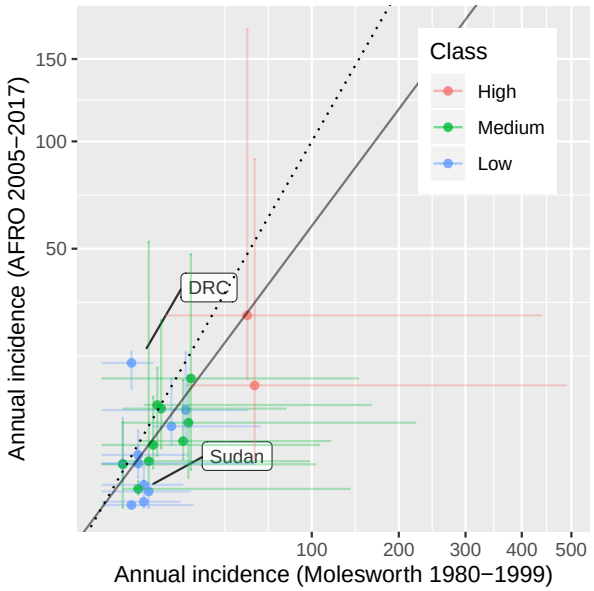


Fig. 3.7 Median (points) and range (error bar) of annual incidence by country from Molesworth 2003 and the database analysed here. Note the scales of the x- and y-axis, which are scaled by the square root.

3.3.5 Incidence before and after MenAfriVac introduction

The impact of MenAfriVac on meningitis incidence is apparent. The classifications proposed by Karachaliou and Trotter are mostly consistent with the ranking of countries by median annual incidence pre-MenAfriVac introduction (introduced in Section 3.1). DRC and CAR rank higher despite being classed as low-incidence; Ghana and Sudan rank low but are classed as medium-incidence countries (Figure 3.8a). The rank by median incidence post-MenAfriVac is markedly different: Benin, DRC, and CAR all rank high although they are classed as low

incidence countries for *Nm*A (Figure 3.8b). Importantly, meningitis incidence does not appear to have increased in these countries, rather, incidence has decreased in other countries.

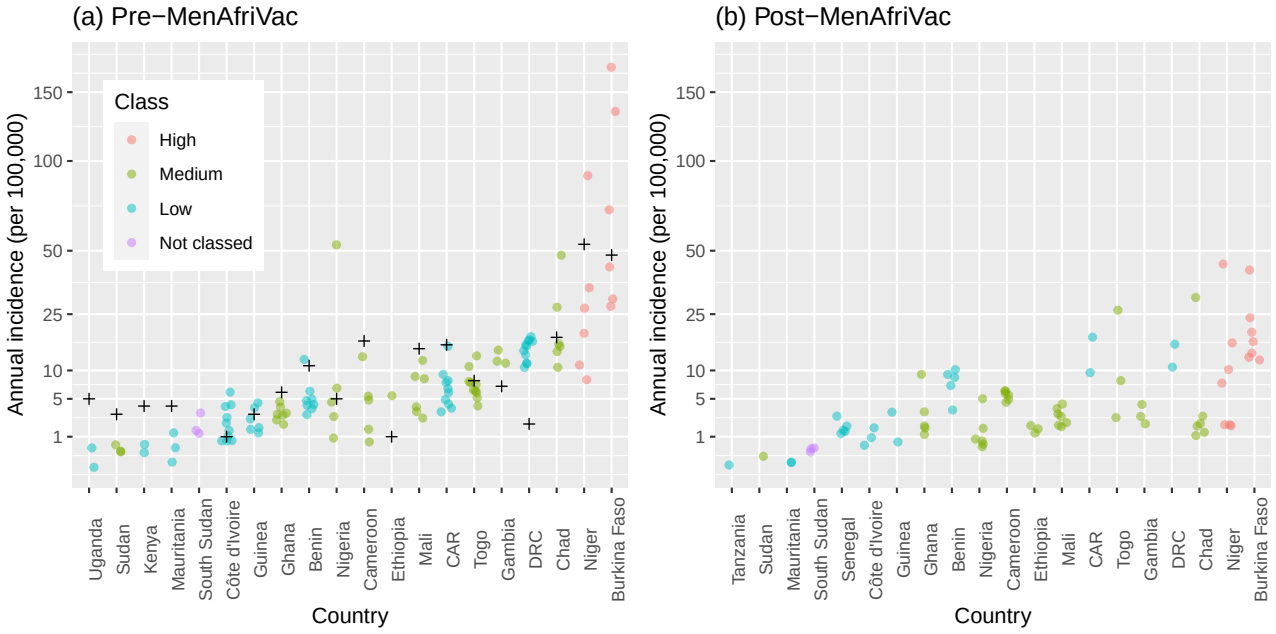


Fig. 3.8 (a) Annual incidence before MenAfriVac introduction, ranked by median value. Median incidence from Molesworth 2003 shown for reference as black crosses. Colours indicate classification by Karachaliou and Trotter. (b) Annual incidence after MenAfriVac introduction, ranked by median value before introduction.

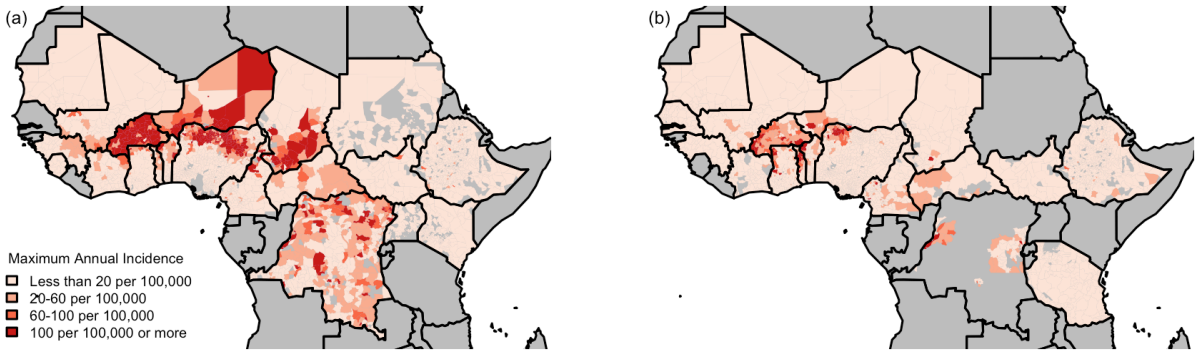


Fig. 3.9 Map showing maximum cumulative annual incidence of suspected cases by district for (a) the period before completion of MenAfriVac mass campaigns and (b) the period after completion of MenAfriVac mass campaigns.

3.3.6 Trends over time

The population under surveillance has increased more than five-fold from 2005 to 2017. The number of districts exceeding outbreak and epidemic thresholds peaked sharply in 2009 and has otherwise remained fairly steady (14-38 outbreaks per year)(Figure 3.10). Similarly, cumulative incidence peaked in 2009 and has remained less than 10 cases per 100,000 since

2010 (Table 3.4). The intensity of incidence in districts triggering the epidemic threshold has not decreased substantially, ranging from 85 to 171 cases per 100,000. A high proportion of the total suspected cases occurs in districts triggering the epidemic threshold, although this varies from year to year, ranging from 15% in 2014 to 76% in 2009. The proportion of cases being confirmed by laboratory tests has increased, particularly in recent years, whereas the proportion of CSF yielding bacterial isolates has declined slightly from more than one-third to approximately one-quarter.

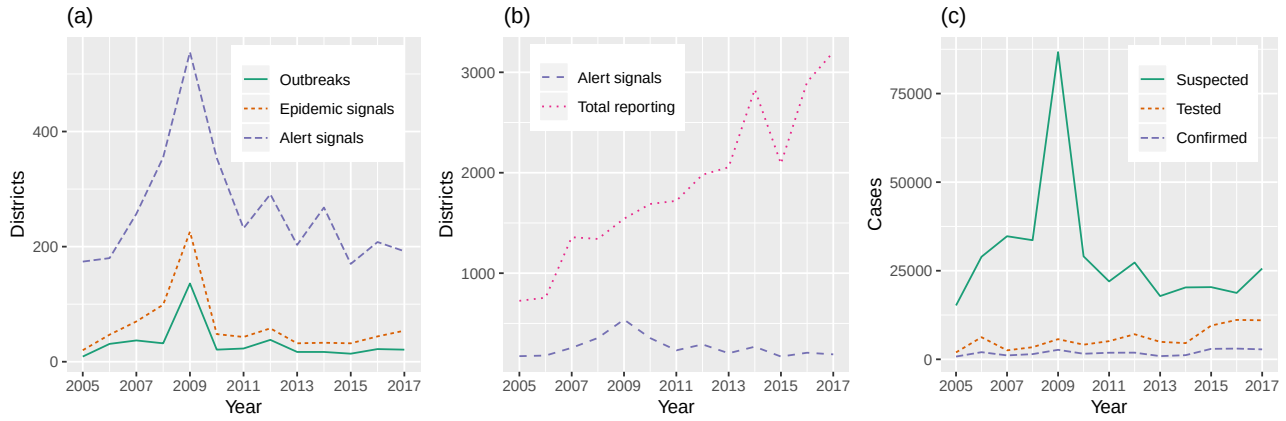


Fig. 3.10 a) District-level epidemic signals, alert signals, and outbreaks by year. b) District-level alert signals and total districts reporting by year. c) Suspected, tested, and confirmed cases of bacterial meningitis by year.

Table 3.4 Summary of surveillance data by year. CSF=cerebrospinal fluid samples. Outbreak defined as exceeding annual epidemic cumulative incidence threshold (100 cases per 100,000). Positive CSF include all samples where bacterial pathogens are isolated. Population given in millions. Cumulative incidence given in suspected cases per 100,000 population.

Year	Population	Proportion of district-years		Annual incidence		Proportion of cases		
		Epidemic signal	Alert signal	Overall	Epidemic signal	In epidemic districts	Confirmed	Tested
2005	125	3%	24%	12	164	23%	40%	13%
2006	134	6%	24%	22	171	63%	32%	22%
2007	237	5%	19%	15	159	63%	43%	7%
2008	238	7%	26%	14	85	44%	43%	10%
2009	270	15%	35%	32	143	76%	47%	7%
2010	307	3%	21%	9	94	23%	38%	14%
2011	324	2%	13%	7	140	37%	36%	23%
2012	370	3%	15%	7	124	34%	27%	26%
2013	390	2%	10%	5	104	19%	18%	28%
2014	513	1%	9%	4	85	15%	26%	23%
2015	433	2%	8%	5	146	48%	31%	47%
2016	562	2%	7%	3	112	27%	27%	59%
2017	685	2%	6%	4	89	41%	25%	43%

3.3.7 Risk factors for outbreaks

Table 3.5 shows the full risk factor analysis for exceeding the epidemic incidence threshold. The occurrence of early cases is not a significant risk factor for exceeding the epidemic incidence threshold for *Nm*A, *Nm*C, or all suspected cases. Considering all suspected cases, both previous year focal status and previous year neighbour status are predictors of exceeding the epidemic incidence threshold in the current year, with no significant difference between exceeding the alert threshold and exceeding the epidemic threshold, and no significant difference between neighbour status and focal status.

There is substantially less data available for *Nm*A- and *Nm*C-specifc analyses, with only district-years from Niger (2008-2009), Burkina Faso (2006-2007, 2007-2008), and Chad (2011-2012) making up the *Nm*A-specific data set and only district-years from Nigeria (2013-2014, 2014-2015, 2015-2016, 2016-2017) and Niger (2015-2016, 2016-2017) making up the *Nm*C-specific data set. For *Nm*A, no significant incidence-based risk factors could be identified. For *Nm*C, both focal epidemic status and neighbour alert or epidemic status in previous year are significant predictors of epidemic risk (OR 3.2 for focal, 8.0 and 12 for neighbour).

Similar risk factors are found for exceeding the cumulative annual incidence threshold of 100 cases per 100,000 population, although substantially fewer districts exceeded the cumulative annual incidence threshold than exceeded the weekly epidemic incidence threshold (Table 3.6). The presence of early cases are not a significant risk factor for exceeding the annual cumulative incidence threshold for *Nm*A, *Nm*C, or all suspected cases. For *Nm*A, only exceeding the alert threshold in the previous year is a significant risk factor for outbreak, and its effect is weak (OR 2.6 95% CI 1.1-6.0). For *Nm*C and all suspected cases, both focal alert or epidemic status and neighbour alert or epidemic status in previous year are significant predictors of epidemic risk.

Table 3.5 Risk factors for exceeding weekly epidemic threshold by predominant serogroup. OR = odds ratio. 95% CI = 95% confidence interval.

Factor	Group A Number of districts	OR (95% CI)		Group C Number of districts	OR (95% CI)		All suspected cases Number of districts	OR (95% CI)	
Status in previous year									
No alert	25/145	1.0		44/2702	1.0		352/15984	1.0	
Alert	34/66	1.9	(0.9-4.2)	4/44	1.9	(0.49-5.7)	211/2187	2.6	(2.1-3.2)
Epidemic	45/97	1.1	(0.48-2.5)	8/31	3.2	(1.1-9.2)	135/686	3.5	(2.7-4.6)
Neighbour status in previous year									
No alert	8/72	1.0		28/2540	1.0		199/12349	1.0	
Alert	16/67	0.82	(0.28-2.5)	12/139	8.0	(3.8-16)	270/4707	2.9	(2.4-3.6)
Epidemic	80/169	1.5	(0.5-4.5)	16/98	12	(4.9-26)	229/1801	3.3	(2.6-4.3)
Early cases (Oct-Dec of previous year)									
No	78/234	1.0		46/2617	1.0		556/16386	1.0	
Yes	26/74	1.1	(0.56-2.0)	10/160	2.2	(0.96-4.7)	142/2471	1.2	(0.97-1.4)
Country									
Niger	23/40	1.00		6/85	1.0				
Burkina Faso	54/94	0.78	(0.30-2.0)						
Chad	26/116	0.22	(0.096-0.47)						
Mali	0/58								
Nigeria				50/2692	1.7	(0.63-5.1)			

Table 3.6 Risk factors for exceeding annual epidemic cumulative incidence threshold (100 cases per 100,000) by predominant serogroup. OR = odds ratio. 95% CI = 95% confidence interval.

Factor	Group A			Group C			All suspected cases		
	Number of districts	OR (95% CI)		Number of districts	OR (95% CI)		Number of districts	OR (95% CI)	
Status in previous year									
No alert	14/145	1.0		10/2702	1.0		150/15984	1.0	
Alert	27/66	2.6	(1.1-6.0)	3/44	6.0	(1.1-26)	133/2187	3.3	(2.5-4.3)
Epidemic	34/97	1.4	(0.59-3.6)	4/31	6.7	(1.3-32)	94/686	5.2	(3.7-7.3)
Neighbour status in previous year									
No alert	4/72	1.0		5/2540	1.0		81/12349	1.0	
Alert	10/67	1.0	(0.29-4.4)	6/139	18	(4.9-65)	152/4707	3.1	(2.3-4.2)
Epidemic	61/169	2.0	(0.59-3.6)	6/98	12	(2.5-57)	144/1801	3.5	(2.5-5.0)
Early cases (Oct-Dec of previous year)									
No	56/234	1.0		14/2617	1.0		300/16386	1.0	
Yes	19/74	1.1	(0.55-2.1)	3/160	1.5	(0.31-5.5)	77/2471	1.1	(0.81-1.4)
Country									
Niger	15/40	1.00		3/85	1.0				
Burkina Faso	41/94	0.85	(0.32-2.2)						
Chad	19/116	0.31	(0.13-0.72)						
Mali	0/58								
Nigeria				14/2692	1.4	(0.37-7.2)			

3.4 Discussion

District-level syndromic surveillance has expanded over the past two decades to cover nearly the entire population of the meningitis belt. This study was able to link the majority of district-years in the surveillance data set to physical locations. This geolocated data set could be used in further studies. The total population under surveillance has increased over time as more countries have joined the surveillance network, and the rate of laboratory testing of cases has also increased, whereas the rate of confirmation has decreased.

The highest rate of district-level outbreaks was seen in country-years where *Nm*A was the dominant cause of meningitis, followed by *Nm*W, then *Nm*C, and finally Spn. However, when outbreaks did occur, they were of comparable size regardless of etiology. Though *N. meningitidis* has historically been recognised as the sole cause of seasonal meningitis outbreaks in the African meningitis belt, numerous studies have identified outbreaks of meningitis with similar high incidence, seasonality, and age distribution where *S. pneumoniae* is the causative agent.[21,61,132,133] The following chapter assesses the potential efficiency and impact of responding to localised outbreaks of pneumococcal meningitis with reactive vaccination.

Average annual incidence was highly variable between countries, and less variable considering only district-years that trigger the epidemic threshold. The highest overall incidence of meningitis is found in Niger, Burkina Faso, and Chad, countries which lie entirely or almost entirely within the meningitis belt.

Considering the full data set of suspected cases, elevated incidence in previous years is a significant risk factor for epidemic signals and outbreaks, both within a given district and between neighbouring districts. This trend was also true where *Nm*C was predominant, but could not be shown for *Nm*A. It is possible that elevated risk in neighbouring districts was demonstrated for *Nm*C outbreaks because it is a novel strain that has only recently emerged and is spreading geographically, whereas *Nm*A was established and widespread. However, given that the same trends were shown in the full data set considering all suspected cases, it seems more likely that there were too few district-years in *Nm*A-predominant settings to draw any significant conclusions. Early cases occurring between October and December of the previous year were not a significant risk factor for epidemic signals or outbreaks.

These findings contrast with previous findings linking early cases with higher risk of outbreaks: one study of confirmed group A meningitis in Niger between 2004 and 2010 and one of suspected cases in Niger between 1986 and 2006.[121,123] One additional study found significantly elevated odds with low magnitude (OR 1.14 95% CI 1.06-1.21).[124]

While many studies have examined climactic risk factors for meningitis outbreaks, few studies have addressed incidence-based factors. A study in Niger found that subdistricts with a higher percentage of neighbours with confirmed *Nm*A cases had a higher risk of cases that same year (incidence rate ratio 2.37, 95% CI 2.08-2.70).[121] One analysis of reactive vaccination campaigns in Ethiopia speculated that, due to the wave-like spread of outbreaks and the delays involved in

organising a reactive response, it may be advantageous to target neighbouring communities.[134] The potential of targeting neighbouring districts in reactive vaccination responses is examined further in Chapter 7.

The question of which countries should prioritise introduction of the pentavalent vaccine is a difficult but very important one. On the basis of median national incidence in the post-MenAfriVac era, the classification of Benin, CAR, and DRC as low risk might need to be reconsidered. There are data quality concerns about DRC that would merit further research, including high but unusually low-variance incidence, low laboratory testing and confirmation rates, and unusually variable reported population sizes. One possible criterion for risk could be having any district-year with cumulative annual incidence greater than 100 suspected cases per 100,000 post-MenAfriVac mass campaign completion. This would include Benin, Burkina Faso, Cameroon, Chad, the DRC, Ghana, Niger, Nigeria, and Togo. As is made clear by this chapter, risk for outbreaks is highly heterogeneous within countries. Southern regions of Nigeria, Benin, Ghana, and Togo, for example, report low incidence of meningitis and outbreaks in these regions are rare.

Another approach might be to consider all countries which have a confirmed non-A meningococcal outbreak. A brief literature search and review of the WHO Weekly Epidemiological Record suggests that this would include Benin, Burkina Faso, Chad, Cote d'Ivoire, the Gambia, Ghana, Niger, Nigeria, and Togo,[135–138] and possibly also Guinea (480 suspected *Nm*W cases in 2013), Kenya (74 suspected *Nm*W or X cases in 2006), Sudan (28 suspected *Nm*W cases in 2006), and Uganda (37 suspected *Nm*W or X cases in 2006), depending on outbreak definition.[139–141] Unfortunately the population and case numbers for outbreaks are not reported, so specific incidence-based definitions cannot be evaluated. Seven countries – Benin, Burkina Faso, Chad, Ghana, Niger, Nigeria, and Togo – fulfil both criteria: any district-year with high suspected cumulative annual incidence post-MenAfriVac mass campaign completion and a confirmed non-A outbreak reported in the literature.

Confidence in this analysis is limited by the underlying assumption that national laboratory confirmation is uniformly representative of all districts and that causes of meningitis outbreaks are homogeneous within countries. This assumption is unrealistic. The choice to place the threshold for predominance at 50% minimum may be too lenient, resulting in localised outbreaks of uncommon serogroups being misattributed. For example, outbreaks caused by both *Nm*W and Spn were observed in Ghana in 2016.[21,142] The analysis is also based on the assumption that localised outbreaks are largely caused by a single serogroup. This assumption is consistent with the current understanding of what is necessary to produce an outbreak as opposed to an endemic seasonal increase in incidence (low population immunity, which is largely serogroup-specific, allows for a rapid increase in transmission) and is backed up by studies in outbreak settings.[126,143] Taken together, these methods should capture most large outbreaks in countries with decent laboratory confirmation, but are not comprehensive.

In most country-years (103 of 195), no single predominant etiology for meningitis could be identified. However, more than 100 districts across 27 country-years reported enough suspected cases of meningitis to exceed the definitional threshold for a bacterial meningitis outbreak. This suggests that multiple serogroups of meningococci or pneumococci coexist simultaneously and at least cause sporadic cases. It is not uncommon for multiple pathogens to cause separate outbreaks in different regions of a single country.[21,142] However, the extent to which "mixed" outbreaks occur - i.e. a single outbreak in a relatively small community (on the scale of a district) caused simultaneously by two pathogens - is debated.[143] Expanded case-based surveillance could help to answer this question.[144] The limited national-level data available now is insufficient to explore heterogeneity within smaller communities.

All the suspected cases in the database used in this chapter are identified based on a specific set of symptoms which are typical of meningitis: fever, neck stiffness, convulsion, headache, nausea, vomiting, photophobia.[34] The decision to report a case of suspected meningitis is made by the local health care professional, and no data on specific symptoms are included in the available data. Surveillance of invasive meningococcal disease in the African meningitis belt has historically focused on signs of meningitis: data on the frequency of alternative presentations, including meningococcemia, arthritis, cutaneous vasculitis, conjunctivitis, and gastrointestinal symptoms, are lacking. In the United States and Europe, about 40-50% of cases present as meningitis. There is some limited evidence that this proportion is higher in the meningitis belt.[145] Presentation may depend on serogroup, with serogroup A manifesting more frequently as meningitis and serogroups C, W, and X as non-meningeal disease.[145–147] This narrow case definition may result in cases of meningococcal disease being missed, particularly in time periods and regions where non-group-A meningococci are prevalent.

Coverage of MenAfriVac mass campaigns has generally been high, with estimates greater than 89% in 12 of 14 countries (Benin,Burkina Faso, Central African Republic, the Gambia, Ghana, Guinea, Mali, Niger, Senegal, Sudan, Togo, and Uganda).[148] Despite lower coverage estimates in Cameroon (74%) and Nigeria (70%), the impact of MenAfriVac on incidence of suspected meningitis in these regions is still dramatic.

Stratifying by country, year, or etiology can be misleading if other factors are not considered. For example, *Nm*C outbreaks appear more uncommon when measured as the percentage of districts reaching the outbreak threshold because *Nm*C emerged in Nigeria, a large country with many districts and only half of its territory lying within the meningitis belt. Over time, more countries have joined the surveillance system, many of which only have a proportion of their territory inside the meningitis belt. This can create the illusion that the incidence of meningitis has decreased more dramatically in recent years than it actually has.

The past decade has been a dynamic period for bacterial meningitis in Africa. The introduction of MenAfriVac has resulted in decreased incidence of suspected cases and outbreaks and has galvanised investment in national meningitis surveillance systems. This analysis is the largest study of meningitis in Africa at the district level. Although it is limited by the inadequacies of

the data produced by an aggregated syndromic surveillance system with limited microbiological confirmation, it represents a good starting point for thinking about what has changed since the introduction of MenAfriVac and what challenges still remain. *Nm*A caused outbreaks more frequently in the pre-MenAfriVac era than do *Nm*C, W, or *S. pneumoniae*, but the intensity of outbreaks where and when they do occur appears to be the same, whether caused by *Nm*A, C, W, or *S. pneumoniae*.

Chapter 4

Modelling reactive vaccination for pneumococcal meningitis outbreaks in the African meningitis belt

The immediate impetus for this work was a request from the Ghana Health Service to the WHO Department of Pandemic and Epidemic Diseases for assistance in responding to an outbreak of bacterial meningitis that met the incidence-based criteria for a meningococcal epidemic but appeared to be caused by a pneumococcal strain. It was undertaken in collaboration with James Stuart from the London School of Hygiene & Tropical Medicine, Olivier Ronveaux and Katya Fernandez from the Department of Pandemic and Epidemic Diseases at the World Health Organization,Charles Okot from the World Health Organization Country Office Ghana, Franklin Asiedu-Bekoe from the Brong-Ahafo Regional Health Directorate, and my supervisor Caroline Trotter. A version of this work is in published in Vaccine (see Appendix A). Charles Okot and Franklin Asiedu-Bekoe provided access to the surveillance data used in this analysis. Olivier Ronveaux and Katya Fernandez provided policy guidance to inform the conceptualisation. Caroline Trotter and James Stuart provided guidance in the structuring and interpretation of results. I performed the data curation, model design, formal analysis, implementation of the code, and prepared the original draft. All authors participated in review and editing of the final manuscript.

4.1 Introduction

With the decrease in group A meningococcal disease and increase in surveillance quality that has accompanied the rollout of the group A conjugate vaccine, MenAfriVac, it has become increasingly clear that pneumococcal meningitis represents a substantial proportion of the burden of bacterial meningitis in the African meningitis belt. A growing body of evidence indicates the ability of *S. pneumoniae* to cause outbreaks of meningitis characterised by strong seasonality, broad host range, and clonality.[21,61,62]

The introduction of 13-valent pneumococcal conjugate vaccine (PCV13) into Ghana's routine immunisation programme in 2013 has significantly decreased the burden of invasive pneumococcal disease in children under five, but appears to have not yet been able to induce herd immunity in the broader population.[149] An outbreak of predominantly serotype 1 pneumococcal meningitis in the Brong-Ahafo region of Northern Ghana in late 2015 and early 2016 demonstrated the ongoing vulnerability of older age groups and the clear potential of *S. pneumoniae* to cause outbreaks of meningitis in the African meningitis belt.[21]

Under the current WHO guidelines for meningococcal meningitis outbreaks, an epidemic response is triggered when districts exceed an incidence threshold of 10 suspected cases per 100,000 population.[34] As part of this response, countries may apply to the International Coordinating Group (ICG) on Vaccine Provision for Epidemic Meningitis Control for meningococcal vaccine to deliver in mass campaigns in affected districts. The aim of this chapter is to explore whether a similar mechanism may be appropriate for responding to outbreaks of pneumococcal meningitis. First, I calculate the sensitivity and specificity of different incidence thresholds for predicting high cumulative incidence of suspected pneumococcal meningitis. Then, using a static model like the ones described in Section 2.4.1, I estimate the potential impact of a mass vaccination response to the 2015-2016 pneumococcal meningitis outbreak in Brong-Ahafo. I then reflect on the generalisability of these results and whether the protocols currently recommended by the WHO in response to meningococcal outbreaks should be expanded to include pneumococcal outbreaks as well. I have further reviewed surveillance studies of the epidemiology of pneumococcal meningitis in the meningitis belt in order to contextualise the following analysis, which relies on data from a single outbreak (see Section 2.5).

4.2 Methods

Line list data on suspected cases of meningitis reported in the Brong-Ahafo Region between 2 December 2015 (week 49, 2015) and 11 April 2016 (week 15, 2016) was obtained from the Ghana Health Service via the WHO. I determined the sensitivity and specificity of a range of incidence thresholds (10, 7, 5, and 3 suspected cases per 100,000 per week) for predicting a range of sizes of outbreaks (20, 40, 60, 80, and 100 cumulative cases per 100,000) in order to choose the optimal threshold for triggering reactive vaccination.

As a variety of laboratory tests were used for case confirmation, likely etiology was inferred according to Table 4.1. In a large proportion of cases (60%), etiology could not be determined. For this reason, cases of pneumococcal meningitis were modelled as

$$C_{Spn,i} = C_{S,i}(1 - p_n)\nu$$

where $C_{S,i}$ is the number of suspected cases reported in week i, p_n is the proportion of CSF samples in the district testing negative, and ν is the proportion of all confirmed cases in the district caused by *S. pneumoniae*.

Table 4.1 Classification of case etiology.

Classification	Criteria
Spn	Any test (Pastorex, culture or PCR) indicating Spn or positive gram stain
Nm	Any test (Pastorex, culture or PCR) indicating Nm or negative gram stain
Negative	Two or more tests (Pastorex, culture, PCR or gram stain) failing to indicate bacteria in CSF
Indeterminate	Any sample not fulfilling any of the above 3 criteria

I then modelled reactive vaccination of 5- to 29-year-olds building on methods developed in an earlier paper,[89] using a threshold of 10 suspected cases per 100,000 per week, the threshold which I found had the highest specificity. Five- to 29-year-olds were targeted because this would effectively extend coverage to all individuals under 30 years of age (individuals under 5 are eligible for three doses of PCV13 under the new vaccine schedule in Ghana). The following additional assumptions were made: i) 5- to 29-year-olds represent 52% of the population;[150] ii) the case fatality ratio for pneumococcal meningitis cases is 23%, as reported for confirmed pneumococcal meningitis cases in this data set; iii) 70% of confirmed cases of pneumococcal meningitis occurred in the 5- to 29-year age group; iv) 84% of cases of pneumococcal meningitis were caused by PCV13 vaccine-type serotypes;[21] v) 5% vaccine wastage.

In a clinical trial, 10- to 18-year-old children having never received a pneumococcal vaccine were given PCV13 and their opsonic pneumococcal activity (OPA) titres against each vaccine serotype tested one month post-vaccination. The lowest seroconversion rate was 94.5% for ST5 (95% CI 90.2 - 97.3).[151] On this basis, I made the additional assumption that reactive vaccination (a single dose of PCV13) would protect at least 90% of individuals 5 to 29 years of age against PCV13 vaccine-type serotypes, giving two weeks for immunological protection to take effect.

In the model, I calculate the cases of pneumococcal meningitis averted by vaccination ($C_{averted}$) as a function of the modeled cases over time ($C_{Spn,i}$), the proportion of cases occurring in the 5- to 29-year age group (a), the proportion of cases caused by PCV13 vaccine-type serotypes (σ), the individual efficacy of a single dose of PCV13 (ϵ), the week the incidence threshold is exceeded (i_t), the delay to implementing a campaign (d), vaccine wastage (w), and the time for seroconversion (assumed to be 2 weeks).

$$C_{averted} = \sum_{i=(i_t+d+2)}^{I} a\epsilon\sigma(1-w)C_{Spn,i}$$

The number of deaths averted is calculated as the product of the case fatality ratio (CFR) and the total cases averted.

The number of doses of vaccine (D) is calculated as

$$D = \alpha P$$

where α is the proportion of the population between 5 and 29 years of age, and P is the total population size of the districts where vaccination occurs.

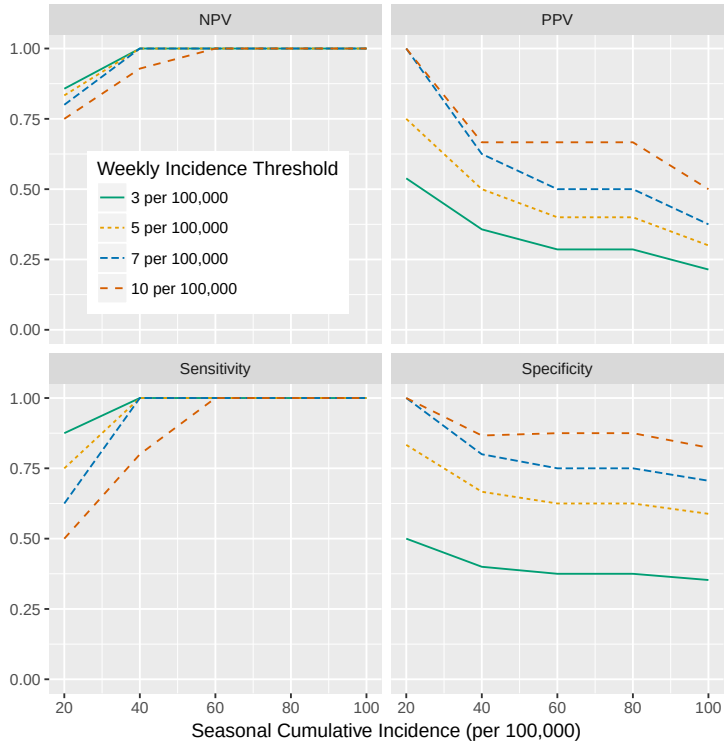


Fig. 4.1 Negative predictive value (NPV), positive predictive value (PPV), sensitivity, and specificity of various incidence thresholds (3, 5, 7, and 10 suspected cases per 100,000 per week) for predicting a range of sizes of outbreaks.

I determined the cases averted, deaths averted, number needed to vaccinate to prevent a case (NNV) and number needed to vaccinate to prevent a death (NNVD) for three scenarios: where vaccination occurs immediately, two, or four weeks after crossing the epidemic threshold (delay of zero, two or four weeks, respectively). In the base case, a delay of 2 weeks is assumed.

As a sensitivity analysis, I repeated the modelling process 10,000 times, resampling following parameters: ρ, ν, a , ϵ, σ, w, α, and CFR (shown in Table 7.4).

Table 4.2 Variables included in sensitivity analysis.

Variable	Meaning	Base	Distribution
ρ	Proportion of CSF samples testing negative	Variable	Binomial
ν	Proportion of confirmed cases caused by *S. pneumoniae*	Variable	Binomial
a	Proportion of cases in 5- to 29-year age group	71%	Binomial(p=0.71, size=119)
ϵ	Individual efficacy of PCV13	90%	Uniform(80%, 100%)
σ	Proportion of cases caused by PCV13 serotypes	84%	Binomial(p=0.84, size=49)
w	Vaccine wastage	5%	Uniform(0%, 10%)
α	Proportion of population in 5- to 29-year age group	52%	Uniform(40%, 60%)
CFR	Case fatality ratio	23%	Binomial(p=0.23, size=168)

4.3 Results

Twenty of the 27 districts of the Brong-Ahafo Region were represented in the line list. Nine of these had cumulative incidence greater than 20 suspected cases per 100,000; five had cumulative incidence greater than 40 per 100,000; four had cumulative incidence greater than 80 per 100,000, and three had cumulative incidence greater than 100 per 100,000 (see Figure 4.1). For predicting larger epidemics of 60 cases per 100,000 and greater, all thresholds had a sensitivity and negative predictive value of 100%, but a threshold of 10 per 100,000 had the highest positive predictive values and specificity.

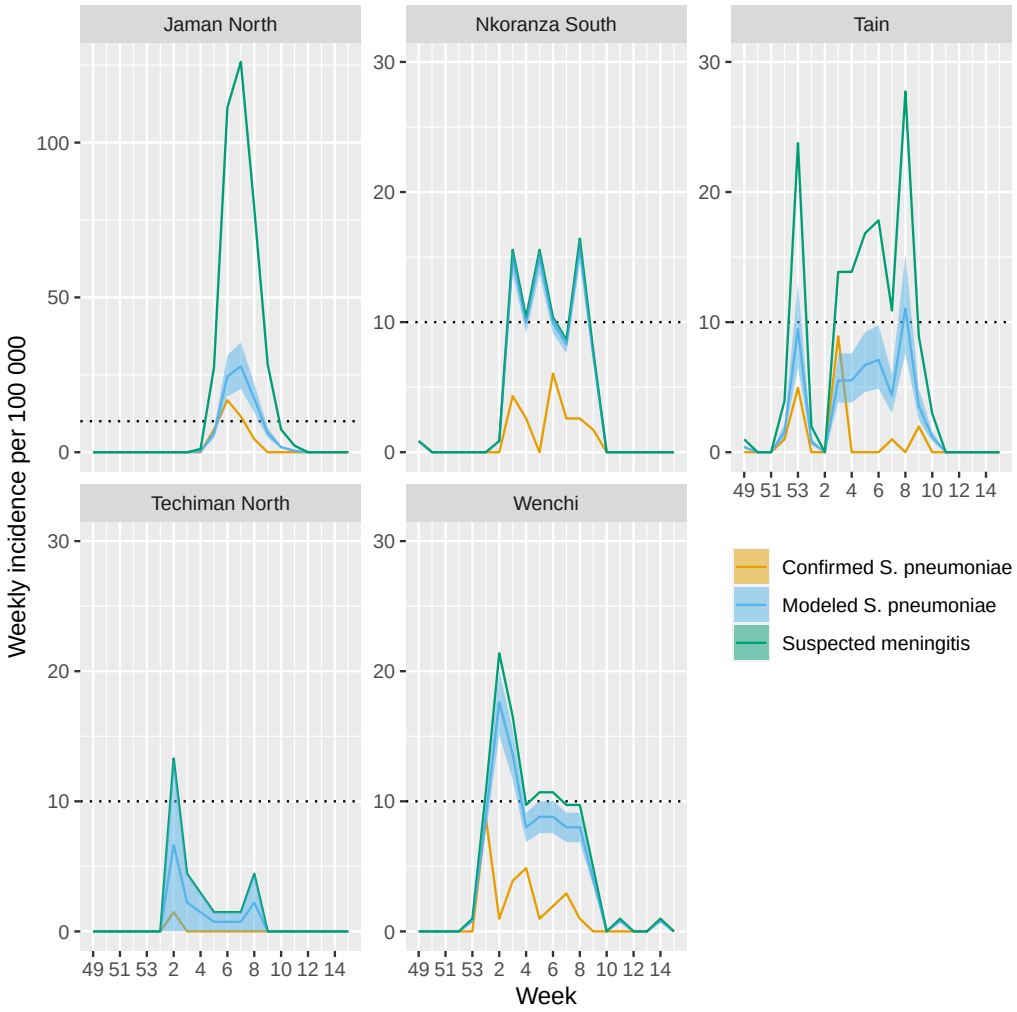


Fig. 4.2 Incidence of suspected, modelled likely, and confirmed pneumococcal meningitis in five districts crossing the epidemic threshold of 10 cases per 100,000. Transparent ribbon shows 2.5th and 97.5th percentile of bootstrapped modelled pneumococcal meningitis incidence.

In six districts (Jaman North, Nkoranza South, Sene West, Tain, Techiman North, and Wenchi), suspected meningitis incidence exceeded the epidemic threshold of 10 cases per 100,000 per week. In three of six of these, cumulative incidence exceeded 100 cases per 100,000 (see Figure 4.2). One district, Sene West, was excluded from the reactive vaccination simulation as

the majority of confirmed cases were caused by *Nm*W. Another district, Jaman North, had a particularly low confirmation rate (132 of 178 samples of cerebrospinal fluid tested negative for any pathogens by two or more laboratory tests) but was still included in the analysis as the majority of cases that were confirmed were caused by *S. pneumoniae* (39 of 46).

Vaccinating individuals between 5 and 29 years of age in the five eligible districts would have required approximately 284,000 doses of vaccine. Figure 4.3 shows modelled incidence with and without reactive vaccination with delays of 0, 2, and 4 weeks. If the campaign were implemented within two weeks of exceeding the epidemic incidence threshold, 59 cases of an estimated 328 likely pneumococcal meningitis cases occurring in the five eligible districts during the epidemic period would have been prevented as a result of direct protection from vaccination, placing the number needed to vaccinate to prevent a case at 4 830 (see Table 4.3). A delay of four weeks roughly halves the number of cases prevented, whereas immediate action roughly doubles it.

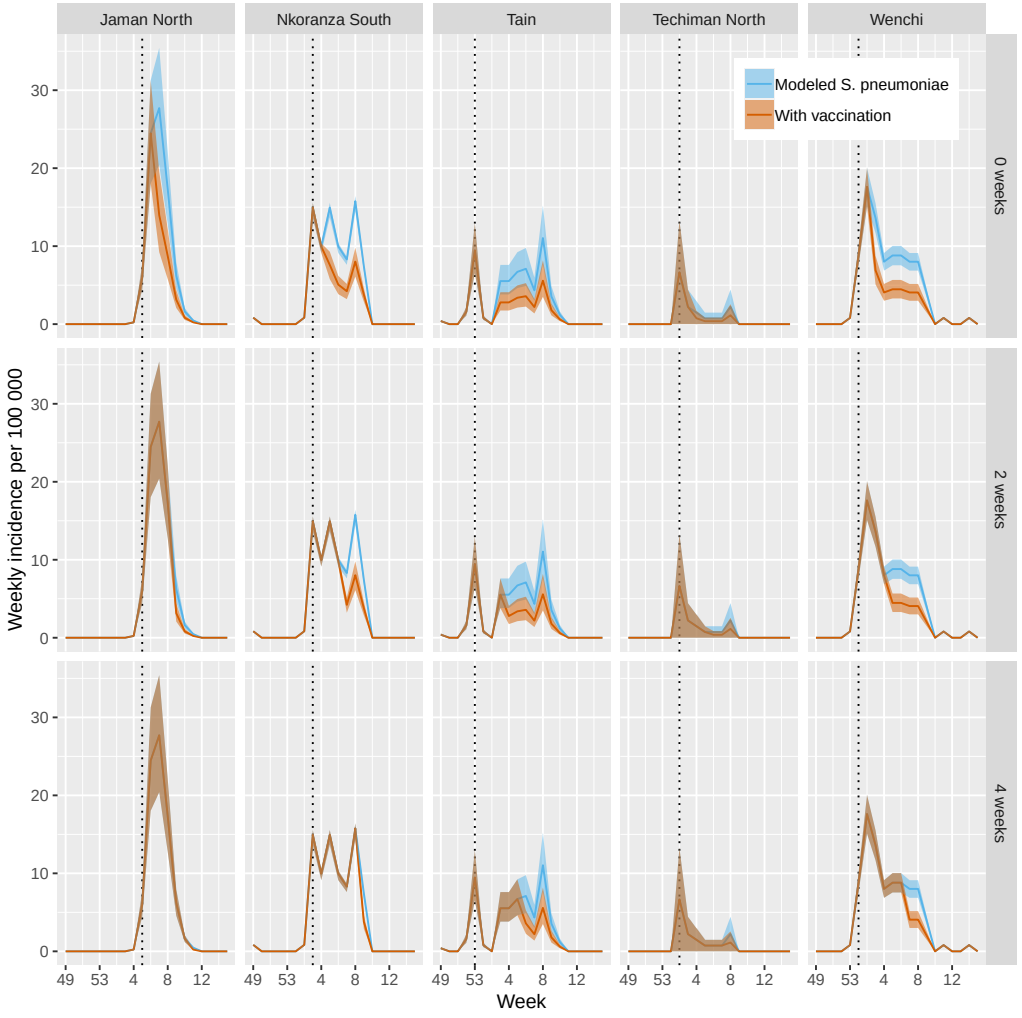


Fig. 4.3 Incidence of modelled pneumococcal meningitis with and without reactive vaccination with a delay of 0, 2 and 4 weeks. Transparent ribbon shows 2.5th and 97.5th percentile of bootstrapped modelled incidence.

Table 4.3 Cases and deaths prevented by direct protection from reactive vaccination with different times to implementation. Numbers in parentheses show 2.5th and 97.5th percentiles of sensitivity analysis.

Delay	Cases	Proportion of cases	Deaths	NNV	NNVD
0	106 (88 - 140)	32% (27 - 41%)	25 (18 - 36)	2670 (1560 - 2980)	11500 (6150 - 14500)
2	59 (48 - 79)	18% (15 - 23%)	14 (10 - 20)	4830 (2780 - 5390)	20800 (11000 - 26400)
4	28 (22 - 38)	9% (7 - 11%)	7 (4 - 10)	10100 (5840 - 11800)	43300 (23300 - 57400)

4.4 Discussion

An incidence threshold of 10 cases per 100,000 per week seems most appropriate given the limited data available. This threshold would also have been triggered in four of five previous likely outbreaks of pneumococcal meningitis (Solenzo, Burkina Faso, 2009; Goundi, Chad, 2009; Karangasso Vigue, Burkina Faso, 2011; Pama, Burkina Faso, 2011) and is consistent with the current meningococcal outbreak threshold.[34] Chapter 3 demonstrated that *S. pneumoniae* is an important cause of outbreaks and sporadic cases of bacterial meningitis in the African meningitis belt. *S. pneumoniae* predominated in 22 country-years, more than any other cause. In these years, 17 districts exceeded the weekly incidence threshold of 10 suspected cases per 100,000, and 9 of these exceeded cumulative incidence of 100 cases per 100,000. No attempt was made to evaluate different microbiological criteria for defining a pneumococcal outbreak. In this case, a simple majority of confirmed cases was required. There is still a need for improved laboratory confirmation of suspected cases of pneumococcal meningitis. This would allow for evaluation of more specific microbiological criteria.

The number needed to vaccinate to prevent a case (NNV) is within the range of previous estimates for reactive meningococcal campaigns (3,700 to 11,600 for 2 to 4 week lag).[89] This analysis suggests that reactive vaccination for pneumococcal meningitis outbreaks may be as effective as current practice for meningococcal meningitis outbreaks. Although the number needed to vaccinate to prevent a death (NNVD) has not been estimated for reactive meningococcal campaigns, the NNVD for pneumococcal outbreaks is likely lower given the high case-fatality rates typically associated with pneumococcal meningitis.[152]

It is not clear how quickly immune response would build up after PCV13 in the targeted age groups, however, a clinical trial of naive 10- to 18-year-olds showed high (>90%) serum bactericidal activity one month post-vaccination.[151] The model presented here only estimates cases prevented as a result of direct protection from the vaccine. A conjugate vaccine will have additional indirect benefits, decreasing carriage and transmission of vaccine-type serotypes where it is used. A dynamic SIR-type model could provide an upper estimate of the impact of reactive vaccination with a conjugate vaccine. Ferrari and colleagues compared two models, a Pinner-type model like the one used here that assumes that all cases in the epidemic are the result of asymptomatic carriers progressing to invasive disease and a dynamic time-series SIR model that assumes all cases are the result of carriage transmission.[95] They found that under the SIR model more than twice as many cases were prevented by vaccine. It is not clear how much

increased transmission during the epidemic contributes to incidence of invasive disease and to what extent cases are simply triggered by environmental effects like increased temperature and dust that increase the risk of invasive disease in existing carriers. These two models represent two extremes in potential models of the outbreak process. Perhaps more importantly, mass PCV vaccination would have a very large impact on the burden of pneumococcal pneumonia and meningitis in following years.

Serotype 1 was predominant in this outbreak. Seven other studies in the meningitis belt have reported serotype distribution of pneumococcal meningitis cases, all in populations with no PCV use.[32,60,62,65,109,111,153] Overall, 45% were serotype 1. Kwambana-Adams and colleagues report a higher proportion of isolates belonging to serotype 1 (67%) in the outbreak described here than in other studies.[21] Among the other studies, there are no marked differences between settings described as "epidemic" or "outbreak" and endemic settings. There are no appropriate data available to support or contradict the hypothesis that outbreaks of pneumococcal meningitis tend to be caused by a single serotype because most serotyping data is published as aggregate data over many years.

This model may be more conservative than the model used to evaluate reactive meningococcal vaccination, which had access to less detailed microbiological and age-specific data because of its broad scope.[89] Whereas the meningococcal outbreak model assumed all cases occurred in individuals under 30, this model assumes that only 70% of cases occur in the targeted age group. The meningococcal model also assumed that 79% of suspected cases were caused by *N. meningitidis* W, whereas this one estimates that on average only 49% of suspected cases during the outbreak were caused by *S. pneumoniae*. For these reasons, this analysis may underestimate the impact of reactive vaccination for pneumococcal outbreaks relative to meningococcal.

The very high suspected incidence in Jaman North was due to an error in reporting that resulted in a large number of probable malaria cases being reported as suspected meningitis (personal communication, WHO). I decided to keep the district in the analysis because there was still a high number of confirmed pneumococcal meningitis cases and the modelling methods adjust for this inaccuracy in reporting.

This analysis assumes no under-reporting in order to maintain consistency with previous studies and because there is already a large amount of uncertainty in the model of likely pneumococcal meningitis cases. However, a study from Northern Nigeria suggests that under-reporting of suspected cases is substantial and variable by ward.[95]

The predictions of this model are dependent on the age distribution of cases, the proportion of cases caused by *S. pneumoniae*, and the shape of the epidemic curve over time. For example, in this outbreak, 14% of suspected cases occurred within four weeks of triggering epidemic response – in other words, 14% of suspected cases would be missed by a response with a lag of two weeks. More suspected cases occurred in the first four weeks of past suspected pneumococcal meningitis outbreaks: 18% in Goundi, Chad in 2009, 28% in Karangasso Vigue, Burkina Faso in

2011, 21% in Pama, Burkina Faso in 2011 and 38% in Solenzo, Burkina Faso in 2009.[34] Reactive vaccination would have had lower impact in these outbreaks.

Our estimates, based on data from the Brong-Ahafo outbreak, suggest that reactive vaccination for pneumococcal meningitis would have prevented fewer cases per dose of vaccine than previous estimates for meningococcal meningitis reactive vaccination, a routine practice in the African meningitis belt. As the size and duration of outbreaks are likely to vary by country and by year, data from future outbreaks are needed to refine these estimates. Nonetheless, this analysis shows that in this particular case, reactive vaccination for pneumococcal meningitis is about as effective as reactive vaccination for meningococcal meningitis, something that is done every year in the African meningitis belt.

It is clear that any reactive response must be timely in order for it to be effective. A particular challenge for timeliness is microbiological confirmation of a reasonable number of cases and serotyping of pneumococcal isolates to determine whether the outbreak is caused by a vaccine-type strain. In the case of Brong-Ahafo, resources for serotyping were limited and no districts had confirmed the serotype of any samples at the time that incidence exceeded the epidemic threshold. On the positive side, PCV may be more readily available than the vaccines used in reactive meningococcal campaigns because it is used in many meningitis belt countries as part of the routine immunisation programme.

This chapter helps to address some of the knowledge gaps identified in the Meningitis 2030 Roadmap around pneumococcal outbreaks and assesses the utility of reactive vaccination in achieving the two aims of eliminating meningitis epidemics and substantially reducing cases and deaths from vaccine-preventable meningitis.[6] Even with an instantaneous response, reactive vaccination in this situation would only have prevented 32% of pneumococcal meningitis cases and deaths, and a reactive strategy cannot, by definition, eliminate outbreaks of pneumococcal meningitis.

Reactive vaccination is not a substitute for figuring out how best to achieve indirect protection of older age groups by routine vaccination, and if implemented, should not direct resources away from routine vaccination. A WHO expert committee is now considering whether a different routine vaccination schedule with a booster at 18 months (2 + 1) would be more appropriate for this setting.[149] It has been shown in high-income countries that routine immunisation with PCV provides indirect protection to older children and adults and that this is accelerated with the use of catch-up campaigns. There is less evidence regarding the scale of indirect effects from PCVs in African countries. Pneumococcal meningitis affects a broader age range of individuals in the African meningitis belt than in high-income countries. There is also evidence that climactic conditions particular to the meningitis belt increase the risk of invasive pneumococcal disease.[38] The only country to show indirect benefit without a catch up campaign in older children (South Africa) used a 2 + 1 schedule.[154] This chapter only considers reactive vaccination as a short-term response to meningitis outbreaks in older age groups not protected by routine vaccination. Finally, it is important to consider that meningitis accounts for only about 1% of

severe cases of pneumococcal disease and 12% of deaths due to pneumococcal infection.[8] The optimal vaccination schedule should take into account the overall burden of disease, including pneumonia.

Chapter 5

Meningococcal carriage prevalence in the African meningitis belt by age: a systematic review and meta-analysis

This work was undertaken in collaboration with Paul A. Kristiansen, Hannah Christensen, Andromachi Karachaliou, and Caroline L. Trotter. Paul Kristiansen shared data from carriage studies undertaken in Burkina Faso. Andromachi Karachaliou duplicated the systematic review and data entry. Hannah Christensen provided guidance on the statistical methodology used in the meta-analysis. A version of this work excluding sections 5.3.2.1, 5.3.2.2, and 5.3.2.3 has been published in Epidemiology and Infection (see Appendix A). I led the systematic review, data analysis, and drafting of the manuscript. All authors contributed to editing the final manuscript.

I would like to further acknowledge Nicole Basta, Judith Mueller, Ryan Novak, Gerd Pluschke, and Pratima Raghunathan for information on previously published work included in this meta-analysis, and the MenAfriCar Consortium for providing additional unpublished data. I also thank Brian Greenwood for his thoughtful comments on the manuscript.

5.1 Introduction

Most transmission of *Neisseria meningitidis* occurs amongst carriers, therefore targeting carriers is the only way to generate herd protection. Experience with conjugate vaccines has shown that with the correct age-specific strategy, such indirect effects make a profound contribution to disease control.[70] To this end, it is important to understand the distribution of meningococcal carriage to allow for efficient targeting of individuals who account for the most transmission. The age distribution of meningococcal carriers in high income countries has been described and synthesised; this showed that prevalence peaks around 19 years of age.[24] Patterns of carriage are however known to differ in the African meningitis belt, a region that experiences the highest burden of meningococcal disease in the world. Here, meningococcal carriage is a relatively common occurrence compared to invasive disease, although population overall prevalence is highly variable, ranging from 0% to 30%.[23,24] Although the distribution of

carriage prevalence by age also appears more variable in the African meningitis belt than in high-income countries, some studies have shown that carriage is most prevalent in children.[23]

Studies of meningococcal carriage in the African meningitis belt have identified a number of risk factors apart from age. A multi-site cross-sectional study found increased odds of meningococcal carriage in rural areas versus urban, and higher prevalence in males.[40] Household crowding and pollution from tobacco and indoor kitchen facilities also increased the odds of carriage significantly.[40] The association between respiratory infection and meningococcal carriage remains unclear, but some studies indicate a positive relationship between carriage acquisition and symptoms of respiratory disease, like sore throat or rhinitis.[127] Localised epidemics of meningococcal meningitis occur frequently in the belt, but there is no clear relationship between epidemic status and the prevalence of carriage. One study found higher rates of serogroup W carriage in a district experiencing a group W epidemic compared to a neighbouring non-epidemic district, prompting speculation that it may be dominance of a strain rather than overall prevalence that links carriage and epidemics.[155]

Season may complicate the relationship between age and carriage. Meningitis epidemics in the meningitis belt occur in the dry season and mathematical models of meningococcal transmission dynamics currently require substantial seasonal forcing of transmission to reproduce the observed patterns of disease.[39] One carriage study found higher odds of carriage of capsular meningococci during the dry season;[40] this has not been demonstrated consistently but is compatible with the idea that the capsule protects the bacterium from drying during aerosol transmission. Carriage of unencapsulated strains does not appear to have any association with season.[40]

Previous reviews of the literature on meningococcal carriage in Africa have not been systematic in nature and have not examined age-specific patterns in any quantitative way. The aim of this chapter is to conduct a systematic literature review of meningococcal carriage prevalence by age and season in the African meningitis belt and to synthesize these data in order to inform future vaccination strategies.

5.2 Methods

5.2.1 Search and study selection

This chapter was prepared in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) and preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[156,157] The literature searches were performed by one author (LVC) in January 2017 and updated in September 2017. PubMed, Web of Science, the Cochrane Library, and the grey literature were searched for papers reporting carriage of *N. meningitidis* in defined age groups in locations within the African meningitis belt, using the following search terms: "("Neisseria meningitidis" OR "N meningitidis" OR meningitis OR meningococcal OR meningococci OR meningococcus OR meningitidis) AND (carriage OR carrier OR carriers)

AND (Africa OR "meningitis belt" OR Gambia OR Senegal OR Guinea-Bissau OR Mauritania OR Guinea OR Ghana OR "Burkina Faso" OR "Upper Volta" OR "Cote d'Ivoire" OR "Ivory Coast" OR Togo OR Benin OR Nigeria OR Niger OR Chad OR Tchad OR Cameroon OR "Central African Republic" OR Sudan OR "South Sudan" OR Eritrea OR Ethiopia OR Uganda OR Kenya OR "Democratic Republic of Congo" OR Zaire)".

Studies were eligible for inclusion if they reported pharyngeal carriage of all meningococcal serogroups in defined age groups in generalisable populations in the African meningitis belt. Longitudinal, cross-sectional, and serial cross-sectional study designs were included. Studies reporting carriage rates among household contacts of Hajjis or other known carriers were excluded. Studies in both English and French were included in the systematic review. Two studies in Russian were excluded because abstracts could not be obtained. The reference lists of included papers were hand-searched to identify any papers that were missed by the electronic search. Details of the search process are given in Figure 5.1.

5.2.2 Data extraction and classification

Authors were contacted for additional information if studies reported age groups wider than 10 years and the median age was not reported or if the time period of the study was not reported. Where carriage prevalence was reported in age groups of range 10 years or less, the midpoint age was used. For open-ended age groups, the midpoint was calculated with an upper age limit of 60 years. Using additional data from the African Meningococcal Carriage Consortium cross-sectional studies, the oldest age group previously reported as 30 plus years was divided into two groups, 30 to 44 years and 45 plus years.

For papers that included results from several populations or studies, data were extracted only for observations meeting the inclusion criteria. Extracted data included the study location, time period, design, any mention of an outbreak or epidemic of meningitis coinciding with the study period, whether the study occurred before or after the MenAfriVac mass campaigns in the study region, use of random sampling, laboratory used to culture the pharyngeal swabs, time between sampling and plating, age range of the individuals, median age of individuals in each age group, number of individuals swabbed, and the number of individuals positive for capsulated meningococcal carriage. Capsule-null isolates were excluded from our definition of capsulated meningococcal carriage, but isolates characterised as non-determinate or non-groupable were included.

Studies were assigned to the dry or rainy season on the basis of the month in which the study took place, defining the dry season as December to June and the rainy season as July to November. Disaggregated data from the studies by Kristiansen and colleagues in Burkina Faso and Ethiopia were used to divide prevalence estimates from these studies into dry and rainy season measures. Studies were classified as having used random sampling if this was specifically reported; otherwise "no" was recorded. Data were extracted independently by LVC and AK, and differences were checked by CLT.

5.2.3 Data analysis

For the meta-analysis, data from age groups wider than 20 years were excluded. For longitudinal studies, only the first observation in the time series was used to avoid over-representing a particular population in the meta-analysis.

A natural cubic spline (a piecewise cubic polynomial function with linear tails) was used to model group median age.[24,158] The basis matrix for the spline was generated using the "ns()" function in the R core package "splines". Boundary knots (points in the spline below and above which the function is defined to be linear) in the spline were placed at zero and thirty years because of the low density of sampling in older age groups. The number of internal knots was selected by comparing the Akaike information criterion (AIC) of models with two and three internal knots, placing knots at appropriate quantiles (inner tertiles for two knots, inner quartiles for three knots. Optimal placement of these knots was determined by evaluating the AIC of models with every possible combination of knots drawn from the set of ages equidistant from every consecutive observed age between zero and 30 years. Internal knots placed at 9.25, 9.75, and 28.5 years of age gave the best model fit.

Season and outbreak status were modelled as a three-tiered fixed effect and a nested interaction term of location and year of swabbing as random effects. I used a fixed effects term for season and outbreak status because I wanted to estimate the overall impact of season across the whole data set and because I wanted to be able to test whether the groups were significantly different by comparing confidence intervals. I used random effects terms for location and year because there were more than ten different locations and years in the data set and these were factors for which only a subset of all possible levels had been observed. Physical laboratory was tested as a proxy for differences in ambient temperature, growth medium, swab type, and other unreported factors which might affect the likelihood of isolating meningococci from a sample, but this did not improve model fit. Other factors that were considered but did not improve model fit included mass group A conjugate vaccination, country, decade, latitude, time to plating, and study.

I started with a simple logistic regression because this is the traditional model for analysing prevalence data. However, when I found that a low proportion of observations fell within the bootstrapped 95% CI, I investigated three additional models which are commonly used to capture overdispersion: an observation-level random effects model, a beta-binomial or hierarchical model, and a zero-inflated binomial model.[159] The simple logistic regression captured more of the variability in the data than the observation-level random effects model and provided a better fit than the beta-binomial and zero-inflated binomial models, so I kept a logistic structure for the final model.

All candidate models allow overall carriage prevalence to vary but constrain the distribution of prevalence by age to be the same across all years and locations.

Models were fit using the lme4, spaMM and glmmADMB packages in R.[160–163] All of these packages use maximum likelihood methods to fit different families of regressions (binomial, beta-binomial, zero-inflated binomial). To generate confidence intervals for the model predictions and random effects, 10 000 iterations of bootstrapping with replacement were performed, and bias-corrected 95% confidence intervals were calculated.[164] Profile confidence intervals for fixed effects parameters were calculated using the "lme4" package.[160] Goodness of fit was measured by AIC and by performing leave-one-out cross-validation, whereby the model is refit on the full data set excluding a single observation and this new model is used to predict prevalence in the excluded observation. This prediction is then compared to the true value. To check the results of the spline model, I identified the age group with the highest carriage prevalence for each study measuring carriage in more than one age group and performed a one-way proportion test between this peak value and prevalence in all other age groups. To adjust for repeated significance testing, a p-value cut-off of 0.0005 was used, yielding an overall confidence of greater than 95%.

For the visual presentation of the fixed effects portion of the model, the observed carriage prevalence ($P_{observed}$) was adjusted to account for the random effects in the full model as follows: $P_{adjusted} = \exp(log(P_{observed}) - \sigma_{Location} - \sigma_{Location-year})$, where $\sigma_{Location}$ and $\sigma_{Location-year}$ are the random effects intercepts for location and year for a given observation.

To estimate the proportion of carriers that would be targeted in a mass vaccination campaign covering four age groups (0 to 15 years, 0 to 17 years, 0 to 19 years, and 0 to 29 years) I assumed a population structure consistent with that of Niger in 2017 and used the fitted estimate of carriage prevalence for the rainy season (although results are consistent across seasons).[150] Uncertainty in this estimate was measured by simulating 100,000 draws from a uniform distribution with boundaries at the 2.5th and 97.5th percentile of the fitted prevalence, using these draws as the rates for a random binomial draw with population size corresponding to each single year age cohort in Niger 2017, and then taking the 2.5th and 97.5th percentiles of the proportion covered to yield a 95% confidence interval.

5.2.4 Assessment of study quality and heterogeneity

The role of study design was assessed by comparing a model with and without sampling procedure (random vs. non-random) and with and without time to plating of swabs as fixed effect variables.

Ten of 16 studies included in the meta-analysis reported carriage in more than two age groups (the minimum number of points required to fit a spline). To investigate the heterogeneity between these 10 studies in trends related to age and season, the final mixed effects model was fit using subsets of the overall data from each study. The overall model is a mixed effects model with random effects for location and year and some studies encompassed multiple locations or years, so three different approaches were compared for the individual study fits. First, mixed effects models were fit where appropriate (where more than one location or year is reported),

using the best fit knots from the overall analysis. Second, fixed effects only models were fit for all studies, again using the best fit knots from the overall analysis. Third, mixed effects models were fit where appropriate but with internal knots at the 25%, 50%, and 75% percentiles of median age for each data subset, hereafter referred to as "free knot" fits. Table 5.1 gives a summary of the model construction for each study. In order to make fair comparisons, a fixed effects model was fit on the overall data set.

Table 5.1 Summary of model construction for individual study fits.

	Fixed effects	Random effects		
Model	Age	Season	Location	Location-year
Overall	***	***	***	***
Barnes 2016[165]	***	***		
Burian 1974[166]	***			
Forgor 2005[167]	***			
Kristiansen 2011[41]	***	***	***	
Kristiansen 2013[168]	***	***	***	***
Kristiansen 2014[73]	***		***	
Leimkugel 2007[169]	***			
MenAfriCar 2015[40]	***	***	***	***
Mueller 2011[170]	***			
Trotter 2013[171]	***			

The odds ratios from these models for the dry versus rainy season measures were compared to assess heterogeneity in season effects across studies. For the season heterogeneity analysis, four studies reported carriage in both dry and rainy seasons and could thus be included: MenAfriCar 2015, Kristiansen 2011 and 2013, and Barnes 2016.[40,41,165,168] No studies reported carriage during both outbreak and non-outbreak periods, so heterogeneity with this respect could not be assessed. I also compared the curve of carriage prevalence by age for each study and the proportion of carriers under 16, 18, 20, and 30 years of age to show between-study variability in age patterns. Finally, for both season- and age-related trends I compared the impact of including random effects terms for location and location-year for those studies where more than one location or year is reported (Kristiansen 2011, Kristiansen 2013, Kristiansen 2014, and MenAfriCar 2015).[41,73,165,168]

5.2.5 Site-specific analysis

In order to validate some of the authors' claims about the season and the urban or rural character of study sites, I used global gridded data on population density to capture urbanicity and data on precipitation and relative and specific humidity to capture seasonality. Geographic areas of relevance were defined for each study using the following methods: where a map of study site is given, this is digitised and the full extent taken; where latitude and longitude are given, the study site is assumed to occupy a 2 kilometre radius circle around the study centre; where only a place name is given, the GeoNames API is used to obtain coordinates for the location and then a 2 kilometre radius circle is assumed as above.

Data on population density are taken from the WorldPop Africa Continental Population Datasets and give the estimated number of people per square kilometre for timepoints between 2000 and 2020 at five-year intervals.[172,173] I use precipitation data from the National Oceanic and Atmospheric Administration (NOAA) Precipitation Reconstruction over Land (PREC/L) and the Climate Prediction Center Merged Analysis of Precipitation (CMAP) datasets and specific humidity data from the National Centers for Atmospheric Prediction and the National Center for Atmospheric Research (NCEP/NCAR) Reanalysis dataset.[174–176] All three datasets are publicly available and are provided by the NOAA on their website at https://www.esrl.noaa.gov/psd/. Table 5.2 provides detailed information on the resolution, range, and units of the three gridded datasets used in these analyses. For the climate analysis, I take the mean value of these measures over the relevant time period reported for swabbing and over the area included in the study locations. In the case of population density, I choose the measure at the closest point in time to when swabbing is reported.

I then coded each of these variables categorically, using the median value for a cutoff to distinguish low and high, and included these variables as fixed effects in a logistic regression, adjusting separately for presence or absence of reported outbreak. I additionally compared author reporting of urban versus rural sites with the mean population density given by WorldPop for these sites and fit two log-normal density distributions to urban and rural observations to determine a population density cutoff for urbanicity consistent with the literature. I then used this cutoff to classify sites where the authors had not described the urban or rural character of the sites and included this as a categorical variable in the logistic regression for carriage prevalence.

I checked our season definition - studies assigned to the dry or rainy season on the basis of the month in which the study took place, defining the dry season as December to June and the rainy season as July to November - against average monthly rainfall and specific humidity anomalies for the period 1981 to 2010 in each site (Figure C.3, Table 5.2) and against average rainfall and humidity during swabbing periods (Figure 5.7) using publicly available data from the NOAA described above. In a sensitivity analysis, I excluded data from four sites with non-characteristic rainfall patterns. These sites all fell on the edges of the meningitis belt: Butajira, Ethiopia (2 sub-sites), Arba Minch, Ethiopia (4 sub-sites), and Kpalkpalgbeni, Brong-Ahafo District, Ghana.

5.2.6 Serogroup-specific analysis

As nearly all studies presented data on the serogroups or genogroups of carriage isolates, I wished to analyse separately trends in carriage of *Nm*A, *Nm*W, *Nm*X, and *Nm*Y by age and season. I excluded *Nm*B, *Nm*C, and capsule-null from this type of analysis as these were very rarely reported. I fitted the same logistic regression with a cubic spline of age, fixed effect of season, and random effects from location and location-year that I used to model carriage of any capsulated meningococci to data on carriage of *Nm*A, *Nm*W, *Nm*X, and *Nm*Y and compared

Table 5.2 Summary of gridded data.

Measure	Unit	Data source	Spatial resolution	Time period used	Time resolution
Specific humidity	g water vapour per kg air	NCEP/NCAR Reanalysis	2.5 degrees (approx. 277 km at the Equator)	1970-2018	Monthly mean
Precipitation	mL per day	CPC Merged Analysis of Precipitation	2.5 degrees (approx. 277 km at the Equator)	2012-2014	Monthly mean
Precipitation	mL per day	NOAA Precipitation Reconstruction over Land (PREC/L)	0.5 degrees (approx. 56 km at the Equator)	1970-2012	Monthly mean
Population density	Persons per sq km	WorldPop Africa Continental Population	0.0083 degrees (approx. 1 km at the Equator)	2000-2015	Five-year intervals

the central estimates from these models to one another and to the findings from the overall model.

I also fitted a logistic regression with a cubic spline of age, fixed effect of season, and random effects from location with an additional fixed effect of whether the study occurred before or after mass introduction of MenAfriVac in the study location to assess the impact of group A conjugate vaccination on *Nm*A carriage. I dropped the location-year random effects term because this resulted in singularities in the data because the MenAfriVac introduction term is necessarily time-dependent.

5.3 Results

Twenty-three relevant articles were identified that reported unique studies of carriage by age in generalisable populations in the African meningitis belt representing eight countries: Burkina Faso, Chad, Ethiopia, Ghana, the Gambia, Mali, Nigeria, and Niger. Eleven were cross-sectional studies; five serial cross-sectional, four longitudinal, and three were vaccine trials (two polysaccharide and one conjugate vaccine). Twelve of 23 articles did not report randomisation in participant selection. Sixteen studies were eligible for inclusion in the meta-analysis (Table C.1). Seven of these sixteen did not report random sampling. Eighteen of 23 studies in the systematic review and 15 of 16 eligible for inclusion in the meta-analysis reported information on the serogroups or genogroups of the carriage isolates (Table 5.4). See Figure 5.1 and Tables C.2 and C.3 for further details of search and reasons for exclusion.

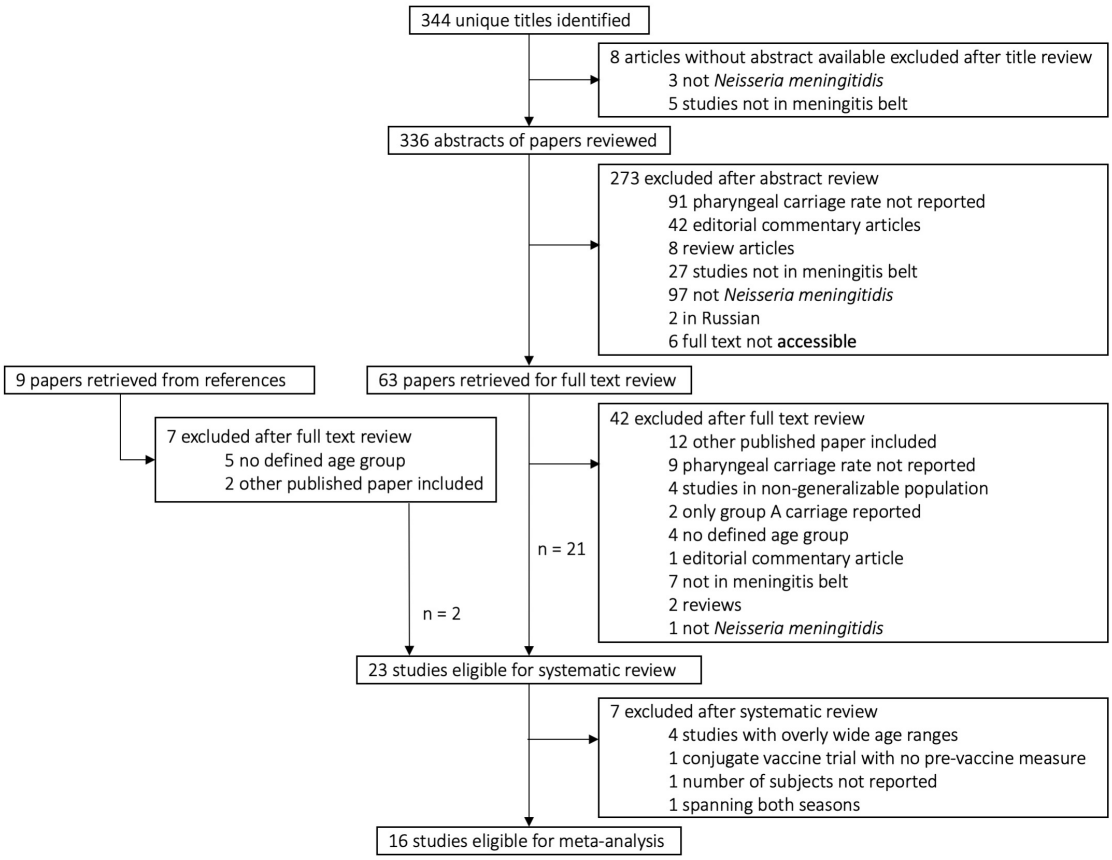


Fig. 5.1 Selection of studies on meningococcal carriage prevalence for systematic review and meta-analysis.

5.3.1 Systematic review

5.3.1.1 Longitudinal studies

Longitudinal studies reported high variation in carriage rates over time (1-35%), but no significant differences in carriage prevalence between age groups.[169,177–179] Prevalence recorded around the time of meningococcal outbreaks was generally high in recent studies (2000s and 2010s), with two studies showing particularly high rates in ages 5 to 29 years (16-38%, Table C.3).[167,170,180] Two early studies (1970s) during a group A meningococcal outbreak found lower rates of carriage (2-5%).[181,182]

5.3.1.2 Studies of seasonal change

Most studies which specified beginning and ending months for dry and rainy seasons placed the beginning of the dry season between November and January and the beginning of the rainy season between April and July. One study additionally defined a Harmattan season (October to January) between the rainy and dry seasons.[183] Early studies documented the variability of carriage prevalence in the African meningitis belt but found little support for consistent differences in prevalence by season. A year-long study in Burkina Faso found a wide variation in

carriage rates but no significant changes associated with the onset of the rainy season.[179] Two other studies found similarly variable results with no obvious seasonal patterns.[13,183] One study in rural northern Nigeria displayed highly stable prevalence over the year, with carriage ranging from 2.1% to 2.7% at four sampling intervals.[13] These early studies may have been limited by their relatively short duration or small sample sizes.

An eight-year longitudinal study of a cohort (n≈300) in Northern Ghana measured carriage twice annually, in April (late dry season) and November (late rainy season). Although this was not noted in associated publications, the average carriage rate in November (4.4%) was substantially lower than that in April (7.9%).[169] This was the first study to produce evidence supporting the hypothesis that carriage prevalence increases during the dry season.

A multi-site serial cross-sectional study in Burkina Faso measuring carriage four times annually in 2009 and 2011 found significantly higher carriage prevalence in dry season surveys than in rainy.[41,168] Finally, a serial cross-sectional study across seven countries of the meningitis belt found significantly elevated odds of carriage during the dry season as compared with the rainy (adjusted OR 1.54, 95% CI 1.37-1.75).[40]

5.3.1.3 Laboratory methods

All studies relied on culture for the initial identification of meningococcal isolates. Between one and ten colonies were selected for further testing, most commonly serogrouping. Fourteen of 23 studies (all published after 2000) reported using molecular methods for confirmation and further characterisation of culture isolates. There was no clear difference in prevalence in studies which used molecular methods versus those which did not.

5.3.2 Meta-analysis

Data from 16 papers, comprising 114,331 individual swabs, were available for quantitative data synthesis.

The four model variants tested did not vary greatly in their parameter estimates and goodness of fit (Table C.4). The logistic regression model was selected because the greatest proportion of observations fell within the 95% confidence interval of bootstrapped predictions and the leave-one-out cross-validation correlation was greatest for this model. This best-fitting model had season as a fixed effect and location and year as random effects.

The fixed effects parameters of the final model are shown in Table 5.3. The model suggests that meningococcal carriage prevalence in the African meningitis belt increases rapidly in childhood, peaks at 10 years of age (1.9% in the rainy season, 95% CI 1.9-2.5%), and gradually declines after this point (Figure 5.2). In a country with the same population structure as Niger, our model estimates that 58% of carriers are under the age of 16 and 84% are under the age of 30 (Table 5.5). Odds of carriage were significantly increased for studies taking place during the dry season (1.5 95% CI 1.4-1.7) as compared with the rainy season, and further increased for

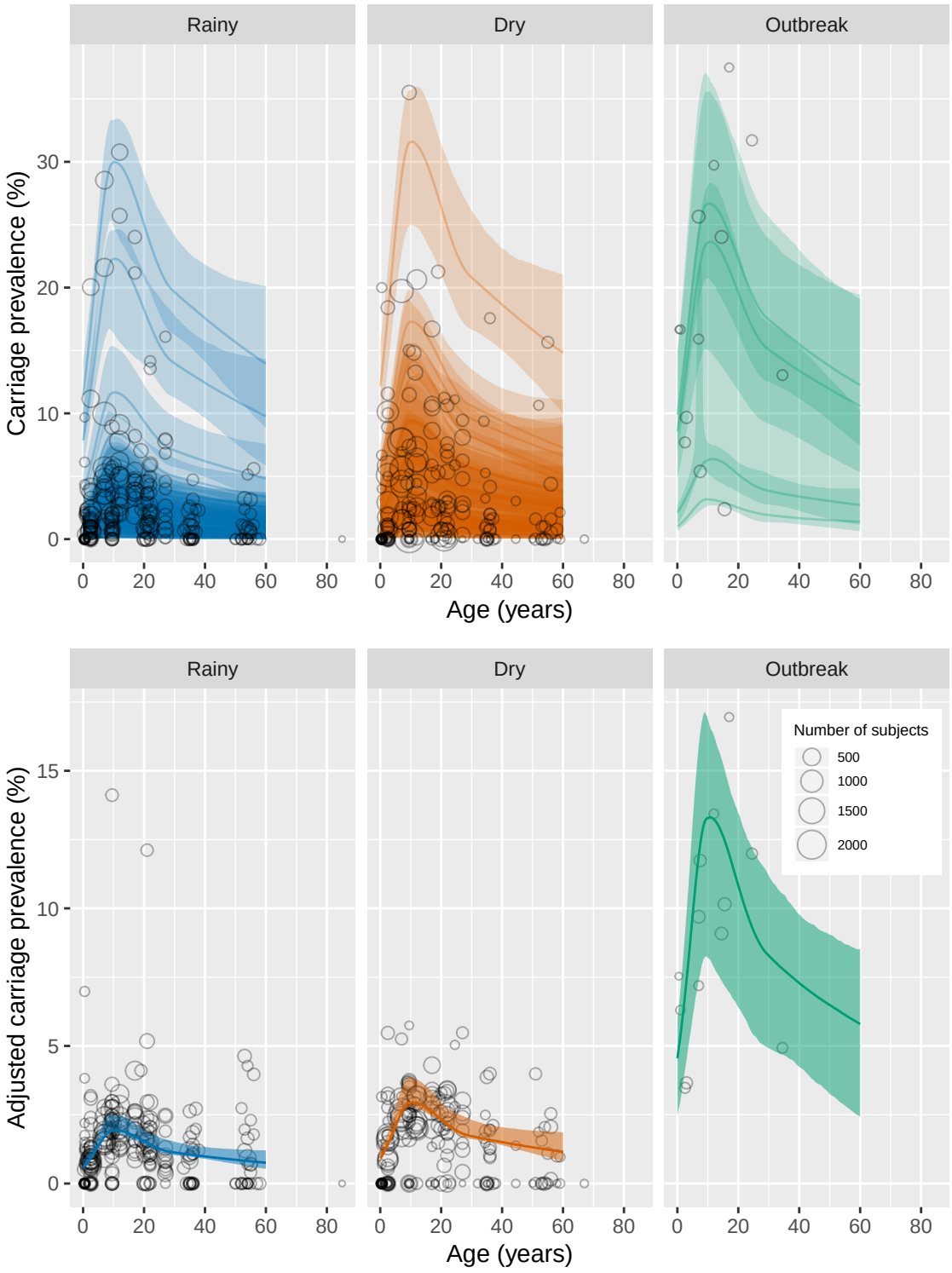


Fig. 5.2 Observed carriage prevalence measures and model predictions. Top panel: Circles show the data points included in the meta-analysis, with the larger circles representing a larger sample size. Solid line shows model predictions including random effects. Shaded ribbon shows 95% bias-corrected confidence intervals. Bottom panel: Circles show the data points included in the meta-analysis, with carriage prevalence adjusted for random effects intercept. Solid line shows model predictions excluding random effects. Shaded ribbon shows 95% bias-corrected confidence intervals. Dry season predictions shown in red; rainy season in blue; outbreak in green.

studies taking place during outbreaks (OR 6.7 95% CI 1.6-29), though the uncertainty in the latter estimate is high as limited data on carriage during outbreaks are available. No other risk factors were found to significantly impact the odds of carriage. Predicted carriage prevalence by age is shown in Figure 5.2.

One-way proportion testing between peak reported carriage prevalence and prevalence in all other age groups confirmed age-related trends, with four of 13 studies showing a peak in age groups containing 10 years of age (the peak age identified by the spline regression model) and the remaining nine showing no significant difference between peak prevalence and the prevalence in the age group containing 10 years of age (Table C.5).

Predicted carriage prevalence was not significantly different when excluding data from sites that were climactic outliers (Table 5.3, Figure C.2). Location and year contributed to substantial variation in overall carriage rates. Random effects intercepts are given in Tables C.6 and C.7. Figure C.1 shows model predictions including random effects. The variance for the location-year interaction intercept was greater than that for the location intercept (1.02 versus 0.55). Neither location nor year alone was a consistent determinant of the location-year intercept (Table C.7). No years showed consistently low or high prevalence at all locations and no locations showed consistently low or high prevalence at all years.

Shown in Figure 5.3, leave-one-out cross-validation predicted values were moderately correlated with true values (Pearson's ρ 0.89). However, the median percent error for non-zero values was substantial, 34%. The model performed poorly at predicting observations of 0% carriage. More than half of all observations were outside the 95% confidence intervals for the model predictions (64%).

Table 5.3 Fixed effects parameters. Predicted odds ratios and profile confidence intervals and median bootstrapped odds ratios and 95% bootstrapped confidence intervals for fixed effects parameters from fit on full data set and on data set excluding climactic outliers.

Factor	Full data set		Excluding climactic outliers	
	Odds ratio (95% profile CI)	Odds ratio (95% bootstrap CI)	Odds ratio (95% profile CI)	Odds ratio (95% bootstrap CI)
Natural cubic spline of age				
Spline I	3.4 (2.9-4.1)	3.5 (2.5-4.6)	3.6 (3-4.4)	3.7 (2.6-4.9)
Spline II	2 (1.6-2.4)	2 (1.5-2.9)	1.8 (1.4-2.2)	1.8 (1.3-2.6)
Spline III	5.2 (3.7-7.2)	4.9 (3-9.6)	4.9 (3.5-7.1)	4.7 (2.8-9.7)
Spline IV	0.79 (0.71-0.87)	0.79 (0.66-0.93)	0.7 (0.63-0.79)	0.71 (0.59-0.83)
Season				
Rainy	1	1	1	1
Dry	1.5 (1.4-1.7)	1.5 (1.3-1.8)	1.6 (1.5-1.8)	1.6 (1.3-1.9)
Outbreak	6.7 (1.6-29)	7.9 (3.9-8.3)	4.9 (0.81-31)	5.7 (1.3-6.4)

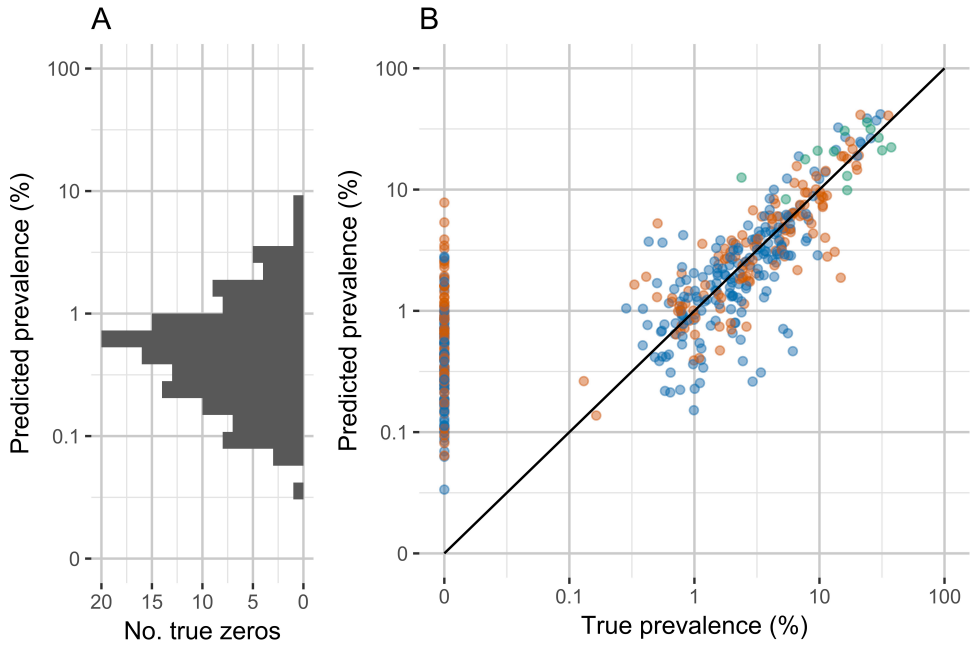


Fig. 5.3 Observed carriage prevalence and model predictions by leave-one-out cross-validation. A) Distribution of model predictions for true zero observations. B) True prevalence and prevalence predicted by leave-one-out cross-validation. Note the discontinuous scale to emphasize zero observations.

5.3.2.1 Study heterogeneity

Almost every study showed a significantly higher prevalence of carriage during the dry season, but the magnitude of this effect ranged from OR 1.17 to 1.86 (see Table 5.6). One study, MenAfriCar 2015, showed a strong opposite effect when fit with a mixed effects model (OR 0.51, 95% CI 0.28-0.86) but the trend was consistent with the others when fit with a fixed effects model (OR 1.47, 95% CI 1.29-1.68). The fixed effects fit OR is very similar to that reported in an earlier logistic regression analysis that took into account other risk factors.[40] The prevalence of carriage in the MenAfriCar study is lower in the 2010 dry season than in the 2010 rainy season: 0.2% compared to 1.5% (see Table 5.7). In 2012, the prevalence of carriage is higher in the dry season (2.9%) than in the rainy season (0%), but the sample size in the rainy season is particularly small (n=304). The overall prevalence of carriage 2010-2012 is higher in the dry season (2.4%) than in the rainy season (1.5%). Knot placement in the cubic spline did not make a difference in the estimates of odds of carriage between the dry and rainy seasons.

The age spline model was fit to the 10 studies with three or more age groups reported. Even where the knot placement was the same for each, the shape of the spline varied widely, especially in studies with small sample size (Figure 5.4). The mixed effects and fixed effects models gave similar estimates except in the cases where a large number of locations and years were sampled, i.e. for MenAfriCar 2015 and for the overall fit. In these cases, the central model predictions were substantially higher for the fixed effects only models than for the mixed effects models. Notable differences in the shape of the curve of carriage by age were found for Forgor 2005,

Table 5.4 Studies reporting serogroup distribution of *N. meningitidis* isolated from carriers in the African meningitis belt. **Excluded from meta-analysis. *Climactic outliers excluded from meta-analysis in sensitivity analysis. #Two group E and five group B carriers also reported. †Percentages do not sum to 100 because full serogroup data not reported.

Study	Year	Prevalence of carriage	Serogroup distribution					
			A	C	W	X	Y	NG
Burian 1974[166]	1970	144/2569 (5.6%)	19%	1%	...	9%	4%	56%
Sanborn 1972[184]** †	1971	179/311 (57.6%)	52%	...	...	...	...	...
Blakebrough 1980[181]†	1977	7/130 (5.4%)	43%	...	...	...	...	...
Blakebrough 1983[182]†	1978	4/168 (2.4%)	50%	...	...	...	...	...
Leimkugel 2007[169]	1998	14/300 (4.7%)	57%	...	7%	0%	29%	7%
Raghunathan 2006[155]**	2002	203/899 (22.6%)	0%	1%	65%	6%	...	28%
Amadou-Hamidou 2006[177]	2003	38/287 (13.2%)	0%	...	34%	...	11%	55%
Forgor 2005[167]*†	2003	48/299 (16.1%)	...	...	71%	...	...	...
Yaro 2007[178]	2003	16/456 (3.5%)	...	...	50%	0%	0%	50%
Mueller 2011[170]	2006	129/615 (21%)	74%	...	...	...	26%	...
Sie 2008[180]** †	2006	24/180 (13%)	92%	...	...	...	...	...
Trotter 2013[171]	2008	12/1037 (1.2%)	...	...	25%	8%	42%	25%
Kristiansen 2011[41]	2009	809/20326 (4%)	10%	0%	9%	11%	56%	13%
Kristiansen 2013[168]	2010	1643/25520 (6.4%)	0%	0%	6%	75%	13%	5%
MenAfriCar 2015[40]*	2010	896/48405 (1.9%)	5%	3%	69%	2%	7%	11%
Kristiansen 2014[73]	2012	390/4964 (7.9%)	0%	6%	87%	8%	3%	2%
Manigart 2016[185]#	2013	33/999 (3.3%)	0%	6%	33%	0%	9%	30%
Barnes 2016[165]*	2014	492/7479 (6.6%)	0%	1%	6%	14%	2%	76%
All meta-analysis	1970-2014	4703/114331 (4.1%)	5%	1%	26%	31%	17%	17%
Pre-MenAfriVac	1970-2014	2637/73202 (3.6%)	10%	2%	25%	9%	23%	27%
Post-MenAfriVac	2010-2012	2066/41129 (5.0%)	<1%	<1%	27%	59%	9%	4%

Table 5.5 Proportion of carriers under 60 years of age directly targeted by vaccination of different age groups.

Age group	Proportion of carriers (95% CI)	
Under 16 years	58%	(57-60%)
Under 18 years	64%	(63-65%)
Under 20 years	69%	(62-74%)
Under 30 years	84%	(82-84%)

Table 5.6 Odds ratios and 95% profile confidence intervals for carriage in dry season as compared to rainy season for individual studies and overall data set using fixed effects models, mixed effects models (fixed and random effects), and models with free internal knots for the cubic spline of age.

Model	Fixed effects OR (95% CI)	Mixed effects OR (95% CI)	Free knots OR (95% CI)
Overall	1.23 (1.16-1.30)	1.55 (1.42-1.69)	1.55 (1.42-1.69)
Barnes 2016[165]	1.36 (1.11-1.66)	...	1.35 (1.11-1.66)
Kristiansen 2011[41]	1.46 (1.27-1.69)	1.46 (1.27-1.69)	1.46 (1.26-1.69)
Kristiansen 2013[168]	1.17 (1.05-1.29)	1.86 (1.64-2.12)	1.86 (1.64-2.12)
MenAfriCar 2015[40]	1.47 (1.29-1.68)	0.51 (0.28-0.86)	0.51 (0.28-0.86)

Trotter 2013, Mueller 2011, Kristiansen 2011, Kristiansen 2013, and MenAfriCar 2015 when the model type was varied. For Forgor 2005 the fit is essentially degenerate using the best fit knots, predicting carriage prevalence higher than 100% for some age groups. The same is true for Trotter 2013 using the free knots. Although very low carriage prevalence was observed in

Table 5.7 Meningococcal carriage prevalence in the MenAfriCar study[40] by year and season.

	Prevalence	
Year	Rainy	Dry
2010	1.5% (n=13106)	0.2% (n=3882)
2011	1.6% (n=15910)	-
2012	0.0% (n=304)	2.9% (n=15203)
Overall	1.5% (n=29320)	2.4% (n=19085)

Trotter 2013 and very high carriage prevalence was observed in Forgor 2005, both studies are characterised by multiple sharp increases and decreases in carriage prevalence as you move through age cohorts, which makes it difficult to fit a model of this relatively inflexible type.

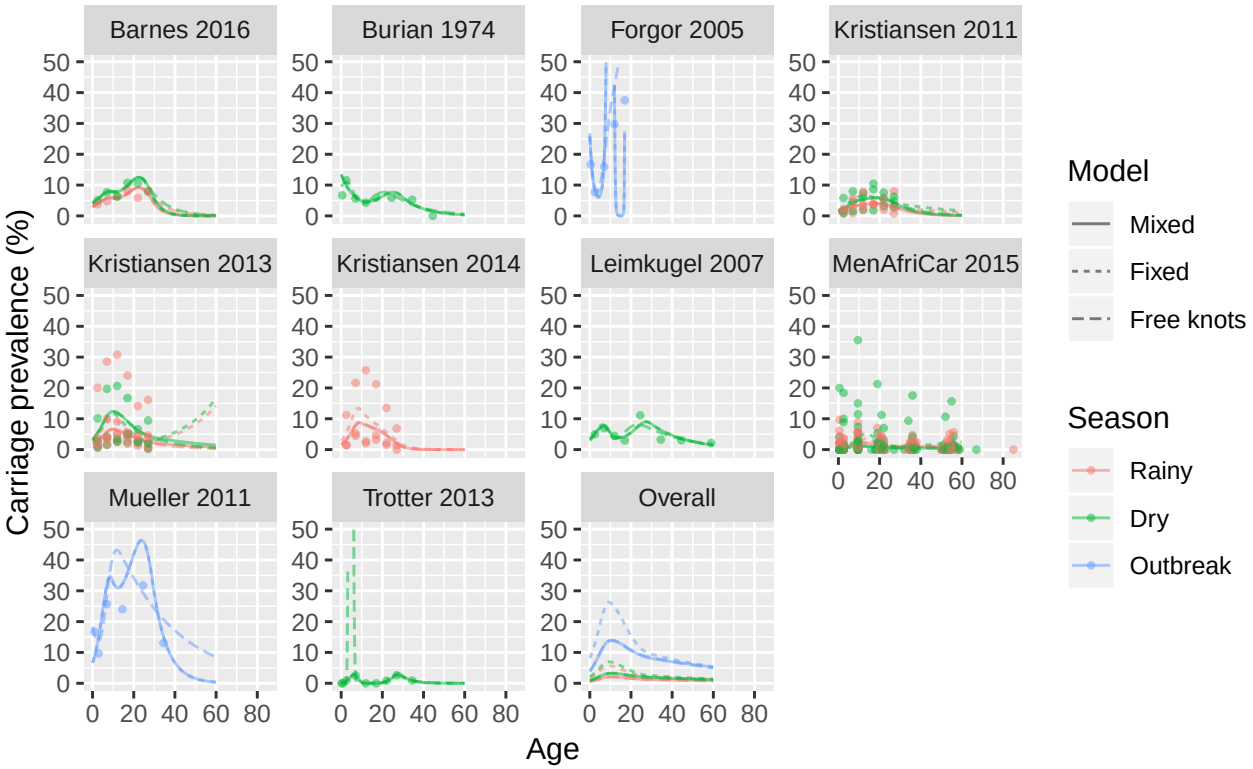


Fig. 5.4 Individual study model fits (lines) and prevalence observations (points). Rainy season predictions shown in red; dry season in green; outbreak periods in blue.

Barnes 2016 and Kristiansen 2011 shows prevalence peaking around 20 years of age, whereas Kristiansen 2013 and 2014 and MenAfriCar 2015 show peaks around 10 years. The overall model shows a peak at 10.0 years with the mixed effects model, 9.2 years with the fixed effects model, and 7.8 years with the free knots mixed effects model.

Taking each study fit independently, the estimates for the proportion of carriers which would be targeted by vaccination of all individuals under 16 years of age ranged from 45% to 78%, for under 18 years 45% to 84%, for under 20 years 46% to 89%, and for under 30 years 60% to 99% (Figure 5.5).

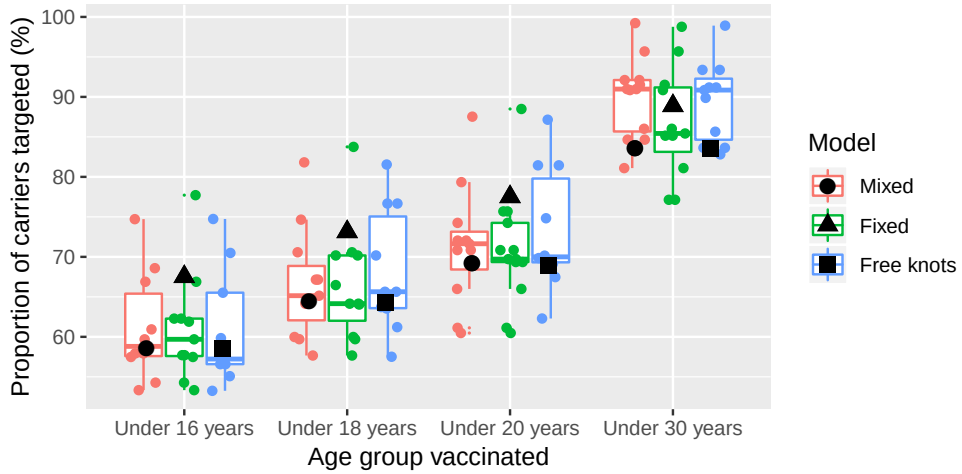


Fig. 5.5 Proportion of carriers under 16, 18, 20, and 30 years of age by model type. Black points indicate overall meta-analysis estimate; coloured points and box plots indicate individual study estimates. Green and triangles indicate fixed effects only model; red and circles indicate mixed effects model; blue and squares indicate free knots model.

5.3.2.2 Site-specific analysis

In general, authors' descriptions of sites as urban or rural were consistent with higher and lower population density, respectively (see Figure 5.6). The log-normal mixture model fitted to population density data placed the cutoff for urbanicity at greater than 1000 persons per square kilometre (95% CI 470 - 3400). Urbanicity did not account for any significant differences in carriage prevalence, either defined as the authors reported or defined using global gridded data on population density (Table 5.8).

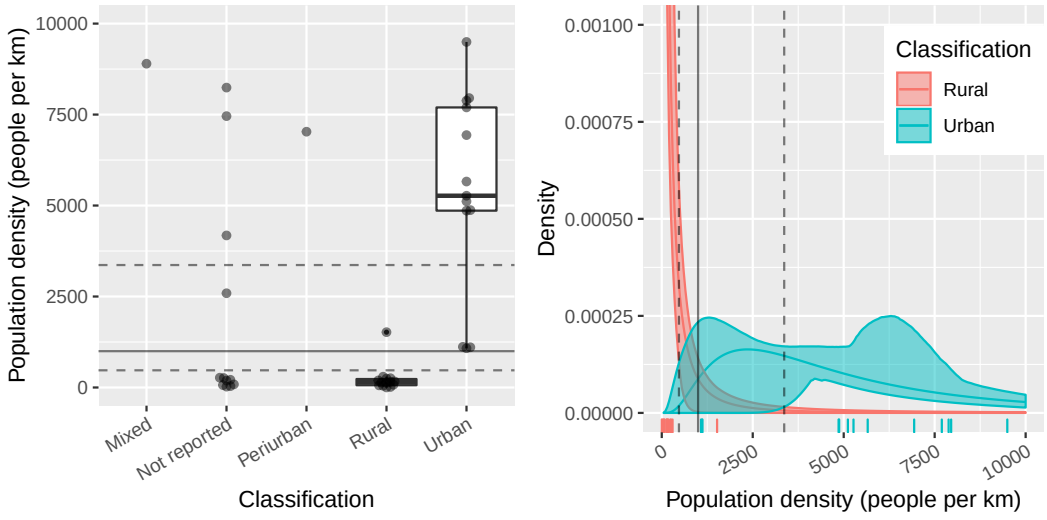


Fig. 5.6 Population density by site description and probability density function (log-normal) of population density for sites described as urban and rural. Solid line shows central cut-off and dotted lines show upper and lower bounds of cut-off.

Our season definition placing the dry season between December and June was generally consistent with rainfall and humidity patterns (Figure 5.7). Annual rainfall and humidity cycles are not synchronised. Most sites show similar in climactic patterns, with three to four months of heavy rains in June to September and a prolonged absence of rain from October to May, punctuated by low humidity between November and April. 26 of 40 sites show negative humidity anomalies between November and April, placing the onset of the dry season in November. 20 of 40 sites show positive rainfall anomalies between June and September, placing the onset of the rainy season in June.

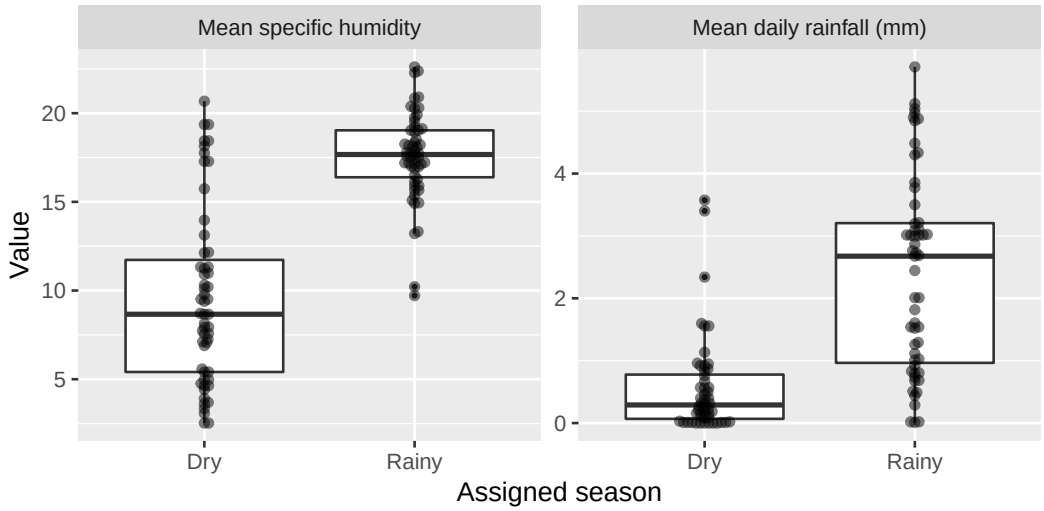


Fig. 5.7 Mean daily rainfall and mean specific humidity by assigned season (Rainy season: December to June; dry season: January to May).

Odds of carriage were increased by similar magnitude during the dry season when using rainfall and specific humidity measures as proxy for season with an odds ratio of 1.7 (95% CI 1.6-1.9) for both low rainfall and low humidity periods (Table 5.8). Rainfall gave a better fit by AIC, so this is presented in the formal comparison of season definition in Table 5.9. This comparison found similar results to the original model which used a uniform season definition with odds ratios of 1.5 (95% CI 1.4-1.7) compared to 1.7 (95% CI 1.6-1.9) for dry season measures and 6.7 (95% CI 1.6-29) compared to 7.3 (95% CI 1.6-35) for outbreak measures, and profile confidence intervals for these parameters overlapping in every case.

5.3.2.3 Serogroup-specific analysis

The seasonal fixed effects parameters of the serogroup-specific models are shown in Table 5.11. Consistent with the main model of all capsulated meningococcal carriage, the four serogroup-specific models for prevalence of *Nm*A, *Nm*W, *Nm*X, and *Nm*Y suggest that meningococcal carriage prevalence increases rapidly in childhood and peaks between 8 and 14 years of age, and gradually declines after this point with the exception of a possible increase in *Nm*Y carriage in older adults (Figure 5.8). The models predicted the earliest peak for *Nm*A (8 years), followed

Table 5.8 Single variable and multi-variable risk factor analysis for carriage of capsulated meningococcal carriage with age and outbreak setting included as *a priori* variables.

Factor	Single variable analysis Odds ratio (95% profile CI)	Multi-variable model Odds ratio (95% profile CI)
Natural cubic spline of age		
Spline I		3.4 (2.9-4.1)
Spline II		2.0 (1.6-2.4)
Spline III		5.1 (3.7-7.1)
Spline IV		0.78 (0.70-0.86)
Outbreak		
No		1.0
Yes		5.0 (1.1-24)
Rainfall		
More than 1 mm daily	1.0	1.0
Less than 1 mm daily	1.7 (1.6-1.9)	1.7 (1.6-1.9)
Specific humidity		
More than 16g per kg	1.0	
Less than 16g per kg	1.7 (1.5-1.8)	
Population density (median cutoff)		
Fewer than 300 persons per km^2	1.0	
More than 300 persons per km^2	0.72 (0.32-1.7)	
Population density (mixture model)		
Rural	1.0	
Urban	0.73 (0.32-1.8)	

Table 5.9 Comparison of fixed effects parameters for model of meningococcal carriage prevalence using uniform dry season definition (December to June) and rainfall-dependent definition (less than 1mm average rainfall during swabbing period).

Factor	With uniform season definition Odds ratio (95% CI)	With climactic indicators Odds ratio (95% CI)
Natural cubic spline of age		
Spline I	3.4 (2.9-4.1)	3.4 (2.9-4.0)
Spline II	2.0 (1.6-2.4)	2.0 (1.6-2.4)
Spline III	5.2 (3.7-7.2)	5.1 (3.7-7.1)
Spline IV	0.79 (0.71-0.87)	0.78 (0.70-0.86)
Season		
Rainy	1.0	1.0
Dry	1.5 (1.4-1.7)	1.7 (1.6-1.9)
Outbreak	6.7 (1.6-29)	7.3 (1.6-35)

by *Nm*X (9.5 years), *Nm*W (10 years), and the latest peak for *Nm*Y (14 years). Consistent with this, in a country with the same population structure as Niger, the models estimate that more than 61% of *Nm*A, *Nm*W, and *Nm*X carriers are under the age of 16 compared to just 47% of *Nm*Y carriers (Table 5.10). I found the lowest overall prevalence for *Nm*A, peaking at less than 0.002% during the rainy season, and the highest overall prevalence for *Nm*W (0.6% during the rainy season).

Odds of carriage were significantly increased during the dry season for *Nm*A (OR 1.9 95% CI 1.2-3.0), *Nm*X (OR 2.1 95% CI 1.8-2.4), and *Nm*Y (OR 1.4 95% CI 1.2-1.7), but not for *Nm*W (OR 0.87 95% CI 0.66-1.1) and further significantly increased during outbreaks for *Nm*A

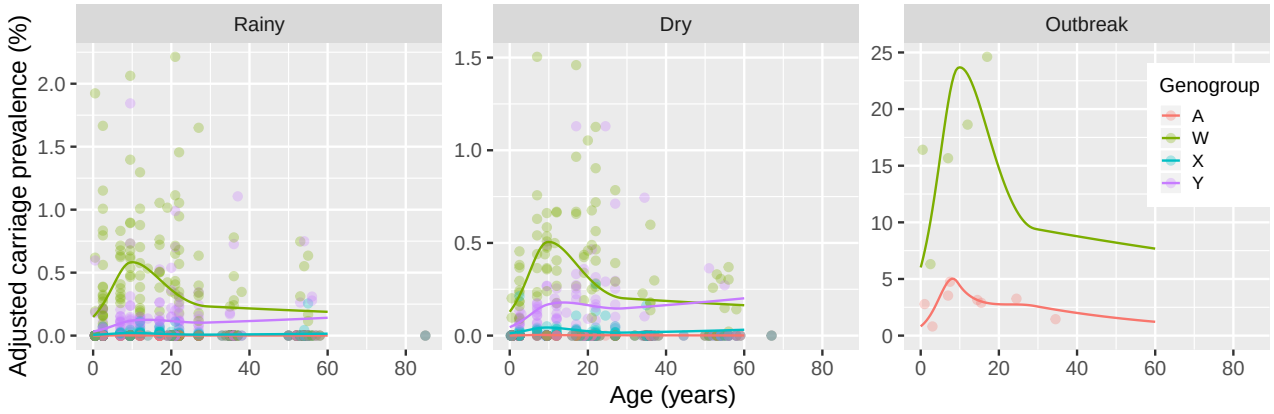


Fig. 5.8 Observed carriage prevalence and model predictions by serogroup and season. Circles show the data points included in the sub-analysis, with carriage prevalence adjusted for random effects intercept. Solid line shows model predictions excluding random effects. *Nm*A shown in red; *Nm*W in green; *Nm*X in blue; *Nm*Y in purple.

Table 5.10 Target age for vaccination: proportion of carriers of *Nm*A, *Nm*W, *Nm*X, and *Nm*Y under 60 years of age directly targeted by vaccination of different age groups.

	Serogroup			
Age group	*Nm*A	*Nm*W	*Nm*Y	*Nm*X
Under 16	61%	64%	47%	63%
Under 18	66%	70%	52%	68%
Under 20	70%	74%	57%	72%
Under 30	84%	86%	73%	82%

(OR 2700 95% CI 28-2.9$x10^6$) but not for *Nm*W (OR 41 95% CI 0.87-2200) (Table 5.11). No data on carriage during outbreaks caused by *Nm*X or *Nm*Y were included in the meta-analysis, so outbreak trends for these serogroups could not be assessed.

Table 5.11 Odds of carriage for dry and outbreak measures as compared to rainy season measures for the serogroup-specific fits.

	Odds ratio (95% profile CI)	
Serogroup	Dry season	Outbreak
NmA	1.9 (1.2-3.0)	2700 (28-2.9×10^6)
NmW	0.87 (0.66-1.1)	41 (0.87-2200)
NmY	1.4 (1.2-1.7)	
NmX	2.1 (1.8-2.4)	

The introduction of MenAfriVac decreased the odds of *Nm*A carriage by a factor of 0.01 (95% CI 0.002-0.03) (Table 5.12). The addition of the vaccination fixed effect did not have a significant impact on the other fixed effects terms (age, season) in the model.

Table 5.12 Impact of MenAfriVac introduction on carriage of *Nm*A, adjusting for age and season as fixed effects and location as a random effect.

Factor	*Nm*A carriers (Proportion of total subjects)	Odds ratio (95% profile CI)
MenAfriVac introduced		
No	252/70326 (0.36%)	1
Yes	2/41129 (0.0049%)	0.010 (0.0017-0.033)
Season		
Rainy	72/63278 (0.11%)	1
Dry	82/47264 (0.17%)	1.9 (1.2-2.9)
Outbreak	100/913 (11%)	1800 (8.8-3.6×10^7)

5.4 Discussion

Meningococcal carriage rates in the African meningitis belt were significantly higher in individuals aged 5 to 19 than in age groups outside this range. A logistic regression showed that carriage prevalence increases from a minimum in infants to a broad peak in children centred at age 10 (1.94% in the rainy season, 95% CI 1.87-2.47%), then gradually decreases in later adolescence and adulthood. The trends in prevalence by age captured by the model are broadly consistent with contact studies in the sub-Saharan Africa, which find the highest intensity of contacts in 5- to 15-year-olds, especially close physical contacts and contacts with individuals outside of the household.[186] In the context of future strategies for use of the pentavalent meningococcal conjugate vaccine, this work shows that a substantial proportion of meningococcal carriers could be targeted while lowering the upper threshold for vaccination from 29 years of age to 17 or 19 years of age. However, 17% of carriers in the data that informed the model carried non-groupable strains, which would not be targeted by a pentavalent vaccine but are also unlikely to be hypervirulent.[187]

The dry season in the African meningitis belt is characterised by low humidity, high temperatures, increased wind speed, and high levels of airborne dust.[43,125] I found that the odds of carriage were significantly increased during the dry season and further increased during outbreaks, all of which occurred during the dry season. This finding is consistent with mathematical modelling which has shown that seasonal forcing in transmissibility of carriage is necessary to reproduce the extreme variability and scale of meningitis incidence characteristic of the African meningitis belt.[39] This finding is also consistent with in vivo studies in mice and in vitro studies of human neutrophils which have shown that exposure to dust is associated with reduced bacterial killing and increased bacterial load in the nasopharynx.[38] This finding was robust to variations in the definition of the dry season, with average rainfall being a slightly better predictor of prevalence than humidity.

It is also demonstrated consistently across multiple studies. One study, MenAfriCar 2015, showed a strong opposite effect when fit with a mixed effects model but the trend was consistent with the others when fit with a fixed effects model.[40] The mixed effects model compares carriage prevalence only in the same year, whereas the fixed effects model compares carriage prevalence

over the entire study. The prevalence of carriage in the MenAfriCar study is lower in the 2010 dry season than in the 2010 rainy season: 0.2% compared to 1.5% (see Table 5.7). In 2012, the prevalence of carriage is higher in the dry season (2.9%) than in the rainy season (0%), but the sample size in the rainy season is particularly small (n=304). This is why the odds ratio in the mixed effects model, which separates comparisons by year, favours higher prevalence in the rainy season.

However, it is important to emphasize that the increased odds of carriage during the dry season and during outbreaks are not sufficient to fully account for the dramatic increase in disease incidence observed during these periods. There is evidence that individual susceptibility to invasive disease also increases during the dry season and during outbreaks.[35]

The serogroup-specific analysis showed some significant differences between serogroups by season, but patterns by age did not vary substantially. It is interesting to note the much higher prevalence of carriage of serogroups W and Y compared to A. This has relevance both for modelling the impact of and designing studies to demonstrate the efficacy of the pentavalent pneumococcal conjugate vaccine. It is unfortunate that I did not have sufficient data to investigate patterns of serogroup C carriage, an important cause of bacterial meningitis in the belt following the emergence of a novel strain in Nigeria in 2013.[47] This is something that will be important to study in the future.

Mass group A conjugate vaccination has no significant effect on overall carriage prevalence in the model. Serogroup A meningococci accounted for just 10% of all carriage isolates in pre-vaccine studies (Table 5.4), so it is not surprising that the overall model did not capture any change due to vaccine-related reductions in group A carriage. As expected, carriage of group A meningococci substantially decreased from 0.4% overall before mass campaigns to less than 0.005% overall after (OR 0.01 95% CI (0.002-0.03)).

This model has some limitations. Cross-validation predictions are well correlated with true prevalence (Pearson's ρ 0.89), but substantial variability in carriage prevalence remains unexplained, with fewer than half of observations falling within the 95% confidence intervals for model predictions. There is additional missing uncertainty in the model due to the assumption that all individuals in a given age group are of the median or midpoint age which is not captured by the bootstrapping process. The amount of information which is lost by grouping individuals by age could be tested by fitting the same model to grouped and ungrouped data and comparing the results. Another approach could be to use a Monte Carlo approach to estimate the underlying function of carriage by age, simulating the grouping process in addition to the uncertainty arising from binomial samples. Additional variability may also be driven by heterogeneity between serogroups, differences in the intensity of seasonality at different sites and different sampling times, and a variety of other risk factors, including smoke exposure, crowded housing conditions, and upper respiratory infection, which are not measured or reported. Some of these individual- and household-level risk factors are investigated in the following chapter.

The model is principally informed by two large serial cross-sectional studies carried out between 2009 and 2012, one based in Burkina Faso (50,810 subjects)[41,73,168] and the multi-country African Meningococcal Carriage Consortium study (48,405 subjects).[40] The results of the study in Burkina Faso were reported over three manuscripts but they used the same study sites, staff, and sampling and laboratory procedures. These are both high quality characteristic multi-site studies, but this does mean that the majority of the data that informed the model come from a particular time period. Thus, while these findings may not necessarily be useful for explaining historical trends, including *Nm*A epidemics, they should be useful in guiding modelling and policy decisions around non-*Nm*A meningitis prevention.

Gender was not included in the model because this was not consistently reported, but the age distribution of carriage may be modified by gender because of differences in social behaviour.[188] A number of studies have also shown higher prevalence of carriage in males overall, but this would not be expected to bias the results of this analysis unless the gender distribution of participants were substantially different between age groups.[40,127] There was no significant difference in carriage prevalence between densely and sparsely populated locations, although a prior study which was included in this meta-analysis did demonstrate increased odds of carriage in rural locations.[40]

Because of the sparseness of sampling in older age groups, a linear relationship between carriage prevalence and age above 30 years was assumed. As a result, carriage appears to decline steadily throughout middle and later adulthood. In reality, carriage may increase in the elderly as immunity wanes. Further study of this age group will be important as older people comprise an increasing proportion of the population in the African meningitis belt.

This chapter finds that older children in the African meningitis tend to be the age group in which carriage is most prevalent. The odds of carriage are significantly higher during the dry season and during outbreaks, and carriage of group A meningococci has substantially decreased in countries where mass MenAfriVac vaccination has been implemented. Given the importance of herd protection from conjugate vaccines, this meta-analysis may help to guide vaccination policy, both to maintain control of group A disease and in the implementation of effective and affordable multivalent vaccination programmes.

Chapter 6

Risk factors for acquisition of meningococcal carriage: a longitudinal household study

This work was undertaken in collaboration with the African Meningococcal Carriage Consortium, the members of which conducted a multi-site serial cross-sectional carriage study in the African meningitis belt between 2010 and 2012. Anna Robson, Caroline Trotter, and James Stuart provided input on the statistical analysis and the interpretation of the findings. I carried out the analysis and wrote the first draft of the manuscript. All authors contributed to the editing and review of the final manuscript. A version of this chapter has been published in Tropical Medicine and International Health (see Appendix A).

6.1 Introduction

The African Meningococcal Carriage Consortium (MenAfriCar) undertook 20 cross-sectional carriage surveys in seven African meningitis belt countries from July 2010 to July 2012, involving the collection of over 48 000 pharyngeal swabs. These studies found a higher frequency of carriage in children aged 5-14 years, in the dry season and in rural populations.[40] During these surveys, households with at least one pharyngeal carrier of *N. meningitidis* were recruited for longitudinal studies.[14] Previous longitudinal studies in the meningitis belt have been undertaken mainly at the population level.[57,168,169] Fewer have investigated the transmission and acquisition of carriage at an individual level.[13,127] The aim of this study was to investigate a comprehensive set of potential risk factors for the acquisition of carriage of *N. meningitidis* across the African meningitis belt.

6.2 Methods

6.2.1 Household surveys

Households included in this study were recruited during the course of cross-sectional surveys conducted in seven countries in the African meningitis belt (Chad, Ethiopia, Ghana, Mali,

Niger, Nigeria, and Senegal) in 2010, 2011, and 2012.[40] Details of the survey methods employed have been published previously.[14] Longitudinal surveys were triggered by the identification of a putative carrier during a cross-sectional survey (Visit 0). This initial identification of carriers relied on conventional microbiology and was later confirmed via molecular methods at the University of Oxford. In some cases, molecular methods did not confirm the presence of meningococci, so 51 of 184 households recruited to the study did not have an index carrier.

Within four weeks of the identification of a carrier, all members of the putative carrier's household were invited to take part in further studies (Visit 1). The head of the household was asked about characteristics of the household, including numbers of rooms and bedrooms, sleeping arrangements, location of kitchen, type of cooking fuel, house construction, drinking water source, toilet facilities, and household assets such as vehicle ownership, livestock, and electrical goods.

A pharyngeal swab sample was obtained from all members of a household who gave their consent and a questionnaire completed which included questions on: smoking, social activities, symptoms of recent respiratory tract infection, socio-economic status and educational level, school attendance, travel history, recent medication including antibiotics, meningitis vaccination, and ethnic group. Carrier households were followed up bi-weekly for two months (Visits 2-5) and monthly for a further four months (Visits 6-9). At each follow up visit, each household member was asked for a pharyngeal swab sample and to answer a short follow-up questionnaire on factors that might have changed since the previous visit, such as symptoms of a respiratory tract infection.

6.2.2 Laboratory methods

Pharyngeal swab samples, taken from the posterior pharynx and tonsillar fossa via the mouth, were plated directly onto Modified Thayer Martin agar plates in the field, taken to the laboratory within six hours of collection, and processed as previously described.[14] A sample of boiled suspensions of Gram negative oxidase positive bacteria was sent to the University of Oxford for molecular analysis. Amplification and sequencing of the rplF gene was used to confirm the presence of, and differentiate between, Neisseria species. Confirmed *N. meningitidis* were further characterised by genogroup (including capsule null) and *porA* genosubtype.

6.2.3 Data management

Data were managed using the Teleform system (version 10.4.1, Autonomy, Cambridge UK) with a separate database module linking the main study database with genetic laboratory results from the Oxford PubMLST database (https://pubmlst.org/neisseria). Data from the longitudinal questionnaires were merged using a common person ID, or census number, person matching was checked, any duplicate entries were removed, and aberrant values excluded.

6.2.4 Statistical analysis

Genogroup-specific acquisition rates were calculated as Poisson rates, counting as events the number of acquisitions occurring in non-index carriers and time at risk as the days between the first carriage-negative swab and the first positive swab. A series of fixed-effects logistic regressions were used to identify significant risk factors for acquisition. In the first round of regressions, individual risk factors were included in a multivariable logistic regression with the *a priori* variables sex, age group, and country. In the second round, risk factors with $p<0.1$ in round 1 were added to a single model with *a priori* variables. In the third round, risk factors with $p<0.05$ in round 2 were retained in the multivariable model. In the fourth round, all factors dropped in round 3 were added back in to the model one by one and all variables with $p<0.05$ were retained, giving the final models. The study-long and visit-by-visit models were then run with household ID and both household and individual ID as random effects, respectively, to account for study design, and factors that were no longer significant ($p\geq0.05$) were dropped.

Acquisition was assessed over the full study period (study-long) and visit-by-visit. Individuals were defined as positive for study-long acquisition if they had a negative swab (no meningococci isolated) at visits 0 or 1 and a positive swab (any meningococci isolated) at any following visit. Individuals were defined as negative for study-long acquisition if they had a negative swab at visits 0 or 1 and no positive swab at any subsequent visit. Individuals with three or more missed visits in total were excluded, as the possibility of acquisition during this missed period could not be ruled out, and individuals carrying at visits 0 or 1 were also excluded.

Individuals were defined as positive for visit-by-visit acquisition on a given visit if the individual had a positive swab at the current visit and a negative swab at the previous visit or carried a different strain at the previous visit and the strain was not previously carried during the study. Strains were assessed by genogroup and porA variable regions 1 and 2. Individuals were defined as negative for visit-by-visit acquisition on a given visit if the individual had a negative swab at the previous visit and a negative swab at the current visit. Individuals carrying an identical strain to that obtained at the previous visit and individuals who cleared carriage were excluded from the analysis. Tables 6.1 and 6.2 provide the classification of cases for study-long and visit-by-visit acquisition.

Table 6.1 Case definition for study-long acquisition.

Classification	Carriage at visits 0 or 1	Carriage at visits 2-9	More than 3 missed visits	Number of individuals
Not acquisition	No	No	No	692
Acquisition	No	Yes	No	169
Excluded	No	No	Yes	231
Excluded	No	Yes	Yes	18
Excluded	Yes	No	No	42
Excluded	Yes	No	Yes	18
Excluded	Yes	Yes	No	159
Excluded	Yes	Yes	Yes	22

Table 6.2 Case definition for visit-by-visit acquisition.

Classification	Carriage at previous visit	Carriage at current visit	Strain previously observed	Number of visit pairs
Not acquisition	No	No	Not applicable	6768
Acquisition	No	Yes	No	226
Acquisition	Yes	Yes	No	47
Excluded	No	Yes	Yes	183
Excluded	Yes	Yes	Yes	366
Excluded	No	No data	Not applicable	1180
Excluded	Yes	No	Not applicable	516
Excluded	Yes	No data	Not applicable	128
Excluded	No data	No	Not applicable	1677
Excluded	No data	Yes	Not applicable	304
Excluded	No data	No data	Not applicable	2115

The dry season was defined as January to May and the rainy season as June to December. Because I found a significant association between sore throat and season and because previous studies have demonstrated an interaction between meningococcal carriage, upper respiratory tract infection, and season, I also tested for interaction between sore throat and season in the final model and found that the model with an interaction term fitted better than the model with no interaction (Tables 6.3 and 6.4).

Table 6.3 Odds of sore throat adjusting for age, country, sex and season.

Factor	Total	Reporting sore throat (%)	OR	95% CI
Age (years)				
30 plus	2024	6.6	1	
Under 5	1914	2.4	0.372	(0.261, 0.522)
5–14	2806	2.6	0.399	(0.295, 0.534)
15– 29	1752	7.4	1.13	(0.873, 1.45)
Country				
Chad	1038	5.8	1	
Ethiopia	940	7.1	1.27	(0.883, 1.83)
Ghana	1135	8.6	1.41	(1.01 , 1.98)
Mali	1854	1.1	0.174	(0.101, 0.287)
Niger	3179	4.3	0.728	(0.532, 1.01)
Senegal	350	0		
Sex				
Female	4424	4.3	1	
Male	4072	4.6	1.14	(0.92 , 1.4)
Season				
Rainy: June to December	3617	4.4	1	
Dry: January to May	4879	4.5	1.27	(1.02 , 1.57)

6.2.5 Ethics

The study was approved by the ethics committee of the London School of Hygiene and Tropical Medicine and by the relevant ethical authorities in each African centre.[14] The head of the household or another responsible adult gave verbal informed consent for the household to be included in the study. Each individual recruited within the household gave written informed

Table 6.4 Likelihood ratio test comparing visit-by-visit model with and without term of interaction between season and sore throat.

Additional variables	Degrees of freedom	AIC	BIC	Log-likelihood	Deviance	Chi-square Statistic	p-value
Sore throat	14	1660	1754	-815.82	1631.6		
Sore throat, season	15	1662	1763	-815.77	1631.5	0.099	0.75
Sore throat, season, interaction	16	1656	1764	-811.97	1623.9	7.6	0.006

consent; for children under the age of 18 years a parent or guardian gave written consent and children aged over 12 years were additionally asked to give written assent.

6.3 Results

6.3.1 Acquisition over course of the study

Overall, 169/861 (20%) of non-index carriers acquired carriage at least once over the course of the study. A higher proportion of 5- to 14-year-olds acquired carriage than other age groups, and a higher proportion of participants acquired carriage in Senegal, Niger, Ghana, and Ethiopia relative to Chad and Mali (Table 6.5).

A wide variation in acquisition rates and predominant serogroups was observed between countries. *Nm*A was predominant in Chad, *cnl* and *Nm*Y in Ethiopia, *Nm*W in Ghana and Mali, *cnl* and *Nm*W in Niger, and *Nm*W and Y in Senegal. Genogroup W and capsule-null (*cnl*) meningococci accounted for the majority (83%) of acquisitions. The acquisition rate of genogroup W meningococci was 2.0% per month (95% CI 1.6-2.4): roughly double that of *cnl* meningococci at 1.0% per month (95% CI 0.74-1.4). Genogroups A, C, Y, and other genogroup (i.e. other than A, B, C, W, X, Y, or *cnl*) acquisitions were uncommon, and no genogroup B or X acquisitions were detected.

Table 6.5 Risk factors for *Neisseria meningitidis* acquisition over the full study period: single risk factor analysis and multi-variable model. Adjustment was made in both single and multi-variable analysis for age, country and sex. N.B. Total number of individuals may not sum to 861 in every case because of missing values. * p-value less than 0.1 in single risk factor analysis. §p-value less than 0.05.

Factor	Single risk factor analysis				Multi-variable model			
	Total	Acquisition (%)	OR	95% CI	Total	Acquisition (%)	OR	95% CI
Age (years)								
30 plus					205	11.7	1	
Under 5					91	28.6	3.12	(1.27 , 8.05)
5–14					108	23.1	3.62	(1.42 , 9.93)
15–29					161	21.1	2.38	(1.22 , 4.76)
Country								
Chad					54	5.6	1	
Ethiopia					64	26.6	7.65	(1.81 , 44.4)
Ghana					74	23.0	6.77	(1.52 , 40.1)
Mali					157	5.7	0.532	(0.110, 3.22)
Niger					206	28.6	10	(2.53 , 57.3)
Senegal					10	40.0	13.3	(1.23 , 159)
Sex								
Female					326	17.5	1	
Male					239	21.8	1	(0.585, 1.71)
Exposure to wood smoke in house (apart from cooking)*								
No	372	20.2	1		261	19.2	1	
Yes	478	19.0	2.74	(1.76 , 4.32)	304	19.4	2.6	(1.26 , 5.59)
Tobacco exposure*								
None	234	14.1	1		230	13.5	1	
Passive smoke	312	22.8	1.92	(0.965 , 3.77)	312	22.8	1.92	(0.823, 4.55)
Active smoker	23	30.4	3.75	(1.23 , 10.8)	23	30.4	3.57	(0.978, 13.0)§
Any sore throat reported *								
No	651	17.8	1					
Yes	208	25.5	1.66	(1.09 , 2.53)				
Any runny nose reported *								
No	184	20.7	1					
Yes	675	19.4	1.57	(0.995 , 2.51)				
Use gas as primary cooking fuel*								
No	832	20.0	1					
Yes	25	12.0	0.311	(0.0664, 1.03)				

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Table 6.5 – *Continued from previous page*

Factor	Single risk factor analysis				Multi-variable model			
	Total	Acquisition (%)	OR	95% CI	Total	Acquisition (%)	OR	95% CI
Completion of primary school (over 17 years)*								
No	269	18.2	1					
Yes	99	11.1	0.381	(0.170 , 0.793)				
Household member completed secondary school*								
No	444	22.3	1					
Yes	415	16.9	0.67	(0.455 , 0.983)				
More than 2 participants per room*								
No	484	14.5	1					
Yes	375	26.4	1.44	(0.996 , 2.10)				
Attending primary school (ages 5 to 17)								
No	52	25.0	1					
Yes	254	23.2	0.721	(0.325 , 1.65)				
Regular social meetings								
None	202	20.3	1					
1–2 per week	68	16.2	0.916	(0.404 , 1.96)				
3–4 per week	48	8.3	0.531	(0.141 , 1.61)				
5–7 per week	52	5.8	0.356	(0.0793, 1.14)				
Index carrier in household								
No	259	12.0	1					
Yes	600	23.0	1.32	(0.826 , 2.16)				
Use wood as primary cooking fuel								
No	31	12.9	1					
Yes	828	19.9	1.02	(0.340 , 3.83)				
Indoor kitchen								
No	660	16.4	1					
Yes	199	30.7	1.28	(0.838 , 1.94)				

In the final multivariable model, the highest odds of acquisition were among 5- to 14- year olds, with odds in all age groups under 30 years of age being significantly higher than the reference group of individuals 30 years and older (Table 6.5). Active smokers had higher odds of acquiring carriage than non-smokers living in households with no smokers, with a lower confidence bound just below 1 (OR 3.57 95% CI 0.98-12.99). Non-smokers living in households with smokers also had elevated odds of acquisition but the difference was not statistically significant. Wood was the ubiquitous cooking fuel, with 96% of participants using this as cooking fuel; 56% of participants had additional wood smoke exposure. Participants with household exposure to wood smoke (independent of using wood as cooking fuel) had higher odds of acquiring carriage than those without (OR 2.60 95% CI 1.26-5.59). Although not significant in the regression analysis, higher acquisition rates were observed in households with an indoor kitchen and in households which used wood as the primary cooking fuel than in those who did not.

6.3.2 Visit-specific acquisition analysis

Participants who reported sore throat since the previous visit during the dry season were significantly more likely (OR 3.67 95% CI 1.95-6.65) to have acquired carriage in that time period than those who did not have a sore throat in the rainy season (Table 6.6). Those who reported taking antibiotics since the previous visit were significantly less likely (OR 0.169 95% CI 0.0271-0.564) to have acquired carriage.

Table 6.6 Risk factors for visit-by-visit *N. meningitidis* acquisition: single risk factor analysis and multi-variable model. Adjustment was made a priori in both single and multi-variable analysis for age, country, and sex. *p-value less than 0.1 in single risk factor analysis.

Factor	Single risk factor analysis				Multi-variable model			
	Total	Acquisition (%)	OR	95% CI	Total	Acquisition (%)	OR	95% CI
Age (years)								
30 plus					1504	1.8	1	
Under 5					1539	3.4	1.99	(1.22 , 3.32)
5–14					2129	4.2	2.76	(1.75 , 4.48)
15–29					1239	3.0	1.83	(1.08 , 3.15)
Country								
Chad					990	0.6	1	
Ethiopia					564	4.6	7.54	(2.59 , 24.5)
Ghana					828	3.5	5.7	(1.96 , 18.6)
Mali					1574	0.9	1.51	(0.483 , 5.13)
Niger					2281	5.2	11.5	(4.53 , 34.5)
Senegal					174	7.5	14.2	(3.6 , 60.7)
Sex								
Female					3405	2.9	1	
Male					3006	3.6	1.23	(0.907 , 1.68)
Antibiotic taken*								
No	6592	3.5	1		6150	3.3	1	
Yes	261	0.8	0.197	(0.0323, 0.623)	261	0.8	0.169	(0.0271, 0.564)
Interaction term*								
No sore throat, rainy	2643	3.3	1		2643	3.3	1	
No sore throat, dry	3481	2.8	0.88	(0.651 , 1.19)	3481	2.8	0.844	(0.617 , 1.16)
Sore throat, rainy	123	2.4	0.906	(0.218 , 2.52)	123	2.4	0.82	(0.192 , 2.39)
Sore throat, dry	164	11	3.72	(2.09 , 6.34)	164	11	3.67	(1.95 , 6.65)
Sore throat*								
No	6566	3.3	1					
Yes	287	7.3	2.64	(1.58 , 4.19)				
Season								
Rainy: June to December	1944	3.1	1					
Dry: January to May	4467	3.3	1.07	(0.78 , 1.47)				
Meningitis vaccination								
No	5743	3.7	1					
Yes	1110	2.0	1.54	(0.899 , 2.55)				
Attendance at social event								
No	3319	4.4	1					

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Table 6.6 – *Continued from previous page*

Factor	Single risk factor analysis				Multi-variable model			
	Total	Acquisition (%)	OR	95% CI	Total	Acquisition (%)	OR	95% CI
Yes	3534	2.5	0.851	(0.63 , 1.14)				
Travel greater than one hour								
No	6055	3.6	1					
Yes	798	2.0	0.955	(0.538 , 1.58)				
Cough								
No	5163	3.6	1					
Yes	1690	3.0	0.955	(0.682 , 1.31)				
Runny nose								
No	4634	3.8	1					
Yes	2219	2.6	0.961	(0.689 , 1.32)				

6.4 Discussion

This longitudinal study found a higher risk of acquisition amongst individuals who reported a sore throat since the previous visit, but only during the dry season. An association between an upper respiratory tract infection and meningococcal carriage has been reported previously.[127] A sore throat could be caused by an initial inflammation of the pharynx from meningococcal colonisation or by a concurrent unrelated infection that predisposes an individual to acquisition.[189] If the latter is true, upper respiratory tract infection in combination with dust and low humidity may be an important driver for the high risk of meningitis epidemics in the dry season. This hypothesis is supported by a recent study indicating an association between incidence of upper respiratory tract infection (otitis, severe sore throat, and rhinopharyngitis) and meningitis outbreaks in Burkina Faso.[190] Such infections could plausibly increase both the risk of acquisition and the risk of invasion after acquisition.

The 5-14 year-old age group had the highest acquisition rate. The highest prevalence of carriage in cross-sectional MenAfriCar studies was similarly highest in 5-14 year olds.[40] An overall acquisition rate of 2.4% (95% CI 1.6 to 4.0%) per month was estimated from this same study using a hidden Markov model.[14] There were no significant differences reported by age group, but data were subdivided by control and index households and there was no adjustment for exposure to other risk factors.

Additional factors linked to acquisition of meningococci over the course of this study were smoking tobacco and exposure to wood smoke. Smoking, passive exposure to smoke, and to smokers has been shown to convey a high risk of carriage and invasive disease in high-income countries.[191–194] Exposure to cigarette smoke has also been linked to the risk of carriage in the meningitis belt.[40,127] The higher risk of acquisition from smoke exposure in this study suggests a direct risk from smoke itself, potentially from interference with mucosal immunity, as exposure to wood smoke was an independent risk factor. Exposure to smoke from wood fires has also been shown as a risk factor for meningococcal meningitis in northern Ghana.[195] Although use of wood as primary cooking fuel was not found to be a significant risk factor, this could be explained by the fact that nearly all study participants relied on wood as primary fuel.

Strengths of this study are the multi-centre design, including a mix of urban and rural populations with a broad age range, the use of standardised field and laboratory protocols, and large sample size. Measuring acquisition rather than carriage ensures that the risk factors identified in this study are not biased by factors associated with longer carriage duration. A comprehensive range of risk factors was included, so that important confounding factors are unlikely to have been missed; however, the sampling of carriers and non-carriers was not random and some misclassification of carriage status is expected.

The acquisition of meningococci measured in this longitudinal study and the prevalence of carriage in the MenAfriCar cross-sectional studies varied considerably by country. Although laboratory methods were standardised across centres, differences in laboratory techniques

and conditions could still have contributed to some of the differences observed. As most meningococcal acquisitions were either genogroup W or capsule null and outside epidemics, it cannot be assumed that risk factors for acquisition of other genogroups or during epidemics would be the same as those identified in this study.[109]

Chad and Mali had the lowest risks of carriage acquisition: about 5% over the course of the study, whereas the other countries had more than 20% acquisition. It is possible that differences in laboratory conditions could have negatively affected the sensitivity of culture in Chad and Mali. The cross-sectional study also found especially low carriage prevalence in these two countries (between 0.5 and 1.7% compared to an average of 3.4%).[40] Most of the isolates in the household study in Chad were NmA (25 of 37) and a high proportion of participants reported receiving a recent meningitis vaccine which was likely MenAfriVac (59%). Vaccination may have reduced transmission of *Nm*A carriage in Chad. In Mali, a high proportion of households lacked index carriers (70%), but acquisition rates were not significantly different in households with index carriers (4 in 66 compared to 6 in 129).

It was surprising that some risk factors such as household crowding that have previously been found to raise the risk of carriage and disease[13,40,196,197] were not associated with acquisition in this study. Crowding was measured by number of individuals sharing a bedroom or bedmat, and by numbers of study participants per room in the household. It is possible that crowded living conditions are so prevalent across the study locations that any effect of crowding on acquisition is not detectable. A study in rural Gambia did not find any differences in crowding between compounds with and without cases of meningococcal meningitis during an epidemic.[198]

This is the largest longitudinal household study of meningococcal carriage in the African meningitis belt to date. One previous longitudinal study had a similar design to this one, sampling members of 37 randomly-selected households in Ghana five times between March 1998 and April 2000.[199] Other household studies have examined prevention of secondary cases of disease by vaccination or chemoprophylaxis for household contacts[200,201] and the global spread of novel variants by Hajj pilgrims to their household contacts.[202,203]

It was not possible to draw any conclusions regarding the relationship between carriage acquisition and disease incidence because none of the study sites reported an outbreak of meningitis during the follow-up period.

Reported vaccination was clustered in particular time periods and countries corresponding to the introduction of group A conjugate vaccine. Vaccination was not found to be protective against carriage acquisition. However, group A conjugate vaccination would not be expected to have a significant impact on carriage in this study as very few group A carriers were detected.

Longitudinal acquisition studies like this one could be used to estimate the efficacy of the new pentavalent meningococcal conjugate vaccine NmCV-5.[204] Further specifics would need to be defined, including whether the comparator would take the form of a non-meningococcal vaccine that did not interfere with the nasopharyngeal environment (measuring efficacy directly) or a currently licensed polyvalent meningococcal conjugate vaccine (measuring non-inferiority),

and whether to measure the effect of the vaccine on acquisition, carriage duration, or both.[205] Longitudinal studies allow measurement of the vaccine effects on both acquisition rates and carriage duration. A Markov model could be used to analyse the resulting data. This method was used to estimate acquisition, clearance, and replacement rates of 27 pneumococcal serotypes in Kenyan children.[17] In this study design it would be important to designate carriage of each serogroup as a separate state, because combining states tends to underestimate acquisition rates and overestimate carriage duration.[17] This would also necessitate a larger study to accurately estimate the additional parameters. Unfortunately, two of the most important causes of outbreaks, *Nm*C and X, were found very rarely in this study. It is not too surprising that *Nm*C was rarely observed because the study took place before the emergence of the hypervirulent *Nm*C strain. Given the dynamic nature of meningococcal carriage in the African meningitis belt, it might be advantageous to run a pilot study across multiple sites to identify places where transmission of relevant serogroups is likely to be observed.[40] These sites could then be followed up in a longitudinal study, with sample sizes estimated from a simulation mirroring the study design and using acquisition rates observed in the pilot study.

This study demonstrated significantly higher acquisition among individuals under 30 years of age, with the highest rate in 10- to 14-year olds, and significantly higher acquisition among individuals reporting sore throat, particularly in the dry season. These findings are consistent with the findings in Chapter 5, which identified a peak in meningococcal carriage prevalence around 10 years of age and significantly higher odds of carriage in the dry season compared to the rainy season. This analysis adds individual risk factors which could not be evaluated in the meta-analysis, highlighting respiratory infection as a potential explanation for the observed seasonality in carriage prevalence. However, this finding is difficult to interpret with certainty because a sore throat could be directly caused by meningococcal colonisation or by a concurrent unrelated infection that predisposes an individual to acquisition. Further research on interactions in the pharyngeal microbiome could help to clarify this relationship.

Chapter 7

Spatio-temporal analysis of serogroup C meningococcal meningitis spread in Niger and Nigeria and implications for epidemic response

This work was undertaken in collaboration with Olivier Ronveaux and Katya Fernandez from the Department of Pandemic and Epidemic Diseases at the World Health Organization in Geneva, Switzerland, Clement Lingani from the Inter-country Support Team for West Africa at the World Health Organization in Ouagadougou, Burkina Faso, Kadade Goumbi from the Ministry of Public Health of Niger, Chikwe Ihekweazu from the Nigeria Center for Disease Control, and Marie-Pierre Preziosi and Antoine Durupt from the Department of Immunization, Vaccines and Biologicals at the World Health Organization in Geneva, Switzerland. A version of this work excluding the Kulldorff spatio-temporal scan and the conjugate vaccination analyses is published in the Journal of Infectious Diseases (see Appendix A). Clement Lingani, Kadade Goumbi, and Chikwe Ihekweazu provided access to the surveillance data used in this analysis. Olivier Ronveaux, Katya Fernandez, Marie-Pierre Preziosi, and Antoine Durupt provided policy guidance to inform the conceptualisation. I performed the data curation, model design, formal analysis, implementation of the code, and prepared the original draft. All authors participated in review and editing of the final manuscript.

7.1 Introduction

Since guidelines were first issued by the WHO in 1995, reactive vaccination policy in the African meningitis belt has evolved in response to changes in disease burden and continuing insights from research. This chapter aims to re-evaluate reactive vaccination policy in light of the recent emergence and continued epidemics of serogroup C meningococcal meningitis in Nigeria and Niger. Prior studies of meningitis patterns in Niger have demonstrated significant spatial heterogeneity and strong inter-annual and intra-district variation in meningitis incidence. Previous modelling studies have suggested that surveillance on finer spatial scales may improve the timeliness and targeting of epidemic response.[97,98,121] Because subdistrict-level data is not

widely available, I wanted to investigate whether vaccinating neighbouring communities at the district level might prevent more cases and allow for more efficient use of vaccine. I extend the scope of these earlier studies by including data from Nigeria in the analysis, and considering the full time period from the outbreak strain's emergence in 2013.[47]

Considering the recent use of conjugate vaccines in reactive vaccination campaigns in response to the emergence of serogroup C and in anticipation of licensure of an affordable pentavalent conjugate meningococcal vaccine for Africa, I also wished to investigate the relative benefit of the use of conjugate versus polysaccharide vaccine in reactive vaccination. Although one previous study modelled the impact of using the conjugate pentavalent vaccine for reactive vaccination in addition to mass preventative campaigns,[81] there has been no previous direct comparison of polysaccharide and conjugate vaccines in the context of reactive vaccination. These findings can help guide the International Coordinating Group (ICG) on Vaccine Provision, which manages the reactive meningococcal vaccine stockpile, in prioritising purchasing conjugate or polysaccharide vaccines.

7.2 Methods

7.2.1 Surveillance data

Surveillance data on suspected cases of meningitis from the enhanced district-level surveillance system established in 2003 were used as proxy for incidence of confirmed bacterial meningitis.[34] A suspected case is defined as any person with sudden onset of fever (>38.5°C rectal or 38.0°C axillary) and any one of the following signs: neck stiffness, flaccid neck (infants), bulging fontanelle (infants), convulsion, or other meningeal signs. Weekly district-level counts of suspected cases are collated nationally and then reported to the WHO Inter-country Support Team (WHO-IST) for West Africa. The analysis focuses on data from Niger and Nigeria during the period from 2013 to 2017, when serogroup C was dominant. Incidence was calculated using the district-level population sizes reported by each country to WHO-IST. This is a subset of the surveillance data set that is used in Chapter 3.

Annual national-level data on confirmed cases of meningitis were used to estimate the overall proportion of cases caused by serogroup C and preventable by vaccination (Table 7.1). CSF samples are tested by national reference laboratories using PCR, culture, or latex agglutination and these results are collated by WHO-IST.[130] Because of the lack of microbiological data for Nigeria in 2016, the etiological proportions were assumed to be the same as in Niger 2016 for the purposes of the model.

Anonymised line list data which includes the age of cases and more detailed laboratory confirmation data for Niger 2015 to 2017 and Nigeria 2017 were also used to validate model assumptions about the age distribution of cases and case confirmation rates during outbreak periods.

Table 7.1 Confirmed and suspected cases of meningitis and estimated proportion of suspected cases that could have been prevented by C, ACW, ACWY vaccines between 2013 to 2017 in Niger and Nigeria (*Nm* = *Neisseria meningitidis*). 95% binomial confidence intervals shown in parentheses.

			Confirmed cases						Covered by vaccine		
Year	Country	Suspected cases	Total *Nm*	A	C	X	Y	W	C	ACW	ACWY
2013	Niger	311	11	0	0	0	0	11	0% (0-28%)	100% (72-100%)	100% (72-100%)
	Nigeria	871	10	3	7	0	0	0	70% (35-93%)	100% (69-100%)	100% (69-100%)
2014	Niger	315	24	0	8	0	0	16	33% (16-55%)	100% (86-100%)	100% (86-100%)
	Nigeria	1 175	38	0	38	0	0	0	100% (91-100%)	100% (91-100%)	100% (91-100%)
2015	Niger	7 978	1436	0	1183	1	0	206	82% (80-84%)	97% (96-98%)	97% (96-98%)
	Nigeria	2 655	20	0	20	0	0	0	100% (83-100%)	100%(83-100%)	100%(83-100%)
2016	Niger	1 976	357	0	312	15	0	25	87% (83-91%)	94% (91-97%)	94% (91-97%)
	Nigeria	831	-	-	22	-	-	-	-	-	-
2017	Niger	3 387	1073	0	848	220	0	4	79% (76-81%)	79% (77-82%)	79% (77-82%)
	Nigeria	9 918	18	1	14	0	0	1	78% (52-94%)	89% (65-99%)	89% (65-99%)

7.2.2 Maps

Districts were matched to their locations on district-level maps obtained from WHO using place names. Where no match was found between the map names and a surveillance database place name, I used the GeoNames database to situate the unknown place name within a known district.[206] Large districts that divided into two or more smaller districts during the study period (2013-2017) were kept as a single district to allow for tracking of vaccine coverage over time and to avoid introducing bias by sudden population changes (Table D.1). Neighbours were defined as those districts sharing a border with the focal district. This definition of neighbouring districts included those across national borders.

7.2.3 Cluster detection

The global Moran's I statistic was used to test for non-random spatial distribution of annual cumulative incidence for each year 2013 to 2017.[207] Measures of spatial autocorrelation can be highly dependent on the imposed spatial structure, i.e. what is considered a neighbour and how each neighbour is weighted.[208] For this reason, Moran's global I statistic was calculated using three different weighting structures - by simple contiguity, great circle distance (within 50 km of centroid), and taking the five nearest neighbours, with distance calculated by great circle centroid-to-centroid (Table 7.2), using the "spdep" package in R.

Table 7.2 Moran's global I statistic for each year using three types of spatial weighting structures. P-values from 999 Monte Carlo permutations.

	Moran's global I statistic		
Year	Contiguity	Distance (50 km)	Five nearest neighbours
2013	0.28 (1e-04)	0.29 (1e-04)	0.33 (4e-04)
2014	0.19 (1e-04)	0.16 (1e-04)	0.15 (9e-04)
2015	0.23 (3e-04)	0.15 (0.0013)	0.21 (0.0012)
2016	0.49 (1e-04)	0.33 (1e-04)	0.40 (1e-04)
2017	0.69 (1e-04)	0.70 (1e-04)	0.68 (1e-04)

For the distance-based weight, distances between 20 and 100 kilometres were evaluated. Fifty kilometres was chosen because it maximised spatial effects in most years. All districts meeting neighbour criterion were weighted equally. The significance of these values was determined by rank within 999 Monte Carlo permutations.

As all weighting methods detected significant positive spatial autocorrelation of similar magnitude in each year, contiguity weights were used for the analysis of local clusters. Anselin's local Moran's I statistics were calculated for each district in each year to locate clusters of districts with high incidence or outlier districts with higher incidence than neighbours.[121,209] Both the "spdep" package in R and GeoDa software were used for methodological comparison. In GeoDa, a permutation approach with 99999 permutations was used to generate pseudo-p-values, which were then compared to the analytical results from the "spdep" package, using an overall

alpha of 0.05 and a Bonferroni adjustment for repeated testing. As the analytical p-values and the pseudo-p-values gave inconsistent results, only the clusters found significant by both methods were reported (Table D.2, Figure 7.2).

Clusters of cases in space and time were also located using the Kulldorff spatio-temporal scan implemented in SaTScan software (freely available at www.satscan.org). The Kulldorff scan statistic identifies circular windows in space with a depth of cluster time length with significantly higher case counts than under the null hypothesis, which in this case was defined as uniform incidence (Poisson-distributed case counts drawing from district population size). The p-values of the log-likelihood ratios (LLR) for clusters were estimated using 999 Monte Carlo simulations. Because this method uses points to situate cases rather than aggregated areas, the district centroid was chosen as a proxy for location of individual cases.[210] The size of the spatial cluster was allowed to range from a 0 km radius (i.e. a single district) to a maximum encompassing 50% of the total population at risk and the cluster time length to range from one week minimum to 156 weeks maximum (50% of the study period 2013-2017).

7.2.4 Definitions

Weekly suspected cases as reported are referred to as observed suspected cases (OSC), and cases expected in the absence of the vaccination campaigns taking place in selected districts in 2015, 2016, and 2017 as modelled suspected cases (MSC). Epidemic and alert incidence thresholds are consistent with current WHO guidelines, with alert defined as more than 3 suspected cases per 100,000 population per week or more than 2 cases total per week for districts with less than 30,000 population and epidemic with as more than 10 suspected cases per 100,000 population per week or more than 5 cases total per week or a doubling of cases in a two-week period for districts with less than 30,000 population.[90] A meningitis outbreak period is defined as the period of time and space in which *N. meningitidis* is the dominant cause of meningitis nationally and the incidence of OSC exceeds the alert incidence threshold.

7.2.5 Estimating cases in the absence of intervention

Reactive vaccination campaigns occurred in 2015, 2016, and 2017 in 56 districts in response to *Nm*C outbreaks using polysaccharide vaccine, monovalent C conjugate vaccine, and quadrivalent ACWY conjugate vaccine. To model suspected cases of meningitis in the absence of vaccination, the following assumptions were made: 1) 80% of suspected cases during the outbreak period are caused by *Neisseria meningitidis* (*Nm*); 2) 20% of cases outside the outbreak period are caused by *Nm*; 3) the serogroup distribution is proportional to national annual proportions; 4) there is a delay of six weeks between triggering of the epidemic threshold and the onset of protection from vaccination (Table 7.3). Where no threshold was triggered but vaccination still took place, a best guess for the timing of the intervention was based on neighbouring districts. For polysaccharide vaccine, the following further assumptions were made: 1) campaigns target

2-29-year-olds, who make up 70% of the population and 90% of cases;[150,211] 2) 80% vaccine efficacy against serogroups A, C, and W;[212] 3) protection lasts for 104 weeks (approximately two years).[213] This type of model has been used previously to estimate the impact of reactive vaccination for meningitis outbreaks.[89,91,93] It assumes no impact of the vaccine on carriage and thus transmission of meningococci.

For the monovalent C conjugate vaccine, output from a dynamic model was used to approximate herd effects, assuming 85% vaccine efficacy against serogroup C meningitis, an average five years duration of protection, and coverage levels calculated from reported population size and vaccine use (see Figure 7.1).[3,214] For the quadrivalent conjugate vaccine, the same dynamic model was used to approximate herd effects, assuming 98% coverage of 2- to 15-year-olds (reflecting the actual coverage in Ouallam), 85% vaccine efficacy against serogroups A, C, W, and Y, and an average five years duration of protection.[215] Vaccine coverage is calculated using the district-level population reported in surveillance data, assuming the targeted population is 2- to 29-year-olds, representing 70% of total population, and the number of doses of vaccine released by the ICG or population vaccinated as reported in the Weekly Epidemiological Record where available.[138,216,217] For all coverage calculations, 10% vaccine wastage was also assumed.

Table 7.3 Summary of model assumptions.

Vaccine	Intervention	Coverage	VE	Serogroups covered	Duration of protection	Delay (week)	Herd effects	Age group
Polysaccharide	Actual	Variable*	80%	ACW	2 y	6	No	2-29 y
Monovalent conjugate	Actual	Variable*	85%	C	5 y	6	Yes	1-19 y
Quadrivalent conjugate	Actual	Variable*	85%	ACWY	5 y	6	Yes	2-15 y
Polysaccharide	Potential	85%	80%	ACW	2 y	4-8	No	2-29 y
Monovalent conjugate	Potential	85%	85%	C	5 y	4-8	Yes	2-29 y
Pentavalent conjugate	Potential	85%	85%	ACWYX	5 y	4-8	Yes	2-29 y

*Calculated from ICG data.

In the model, I calculate suspected cases in the absence of intervention as a function of the observed suspected cases over time i in a given district j ($C_{i,j}$), the proportion of meningococcal meningitis cases occurring in the 2- to 29-year age group (a), the coverage of the reactive vaccination campaign in district j (κ_j), the proportion of cases caused by *N. meningitis* during the epidemic period and outside of the epidemic period (ν_E, ν_N), the proportion of *N. meningitis* cases caused by vaccine-type serogroups (σ), the individual efficacy of a single dose of vaccine (ϵ), the week the incidence threshold is exceeded (i_t), the delay to implementing a campaign (d), and the duration of vaccine protection (δ).

$$\nu = \nu_E, \quad C_i > 2/100000$$

$$\nu = \nu_N, \quad C_i \leq 2/100000$$

$$M_{i,j} = \sum_{i=(i_t+d)}^{i_t+d+\delta} \frac{C_i}{1 - a\kappa_j \epsilon \sigma \nu}$$

For conjugate vaccine, individual efficacy (ϵ), overall coverage (κ), and age coverage (a) are used in a dynamic model to approximate time-varying herd effects, giving $H(i, \epsilon, \kappa, a)$:

$$M_{i,j} = \sum_{i=(i_t+d)}^{i_t+d+\delta} \frac{C_i}{1 - H(i, \epsilon, \kappa, a)\sigma \nu}$$

The campaign coverage is calculated as

$$\kappa_{i,j} = \frac{D_{i,j}(1-w)}{\alpha P_j}$$

where α is the proportion of the population between 2 and 29 years of age, $D_{i,j}$ is the number of doses used in the campaign, P_j is the total population size of the district where vaccination occurs, and w is the wastage percentage.

As a sensitivity analysis, I repeated this process 1,000 times, resampling the following parameters: d, a, ϵ, σ, ν_E,ν_N, w, and δ for polysaccharide vaccine (shown in Table 7.4). I present the 2.5th and 97.5th percentiles of this process as an uncertainty interval.

Table 7.4 Variables included in sensitivity analysis.

Variable	Meaning	Base	Distribution
d	Delay to implementing campaign	6	Discrete uniform(4,8)
δ	Duration of vaccine protection (years)	2	Discrete uniform(1,3)
a	Proportion of cases in 2- to 29-year age group	90%	Uniform(80%, 100%)
ϵ	Vaccine efficacy	80%	Uniform(70%, 90%)
σ	Proportion of *N. meningitidis* cases caused by vaccine-type serogroups	Variable by year and country	Uniform over binomial probability 95% CI
ν_E	Proportion of cases caused by *N. meningitidis* (epidemic)	80%	Uniform(70%, 90%)
ν_N	Proportion of cases caused by *N. meningitidis* (non-epidemic)	20%	Uniform(10%, 30%)
w	Vaccine wastage	10%	Uniform(5%, 15%)

7.2.6 Modelling new vaccination strategies

Uniform application of the current strategy was compared to three alternative reactive vaccination strategies, making the same assumptions as above (Table 7.3). Under the current strategy, mass vaccination takes place on a district level where the weekly incidence of suspected cases exceeds the epidemic threshold and a vaccine-preventable causative serogroup can be identified. The requirement for etiological confirmation was dropped for the modelling analysis because weekly district level lab data were unavailable. In alternative strategy A, vaccination takes place when the alert threshold is exceeded. In strategy B, all neighbouring districts which have not received vaccine in the last five years are targeted in addition to the district exceeding

the epidemic threshold. In strategy C, only those neighbouring districts in alert are targeted in addition to the focal district in epidemic. In comparing these strategies, three types of vaccine were considered: a trivalent ACW polysaccharide, monovalent C conjugate, and pentavalent ACWYX conjugate. For polysaccharide vaccine, the following further assumptions were made: 1) campaigns target 2-29-year-olds with 85% coverage, who make up 70% of the population and 90% of cases;[150] 2) 80% vaccine efficacy against serogroups A, C, and W;[212] 3) protection lasts for 104 weeks (approximately two years).[213] For both conjugate vaccines, output from a dynamic model described above was used to approximate herd effects, assuming 85% coverage of 1- to 29-year-olds, 85% vaccine efficacy, and an average five years duration of protection (Figure 7.1).[3,214] The pentavalent vaccine is assumed to protect against serogroups A, C, W, Y, and X, and the monovalent against C alone. For conjugate vaccination, no districts which have received vaccine in the last five years are targeted in order to avoid repeated vaccination. Delays of 4, 6, and 8 weeks between triggering a vaccine response and onset of vaccine protection are assumed, effectively giving 2, 4, and 6 weeks for implementation and 2 weeks for vaccine protection to take effect after delivery.[212]

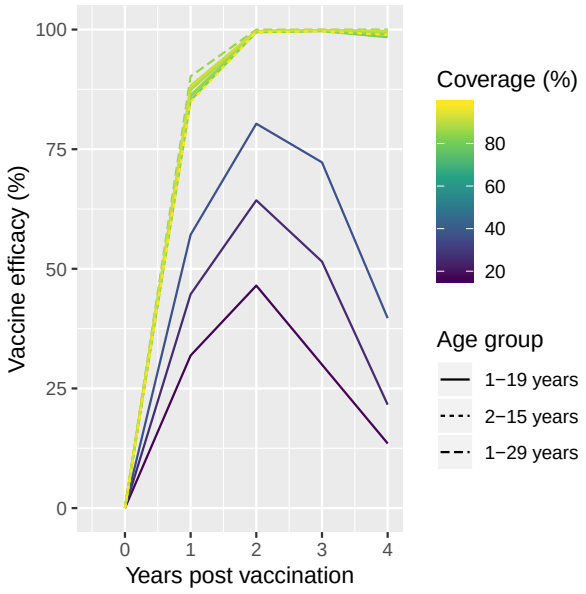

Fig. 7.1 Output of dynamic model used to approximate herd effects at different levels of coverage.

7.2.7 Analysis of model results

The performance of the different strategies and vaccine types was evaluated by calculating the cases averted, doses of vaccine required to prevent a case (NNV), and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each strategy for predicting outbreaks defined by different cumulative annual incidences (from 100 cases per 100,000 to 20 cases per 100,000).

7.3 Results

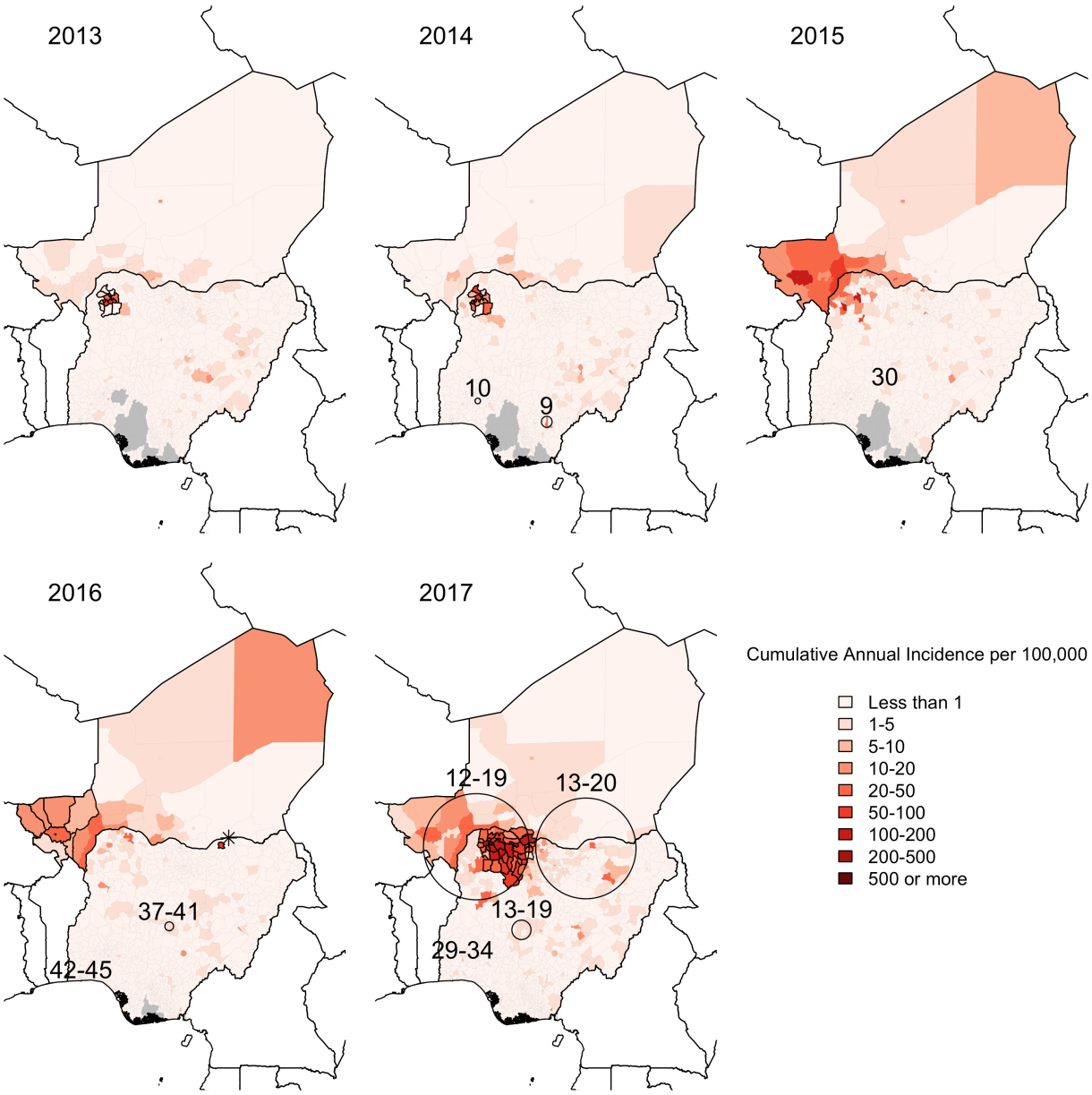

Fig. 7.2 Cumulative annual district-level incidence of suspected cases of meningitis in Niger and Nigeria 2013 to 2017. Significant clusters of high incidence by Anselin's local Moran's I outlined in black. High-incidence outlier in 2016 indicated with asterisk. Spatial extent of Kulldorff spatio-temporal clusters indicated by black circles, temporal extent in weeks noted above circles.

7.3.1 Spatial and temporal characterisation

Outbreak activity was first observed in northern Nigeria in 2013 and continued in 2014 (Figures 7.2 and 7.3). In 2015, activity spread to the southwestern region of Niger, including the urban area of Niamey. Fewer outbreaks were observed in 2016, followed by relatively high case

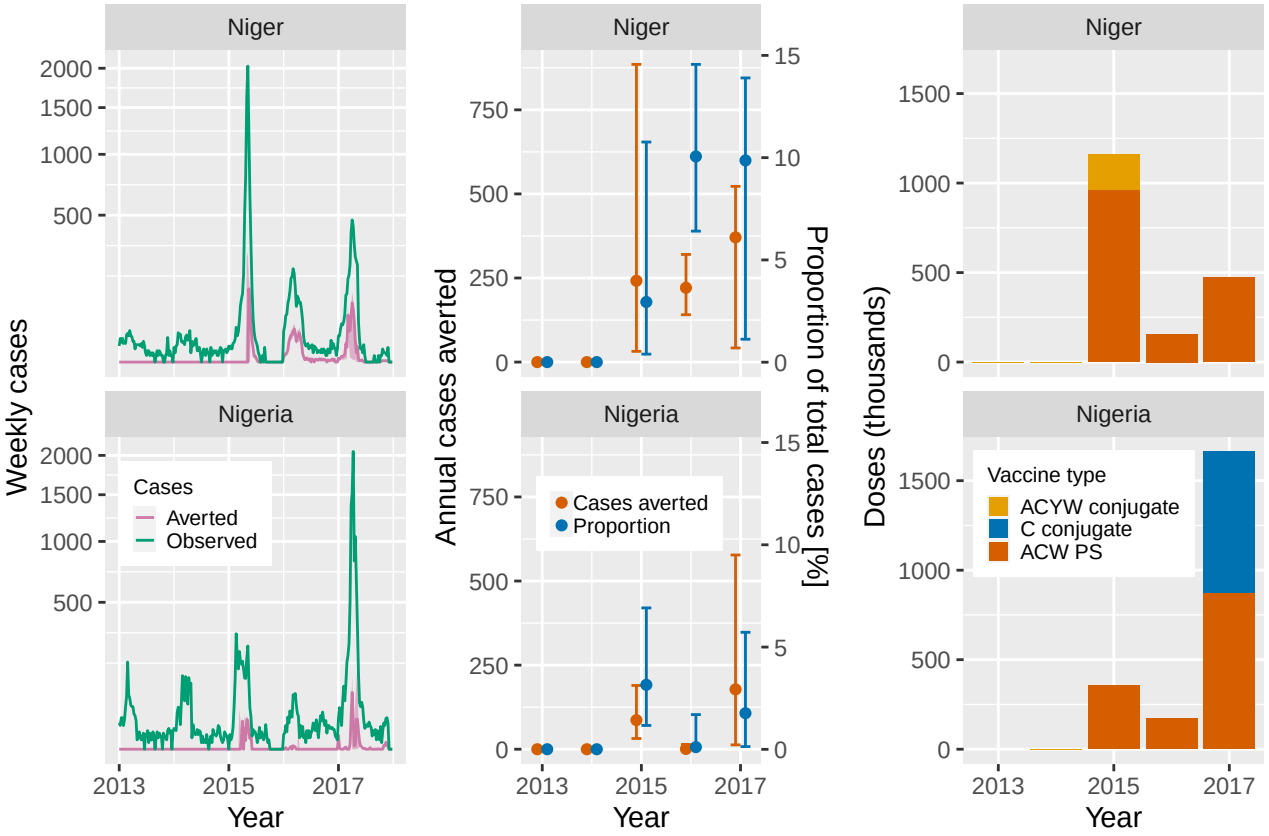

Fig. 7.3 Observed weekly suspected cases and modelled cases averted by vaccination counts, annual cases averted by reactive vaccination, and doses of vaccine delivered in Niger and Nigeria, 2013 to 2017. Shaded ribbon and vertical error bars show 2.5th and 97.5th percentiles of sensitivity analysis for cases averted.

counts in Niger and the highest case counts in Nigeria thus far in 2017. Twenty district-years were detected with high incidence and positive spatial autocorrelation (i.e. centres of clusters of high incidence). There were 46 districts neighbouring these centres, and one district with high incidence and negative spatial autocorrelation, meaning it was an outlier from its neighbours. Tambuwal local governmental area (LGA) in Sokoto State in Nigeria, where the group C outbreak strain was first identified, was detected as the centre of high incidence clusters in 2013 and 2014, but did not pass the weekly epidemic incidence threshold of 10 cases per 100,000 (WIT10) in 2014 and did not exceed a cumulative annual incidence of 100 suspected cases per 100,000 in either year (CAI100).[47] Of the neighbouring districts, two and four districts respectively surpassed the WIT10 in 2013 and 2014 and none exceeded CAI100. No significant clusters were detected in 2015. High incidence clustered around Niamey in Niger in 2016. There was also a spatial outlier of high incidence identified in Nguru LGA in Yobe State in north-central Nigeria. In 2017, two large clusters were detected in Sokoto State and Zamfara State in Nigeria. All 15 of the centre districts and 16 of the 21 neighbouring districts surpassed WIT10 between weeks 10 and 18. Nine of the centre districts in these clusters and two neighbouring districts exceeded CAI100. Table D.2 gives full details of all clusters detected by Moran's local I.

The Kulldorff spatio-temporal scan identified nine clusters with p-value less than 0.01. The largest cluster centred on Augie, Nigeria, encompassing a population of more than 23 million people from weeks 12 to 19 of 2017 with a relative risk (RR) of 120 (Figure 7.2, Table 7.5). A secondary cluster of somewhat lower relative risk was detected that year centred on Biriniwa from weeks 13 to 20 (RR 4.3, p-value <0.001). Two additional smaller clusters were detected in Abaji, Nigeria, and at Ibadan North, Nigeria (RR 4.5 and 25, p-value <0.001 and 0.002, respectively). Two small clusters were detected in 2016, one centred at Karu, Nigeria from week 37 to 41 (RR 18, p-value <0.001) and one at Lagos Island, Nigeria from week 42 to 45 (RR 21, p-value = 0.002). One small cluster was detected in 2015 at Lokoja, Nigeria in week 30 (RR 20, p-value = 0.002). Two clusters were detected at in 2014, one large cluster at week 9 centred on Ebonyi, Nigeria (RR 110, p-value < 0.001) and one smaller cluster at week 10 centred on Atakunmosa West, Nigeria (RR 29, p-value <0.001). No clusters were detected in 2013.

Table 7.5 Clusters identified by Kulldorff spatio-temporal scan. LLR= log likelihood ratio; RR = relative risk. Population given in thousands.

Cluster centre	Week	Year	Coordinates	Radius (km)	Population	Cases Observed	Expected	LLR	RR	p-value
Augie	12-19	2017	12.9, 4.6	286	23 025	9 550	120	34 000	120	<0.001
Ebonyi	9	2014	6.5, 8.1	30	898	58	0.51	220	110	<0.001
Atakunmosa West	10	2014	7.5, 4.7	15	794	13	0.45	31	29	<0.001
Ibadan North	29-34	2017	7.4, 3.9	0	408	17	1.5	11	25	<0.001
Lagos Island	42-45	2016	6.5, 3.4	0	274	11	0.66	17	21	0.002
Lokoja	30	2015	8.2, 6.5	0	251	7	0.15	48	20	0.002
Karu	37-41	2016	9.0, 7.8	24	384	21	1.2	41	18	<0.001
Abaji	13-19	2017	8.9, 6.9	52	1 473	31	4.5	22	4.5	<0.001
Biriniwa	13-20	2017	12.8, 10.1	272	33 430	702	170	480	4.3	<0.001

Table 7.6 Cases of meningococcal meningitis prevented by reactive vaccination in Niger and Nigeria, 2015-2017. Numbers in parentheses show 2.5th and 97.5th percentiles of sensitivity analysis.

Country	*Nm* cases prevented	Proportion of *Nm* cases prevented	Total *Nm* cases (in absence of vaccination)	Suspected meningitis cases (reported)
Niger	834 (215 - 1 730)	9% (4 - 14%)	9 250 (7 560 - 11 200)	13 400
Nigeria	265 (45 - 781)	3% (1 - 5%)	8 980 (7 550 - 10 600)	13 300
Total	1 100 (260 - 2 510)	6% (3 - 10%)	18 200 (15 100 - 21 800)	26 700

7.3.2 Impact of reactive campaigns

Reactive vaccination campaigns were conducted in 2015, 2016, and 2017 in 60 districts in response to *Nm*C outbreaks using roughly 4 million doses of polysaccharide vaccine, monovalent C conjugate vaccine, and quadrivalent ACWY conjugate vaccine (Table D.3). Our model estimates that these campaigns prevented 1,100 of 19,000 (6%) cases of meningococcal meningitis overall during the period 2015 to 2017 (270 of 10,000 [3%] cases in Nigeria and 830 of 9,000 [9%] cases in Niger (Table 7.6). In the sensitivity analysis, the proportion of cases prevented ranged from 3 to 10% overall, 4 to 14% in Niger and 1 to 5% in Nigeria.

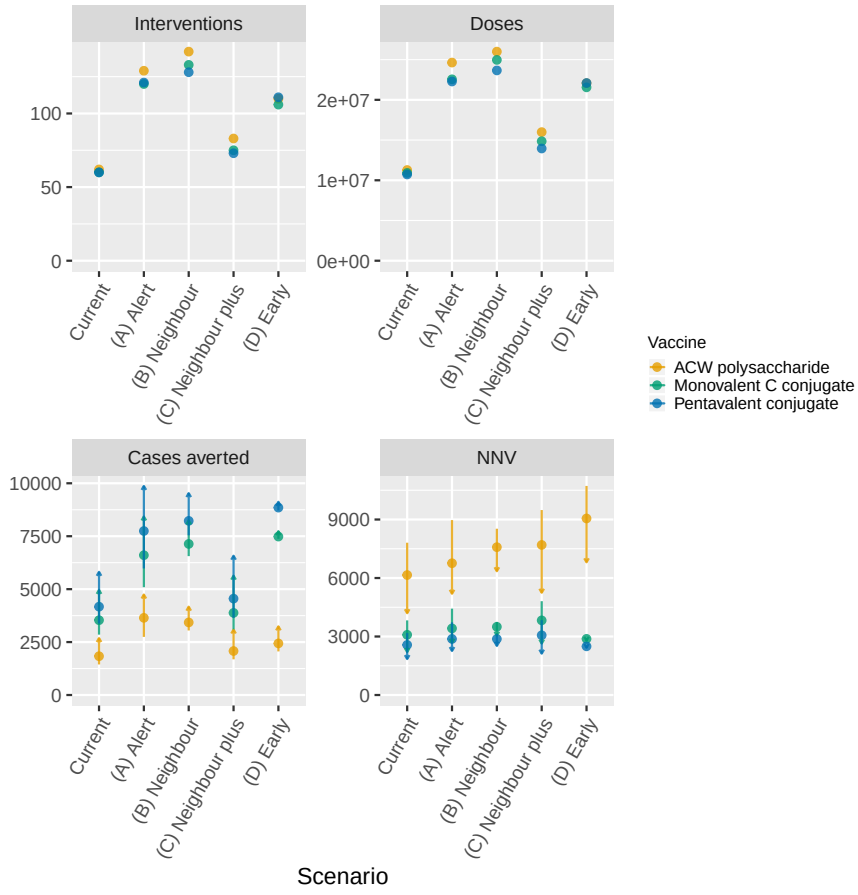

Fig. 7.4 Number of interventions (individual districts vaccinated), doses, proportion of total cases averted, and number needed to vaccinate to prevent a case over the period 2013-2017 for different reactive vaccination strategies using ACW polysaccharide, C conjugate, and ACWYX conjugate vaccine. Points show estimates for four-week delays, lines show two- and six-week delays, with arrow heads indicating shorter delays.

7.3.3 Modelling alternative polysaccharide vaccination strategies

The current strategy required fewest interventions with 63 districts requiring 11 million doses of polysaccharide vaccine between 2013 and 2017, followed by alternative strategy C which would have targeted an additional 21 districts with 5 million additional doses. Strategies A

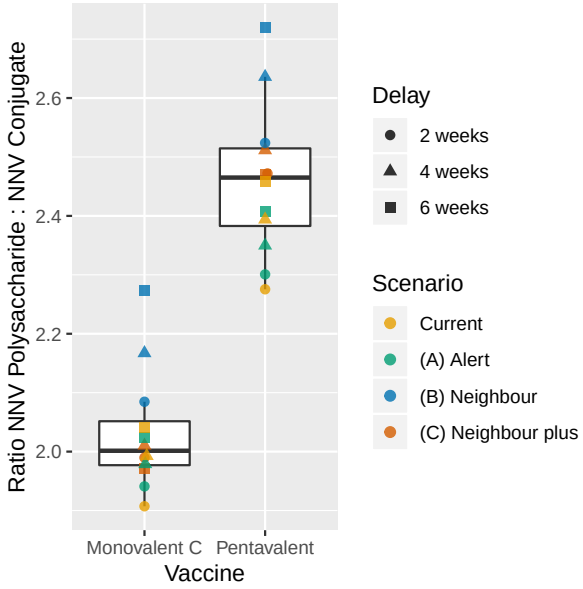

Fig. 7.5 Ratio of NNV using ACW polysaccharide to NNV using conjugate vaccine.

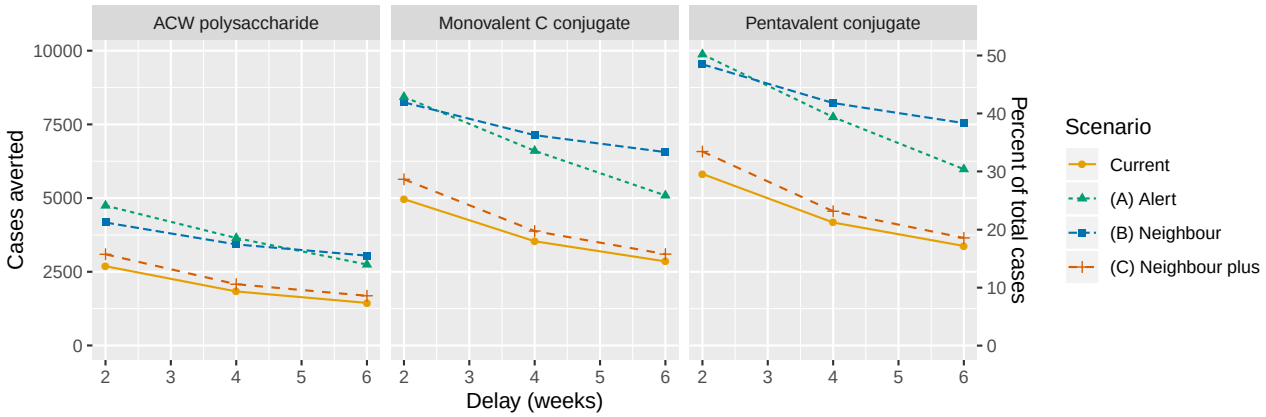

Fig. 7.6 Cases averted by strategy, delay, and vaccine type.

and B would have required targeting 73 and 82 additional districts respectively, requiring an additional 14 and 15 million doses of polysaccharide vaccine.

Strategy C had the greatest sensitivity in predicting small outbreaks, whereas the current strategy had the least (Figure 7.7). Sensitivity was comparable across all strategies for large outbreaks. The current strategy had the highest PPV at any cumulative incidence threshold, followed by strategy C. Specificity and NPV were similar across all strategies.

Strategies A and B prevented the most cases, 19% and 18% of all meningococcal meningitis cases, followed by strategy C (11%) and the current strategy (10%) (Figure 7.4).

With shorter delays of two weeks, A prevented the most cases; with longer delays of six weeks, B prevented the most cases (Figure 7.6). Across all strategies, interventions with delays of two weeks prevented between 1.3 and 1.9 times as many cases those with delays of six weeks. Shortening the delay by two weeks while maintaining the current strategy would have

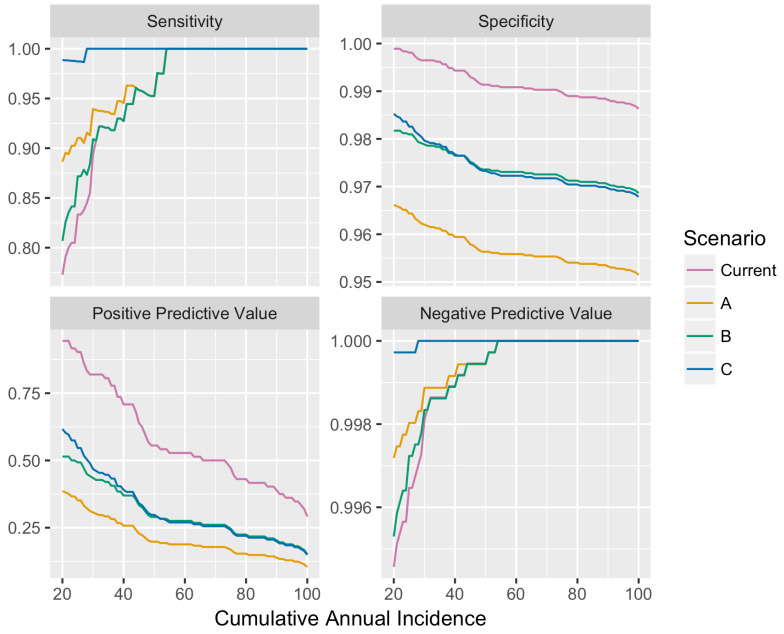

Fig. 7.7 Sensitivity, specificity, positive predictive value, and negative predictive value of different vaccination strategies for predicting cumulative annual incidence between 20 and 100 suspected cases per 100,000.

prevented 14% of cases, close to the proportion prevented by strategies A and B while requiring no additional vaccine. No strategy outperformed the current strategy in terms of NNV, but A was the second most efficient use of vaccine, with an NNV of 6 800 compared to the current strategy at 5 900.

7.3.4 Modelling alternative conjugate vaccination strategies

Using polysaccharide vaccine resulted in between 3 and 28 more interventions than conjugate vaccine depending on the strategy adopted. Using the pentavalent conjugate vaccine prevented between 2.1 and 2.5 times as many cases as the polysaccharide vaccine (Figure 7.4). Conjugate vaccine was more efficient in terms of NNV than polysaccharide. Comparing situations with the same targeting strategies and the same delays, using polysaccharide vaccine requires between 1.9 and 2.7 times as many doses to prevent the same number of cases (Figure 7.5). Ignoring operational costs of interventions, as these will be the same regardless of vaccine type, this means that pentavalent conjugate vaccine could be at least equally cost effective at about 1.9 times the cost of the polysaccharide vaccine.

7.4 Discussion

There was significant clustering of high incidence districts in every year, with local clusters occurring around Tambuwal in Nigeria in 2013 and 2014, around Niamey, Niger in 2016, and two around Sokoto and Zamfara States in Nigeria in 2017. These two 2017 clusters were also identified by spatio-temporal scan in a single cluster occurring between weeks 12 and 19 and

centred on Augie. No significant local cluster was identified in 2015 although incidence was high in Niamey and Tillaberi Regions, perhaps because the distribution of incidence was more even in space. None of these clusters had previously been identified by formal statistical analysis, but the 2013 and 2014 clusters were described by Funk and colleagues in their initial report on the novel strain.[47]

There is no strong evidence to support a change in the methods currently used for predicting and targeting outbreaks. The current weekly incidence threshold of 10 suspected cases per 100,000 is highly specific and sensitive to large outbreaks. Shortening delays between outbreak detection and response offers a substantial benefit. These two results are consistent with previous findings regarding group W outbreak response.[89] Although the absolute values in NNV may differ slightly between this and previous studies, adjustment for differing assumptions about coverage and vaccine efficacy can largely account for these differences.[89,97]

These results demonstrate the importance of timeliness in effective reactive vaccination campaigns. Delays are often associated with vaccine procurement. A recent trial of village-wide antibiotic prophylaxis in response to an *Nm*C outbreak in Niger demonstrated significant reductions in incidence and no significant increase in carriage of antibiotic-resistant enterobacteria.[201,218] Because antibiotics are much more readily available than meningitis vaccines, the delay between detection and response to an outbreak can be substantially shortened. However, despite the positive initial findings, the risk of antibiotic resistance is generally perceived to be too great to justify widespread use of reactive chemoprophylaxis.

This study also highlights the substantial difference between the number of doses of vaccine required to intervene as per WHO policy (roughly 11 million) and the number of doses that were used in reactive vaccination campaigns between 2013 and 2017 (roughly 4 million). Although some of this shortfall can be explained by the necessity of dropping the etiological confirmation requirement in this model, it is clear that vaccine scarcity had an impact on decisions about where and in which age groups to carry out reactive vaccination. A further development of this work could identify a threshold that maximises case prevention for a constrained number of doses of vaccine. This could make it easier to efficiently manage the ICG vaccine stockpile as well as maximising the overall impact of reactive campaigns.

This analysis estimates that the reactive vaccination campaigns that took place between 2015 and 2017 prevented fewer than 10% cases of meningococcal meningitis. This is probably due in part to the smaller scope of campaigns necessitated by vaccine scarcity. However, it is important to emphasise that even under ideal conditions, reactive vaccination would only have prevented 20% of cases. Two key aims of theMeningitis 2030 Roadmap are eliminating meningitis epidemics and substantially reducing cases and deaths from vaccine-preventable meningitis.[6] Even with a timely and broad response, reactive vaccination alone would not achieve either of these aims.

This is the first study to model reactive vaccination in a multi-year framework, recognising that the benefits of outbreak response may be long-term as well as immediate. The model

suggests that even over a relatively short period of time, using conjugate vaccine is more efficient per dose than polysaccharide in this context, and may be more cost-effective depending on how the vaccine is priced. Considering that conjugate vaccines have a long-lasting impact on immunity and a substantial response was modelled in 2017 at the end of the period for which data were available, this analysis presents an underestimate of the per dose impact of conjugate vaccination. In future, the analysis could be extended to estimate the full benefit of doses delivered in 2017.

Vaccination was modelled in a relatively broad age group (2 to 29 years) in order to remain consistent with previous practice. However, it is possible that a similar effect could be achieved by targeting a narrower age range of individuals most involved in carriage transmission. Further simulations using an age-structured transmission model could help to inform potential future targeting of particular age groups.

Although data from Nigeria on laboratory confirmed cases of meningitis were lacking, one study confirmed our assumption that *Nm*C was the predominant cause of meningitis in Nigeria, with 172 of 173 *Neisseria meningitidis* isolates being from serogroup C.[131]

Table 7.7 Comparison of laboratory results in outbreak and non-outbreak periods. Data from Niger line list 2015-2017 and Nigeria line list 2015.

Laboratory result	Non-outbreak period		Outbreak period	
No test reported	5 677	44%	7 538	47%
Test reported	7 257	56%	8 464	53%
Test result				
Negative	4 636	64%	5 995	71%
N. meningitidis	2 175	30%	2 299	27%
S. pneumoniae	355	5%	139	2%
H. influenzae	83	1%	27	<1%
Other bacteria	8	<1%	4	<1%

Informed by expert opinion, this model assumes that 80% of suspected meningitis cases occurring during outbreaks are caused by *N. meningitidis*, with just 20% of suspected cases caused by *N. meningitidis* outside of outbreak periods. The rationale behind this assumption is that a high incidence of suspected cases of meningitis indicates some common underlying cause, and *N. meningitidis* is the most common cause of meningitis outbreaks in this region and time period. However, line list data from Niger between 2015 and 2017 and Nigeria in 2015 suggests that only 27% of suspected cases occurring during outbreaks are confirmed as meningococcal meningitis, with a similar proportion occurring outside of outbreak periods (Table 7.7). A majority of CSFs test negative for common bacterial pathogens both during and outside of outbreak periods. A variety of factors may contribute to a high rate of false negatives, including administration of antibiotics before collecting CSF, sample degradation due to testing delays, and the use of lower-sensitivity culture-based methods and latex agglutination tests.[219–222] However, some degree of clinical misclassification of suspected meningitis cases cannot be excluded. Misidentification of malaria cases seems unlikely because the malaria and meningitis

seasons in this region are not concurrent.[223] Misidentification of measles, though possible due to its seasonal co-occurrence with meningitis, also seems unlikely because of measles' characteristic rash. Nonetheless, this model may overestimate the burden of preventable bacterial meningitis.

Meningococcal meningitis in the African meningitis belt is notoriously difficult to predict. The aim of this analysis was to evaluate the magnitude of spatiotemporal heterogeneity and its implications for outbreak response, not to explain the drivers of this heterogeneity. Diverse factors including variation in local levels of immunity, household crowding, smoke exposure, and co-circulation of viral infections may contribute to small-scale spatial heterogeneity, while climactic factors appear to drive year-to-year variation on a larger spatial scale.[105,126,127,195,224] The results described here are only relevant insofar as the behaviour of group C meningitis remains roughly the same. There is a high degree of uncertainty about which epidemiological characteristics may be considered typical given the strain's recent emergence. In any case, it is important to continue with careful surveillance throughout the meningitis belt, striving especially to improve laboratory diagnostics in outbreak settings.

Chapter 8

Discussion

Numerous challenges must be overcome to achieve the aims stated in the global roadmap to defeat meningitis in the African meningitis belt by 2030. Short-term strategies are required to respond to meningococcal meningitis epidemics in the absence of NmCV-5, and long-term plans need to be formulated about the eventual use of NmCV-5. It has become increasingly apparent that *S. pneumoniae* causes a substantial proportion of bacterial meningitis in Africa, and is capable of causing localised outbreaks similar to *N. meningitidis*. At the time of writing, there are no guidelines for response to outbreaks of pneumococcal meningitis.

The aim of this thesis was to characterise the epidemiology of bacterial meningitis in the African meningitis belt, in particular focusing on non-A meningococci and *S. pneumoniae*, which are the predominant causes of bacterial meningitis in the region following the successful introduction of MenAfriVac. In particular, I considered the impact of mass reactive vaccination campaigns in response to outbreaks caused by *Nm*C in Niger and Nigeria and *S. pneumoniae* in Ghana and modelled potential alternative strategies to increase efficiency and impact of these campaigns. Although reactive campaigns are inefficient and offer imperfect protection, they represent the best short-term response to outbreaks of meningitis in the region. I described patterns of meningitis in space, characterising district- and national-level incidence before and after the introduction of MenAfriVac and examining whether spatial information could be used to improve reactive vaccination strategies. In addition to studying patterns of disease, I also examined carriage, a phenomenon that is essential to establishing herd immunity. Knowledge of carriage patterns by age and according to serogroup will inform the use of conjugate vaccines in reactive campaigns and the preventative use of NmCV-5. Finally, I quantified seasonality in carriage prevalence and acquisition. Understanding seasonality can contribute to predicting when and where outbreaks occur are likely to occur.

8.1 Summary of findings

There is little evidence to suggest that district-level outbreaks of bacterial meningitis differ in character according to country or etiology, including *S. pneumoniae*, but they do occur with differing frequency. Numerous studies have identified outbreaks of meningitis with similar high

incidence, marked seasonality, and broad age distribution where *S. pneumoniae* is the causative agent.[21,61,132,133] The results presented in Chapter 4 suggest that reactive vaccination could be equally effective in response to outbreaks of pneumococcal meningitis as for meningococcal meningitis.

Elevated incidence in previous years and neighbouring districts were significant risk factors for meningitis outbreaks, consistent with the hypothesis that transmission is sustained in intervening rainy seasons. Although clear spatiotemporal structure of *Nm*C outbreaks is demonstrated, there is no strong evidence to support a change in the methods currently used for predicting and targeting outbreaks in response to the re-emergence of *Nm*C. Shortening delays between outbreak detection and vaccination and choosing conjugate vaccine over polysaccharide offers a substantial benefit.

This work identifies possible criteria for the introduction of the pentavalent vaccine, including previous occurrence of suspected and confirmed non-A outbreaks. District-level analysis reaffirms the importance of subnational variation in meningitis risk.[120]

Prevalence of predominantly non-*Nm*A meningococcal carriage peaks at 10 years of age in the African meningitis belt. The longitudinal household study presented in Chapter 6 also found the highest acquisition rates in 5- to 14-year-olds. This contrasts with patterns in Europe, where carriage peaks at 19 years of age,[24] and may be explained by differences in social contact patterns.[186]

Changes in carriage prevalence contribute to seasonal hyperendemicity and outbreaks of meningitis. Prevalence of carriage is significantly higher during the dry season and where outbreaks are reported. Carriage acquisition is also associated with history of sore throat during the dry season. These findings are consistent with modelling which has shown that seasonal forcing in transmissibility of carriage is required to reproduce the variability and magnitude of incidence characteristic of the African meningitis belt.[39] However, the mechanism underlying this seasonality is uncertain - it may be directly caused by environmental factors[38] or indirectly by associated cofactors, including seasonal circulation of respiratory viruses.[127,190]

8.2 Strengths and limitations

This thesis draws on a broad range of data sets to characterise the epidemiology of bacterial meningitis in the African meningitis belt, incorporating information on both carriage and invasive disease across 23 countries and 19 years, and utilising diverse methods, including mathematical modelling, geospatial statistics, and statistical regression. I address both *N. meningitidis* and *S. pneumoniae*, the two predominant causes of bacterial meningitis in the African meningitis belt. Chapter 5 presents the first formal meta-analysis of meningococcal carriage data from the African meningitis belt and demonstrates seasonality and age patterns which are unique to the region. Chapter 4 is the first analysis modelling a systematic response to pneumococcal meningitis outbreaks and helped to inform the 2017 WHO position paper on pneumococcal

conjugate vaccines.[225] In further evidence of the quality and novelty of the work presented here, the analyses in Chapters 4 to 7 have all been published in peer-reviewed journals.

The findings summarised above are limited principally by reliance on suspected case data and inadequacy of the chosen methods to capture the full stochasticity inherent in the system. The case definition used in meningitis surveillance is non-specific and laboratory confirmation of cases is still too limited. Confidence in the surveillance data analysis in Chapter 3 is limited by the underlying assumption that national laboratory confirmation is uniformly representative of all districts and that causes of meningitis outbreaks are homogeneous within country-years. Chapters 4 and 7 also rely on limited laboratory confirmation to infer the cause of suspected cases.

Meningococcal meningitis in the African meningitis belt is notoriously difficult to predict. The results described in Chapter 7 are only relevant insofar as the behaviour of group C meningitis remains roughly the same. There is a high degree of uncertainty about which epidemiological characteristics may be considered typical given the strain's recent emergence. Similarly, the findings of Chapter 4 are highly dependent on the age distribution of cases, the proportion of cases due to *S. pneumoniae*, and the overall shape of the epidemic incidence curve over time.

Substantial variability in carriage prevalence remains unexplained by the model developed in Chapter 5. This is in part due to the unrealistic assumption that all individuals in a given age group are of the median or midpoint age, and that carriage prevalence changes with respect to age in the same way in all settings. Because of the sparseness of sampling in older age groups, a linear relationship between carriage prevalence and age above 30 years was assumed. The model is also principally informed by two large serial cross-sectional studies carried out between 2009 and 2012.[40,41,73,168]

8.3 Implications for policy

These findings have particular relevance to four specific policy questions. The first question is whether the current policy for reactive vaccination for outbreaks caused by meningococci should be adopted for outbreaks caused by pneumococci. Chapter 4 demonstrated that reactive vaccination for meningitis outbreaks caused by *S. pneumoniae* is inefficient, but it is no less efficient than for meningitis outbreaks caused by *N. meningitidis*. Considering the high CFR associated with pneumococcal meningitis, a large number of deaths could be averted by adopting this policy. However, there are other approaches to reducing the burden of pneumococcal meningitis in the African meningitis belt. Age-structured mathematical modelling taking into account both the burden of pneumonia and meningitis caused by *S. pneumoniae* could indicate whether switching from 3+0 to 2+1 routine immunisation schedule would help to extend herd immunity to older age groups, or whether a catch-up dose for older children might be warranted. Reactive vaccination is not a substitute for figuring out how best to achieve indirect protection

of older age groups by routine vaccination, and if implemented, should not direct resources away from routine vaccination.

The second question is whether conjugate vaccines should be used in preference to polysaccharide vaccines for reactive responses to meningococcal meningitis outbreaks. Conjugate meningococcal vaccines have higher individual efficacy than polysaccharide vaccines and reduce carriage acquisition, resulting in higher population-level efficacy. They are also more expensive than polysaccharide vaccines. Chapter 7 compared using conjugate and polysaccharide vaccines over a five year period and found that they would have prevented roughly twice the number of deaths.

The third question is whether the current strategy for predicting meningococcal outbreaks needs to be updated to reflect the changes in epidemiology since the introduction of MenAfriVac. Originally designed to detect NmA outbreaks, this threshold has since been validated for NmW. The findings in Chapter 7 indicate that the current weekly incidence threshold for detecting meningococcal meningitis outbreaks is still sensitive and specific where NmC is predominant.

Finally, it is unclear where and how NmCV-5 should be used when it becomes available. The findings in Chapter 5 indicate that undertaking a mass campaign two-thirds the size of the previous MenAfriVac campaigns would reach more than half of all carriers. The data collected in this chapter could be used to parameterise a mathematical model that would be used to inform the choice of specific vaccination schedules, quantifying the additional benefit of mass vaccination or smaller catch-up campaigns compared to routine immunisation alone. Chapter 3 identifies at least seven countries that are at high risk for non-NmA outbreaks and would be strong candidates for NmCV-5 introduction.

8.4 Further development of this work

The work in this thesis sets up several avenues for further investigation. The findings presented in Chapters 5 and 6 demonstrated increased carriage prevalence and acquisition rates during the dry season, when meningitis outbreaks occur. I was not able, however, to disentangle the roles played by climactic factors and associated co-factors, such as respiratory viruses, in this seasonality. Understanding the relative contribution of changes in carriage and susceptibility to invasion helps us to know what to do in response to outbreaks and seasonal hyperendemicity - whether to prioritize protecting the most susceptible individuals or those most involved in transmission.

The findings on carriage prevalence and acquisition patterns by age and serogroup can inform the design of future evaluation studies for the pentavalent meningococcal vaccine. The spatial characterisation of outbreak risk can be used to update the meningitis belt map, which has not been re-evaluated since 2003. Together these findings can aid in the development of more realistic age-structured and country-specific models, which can be used to help inform decisions around the introduction of the pentavalent vaccine.

Epidemiological information about carriage by serogroup are still scarce for the African meningitis belt, but recent studies have demonstrated striking differences in the prevalence of the different serogroups.[40,73] Although Chapters 5 and 6 addressed carriage of *Nm*W, X, and Y, there is a distinct lack of data on *Nm*C. A carriage study in Niger or Nigeria where it is known to be circulating could provide valuable information on the prevalence, acquisition rate, duration of carriage, and age patterns of this re-emergent serogroup.

8.5 Conclusions

The introduction of MenAfriVac in 2010 has significantly reduced incidence of meningitis across the African meningitis belt. However, other meningococcal serogroups and *Streptococcus pneumoniae* continue to cause outbreaks of meningitis in the region. This thesis set out to evaluate the remaining challenges to control of bacterial meningitis in the African meningitis belt and elimination of epidemic meningitis. It demonstrates that outbreaks caused by other serogroups and *Streptococcus pneumoniae*, though less frequent, are not fundamentally different from those caused by *Nm*A. Therefore, similar control strategies should be effective. These strategies can be enhanced by focusing on reducing transmission by vaccinating particular age groups and using conjugate vaccines, targeting the most at-risk regions, and responding quickly to outbreaks.

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Appendix A

Published papers by the candidate during the course of this PhD

A. Papers published from this thesis

1. Cooper LV, Stuart JM, Okot C, et al. Reactive vaccination as a control strategy for pneumococcal meningitis outbreaks in the African meningitis belt: Analysis of outbreak data from Ghana. Vaccine 2018;37:5657–63
2. Cooper LV, Kristiansen PA, Christensen H, Karachaliou A, and Trotter CL. Meningococcal carriage by age in the African meningitis belt: a systematic review and meta-analysis. Epidemiology and Infection 2019;147:e228
3. Cooper LV, Robson A, Trotter CL, et al. Risk factors for acquisition of meningococcal carriage in the African meningitis belt. Tropical Medicine & International Health 2019;24:392–400
4. Cooper LV, Ronveaux O, Fernandez K, et al. Spatiotemporal Analysis of Serogroup C Meningococcal Meningitis Spread in Niger and Nigeria and Implications for Epidemic Response. The Journal of Infectious Diseases 2019;220:S244–S252

B. Papers published outside this thesis

1. Trotter CL, Lingani C, Fernandez K, et al. Impact of MenAfriVac in nine countries of the African meningitis belt, 2010–15: an analysis of surveillance data. The Lancet Infectious Diseases 2017
2. Cooper LV, Boukary RM, Aseffa A, et al. Investigation of correlates of protection against pharyngeal carriage of Neisseria meningitidis genogroups W and Y in the African meningitis belt. PLoS ONE 2017;12
3. Kang SY, Battle KE, Gibson HS, et al. Heterogeneous exposure and hotspots for malaria vectors at three study sites in Uganda. Gates Open Research 2018;2
4. Cooper L, Kang SY, Bisanzio D, et al. Pareto rules for malaria super-spreaders and super-spreading. Nature Communications 2019;10:3939

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Reactive vaccination as a control strategy for pneumococcal meningitis outbreaks in the African meningitis belt: Analysis of outbreak data from Ghana

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ABSTRACT

Streptococcus pneumoniae is increasingly recognised as an important cause of bacterial meningitis in the African meningitis belt. The World Health Organization sets guidelines for response to outbreaks of meningococcal meningitis, but there are no current guidelines for outbreaks where *S. pneumoniae* is implicated. We aimed to evaluate the impact of using a similar response to target outbreaks of vaccine-preventable pneumococcal meningitis in the meningitis belt. Here, we adapt a previous model of reactive vaccination for meningococcal outbreaks to estimate the potential impact of reactive vaccination in a recent pneumococcal meningitis outbreak in the Brong-Ahafo region of central Ghana using weekly line list data on all suspected cases over a period of five months. We determine the sensitivity and specificity of various epidemic thresholds and model the cases and deaths averted by reactive vaccination. An epidemic threshold of 10 suspected cases per 100,000 population per week performed the best, predicting large outbreaks with 100% sensitivity and more than 85% specificity. In this outbreak, reactive vaccination would have prevented a lower number of cases per individual vaccinated (approximately 15,300 doses per case averted) than previously estimated for meningococcal outbreaks. Since the burden of death and disability from pneumococcal meningitis is higher than that from meningococcal meningitis, there may still be merit in considering reactive vaccination for outbreaks of pneumococcal meningitis. More outbreak data are needed to refine our model estimates. Whatever policy is followed, we emphasize the importance of timely laboratory confirmation of suspected cases to enable appropriate decisions about outbreak response.

1. Introduction

Following the rollout of the serogroup A conjugate vaccine, MenAfriVac, across the African meningitis belt since 2010, the incidence of meningococcal meningitis due to serogroup A has sharply declined [1]. With an accompanying increase in surveillance quality, it has become increasingly clear that meningitis due to *Streptococcus pneumoniae* (Spn) represents a substantial proportion of the burden of endemic meningitis in this region. In addition to this, localized outbreaks of pneumococcal disease, in excess of normal seasonal activity, have been reported [2–7].

The introduction of a 13-valent pneumococcal conjugate vaccine (PCV13) into Ghana's routine immunization programme as a 3 + 0 schedule in 2013 is expected to have decreased the burden of invasive pneumococcal disease in children aged under five years, based on observations from other African countries [8]. It has been shown in high-income countries that PCVs provide indirect protection against invasive pneumococcal disease to older children and adults and that this is accelerated with the use of catch-up campaigns, however the only country to show indirect benefit without a catch up campaign in older children used a 2 + 1 schedule [9,10]. The scale of indirect effects that might be achieved following

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routine infant PCV immunization in African countries is not yet clear. An outbreak of predominantly serotype 1 pneumococcal meningitis in the Brong-Ahafo region of Ghana in late 2015 and early 2016 demonstrated the ongoing vulnerability of older age groups and the continuing potential of Spn to cause meningitis outbreaks in spite of high PCV coverage in infants (94%) [2,11].

Outbreaks of meningococcal meningitis in the African meningitis belt trigger a reactive vaccination response, with the public health goal of curtailing the outbreak and thus preventing cases and deaths. It has been suggested that outbreaks of pneumococcal meningitis due to a vaccine-preventable serotype could also merit such a response [7,12]. To quantify the potential benefits of reactive vaccination for pneumococcal meningitis outbreaks we modelled a reactive vaccination response to the Brong-Ahafo pneumococcal meningitis outbreak. Under the current WHO guidelines applied to outbreaks of meningococcal meningitis, when districts exceed a threshold of 10 suspected cases per 100,000 population in a week, an epidemic response is triggered [13]. Countries may submit a request to the International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control for supplies of meningococcal vaccines to deploy in affected districts. However, this process takes some time as a request must be completed and reviewed and vaccine stocks must be delivered, often to inaccessible areas. For this model, we considered the potential impact of mass vaccination response in affected districts with PCV13, to see whether similar guidelines may be appropriate for outbreaks of pneumococcal meningitis.

When discussing disease in the African meningitis belt, it is important to distinguish between seasonal fluctuations in endemic disease, outbreaks – which may be defined as an isolated district surpassing the epidemic weekly incidence threshold, and widespread epidemics, which affect whole regions or countries in a season. For the purposes of this study, we define an outbreak of pneumococcal meningitis using two criteria: (i) weekly incidence on the regional or district level of suspected meningitis over a single dry season exceeding some epidemic threshold that reflects the upper bound of dry season endemic incidence, (ii) where pneumococcus is the predominant cause. We retain the term "epidemic threshold" for consistency with meningococcal vaccination policy, but do not mean to imply that these events constitute widespread epidemics.

2. Methods

Line list data on all suspected cases of meningitis reported in the Brong-Ahafo Region between 2 December 2015 (week 49, 2015) and 11 April 2016 (week 15, 2016) were obtained from the Ghana Health Service. Brong-Ahafo is a predominantly rural region located in central Ghana, an area previously considered to be just outside the main meningitis belt. A suspected case of meningitis was defined as any person with sudden onset of fever and one of the following signs: neck stiffness, flaccid neck (in infants), bulging fontanelle (infants) convulsion, or other meningeal signs [14]. We determined the sensitivity and specificity of a variety of incidence thresholds (10, 7, 5, and 3 suspected cases per 100,000 per week) for predicting a range of sizes of outbreaks (20, 40, 60, 80, and 100 cumulative cases per 100,000). We then modelled reactive vaccination of 5- to 29-year-olds building on methods developed in an earlier paper, using an epidemic threshold of 10 suspected cases per 100,000 per week to define the beginning of the outbreak and an endemic threshold of 2 suspected cases per 100,000 per week to define the end of the outbreak [15]. We also performed a sensitivity analysis using a lower epidemic threshold of 3 suspected cases per 100,000 per week, which corresponds to the alert threshold for meningococcal meningitis. We chose to target 5- to 29-year-olds because this would effectively extend coverage to all individuals under 30 years of age (we assumed children under the age of 5 years were protected by the routine infant PCV13 vaccine schedule) and because the highest incidence of confirmed pneumococcal meningitis was observed in the 10 to 14- and 15 to 29-year age groups.

As a variety of laboratory tests were used for case confirmation, aetiology was classified according to Table 1. In a large proportion of cases (60%), aetiology could not be definitively determined. For this reason, we modelled true cases of Spn meningitis weekly for each district as (see Table 2)

$$C_{Spn} = C_{s,i}(1 - p_n)p_{Spn}$$

where $C_{s,i}$ is the number of suspected cases reported in week i, p_n is the proportion of CSF samples in the district testing negative (in Table 1, both probable and confirmed negative cases), and p_{Spn} is the proportion of all confirmed cases in the district due to Spn. This modelled case count is hereafter referred to as likely Spn cases. Because there was some uncertainty regarding false negative tests, we performed a sensitivity analysis where p_n is only the proportion of CSF samples in the district testing negative by two or more tests (in Table 1, confirmed negative cases).

We then simulated vaccination with PCV13 using the same methods described in Trotter et al. [15], making the following assumptions:

- 5- to 29-year-olds represent 52% of the population [16]
- Case fatality ratio for pneumococcal meningitis cases is 23%, as reported for confirmed pneumococcal meningitis cases in this data set
- 79% of cases of pneumococcal meningitis were caused by PCV13 vaccine-type serotypes [2]
- A single dose of PCV13 would protect at 90% of individuals 5–29 years of age against PCV13 vaccine-type serotypes, giving two weeks for the protection to take effect [17]
- 5% vaccine wastage

One district, Sene West, was excluded from the analysis despite having crossed the epidemic threshold because the majority of confirmed cases were due to Nm.

We determined the cases prevented, deaths prevented, number needed to vaccinate to prevent a case (NNV) and number needed to vaccinate to prevent a death (NNVD) for three scenarios: where vaccination occurs immediately, two, and four weeks after crossing the epidemic threshold (lag of zero, two or four weeks, respectively).

Table 1
Classification of case etiology; frequency and case fatality rates by etiology.

Classification	Criteria	Number of cases	Case fatality rate
Spn	Any test (Pastorex, culture or PCR) indicating Spn or positive gram stain	168	23%
Nm	Any test (Pastorex, culture or PCR) indicating Nm or negative gram stain	40	23%
Indeterminate	Any sample with no test results	209	15%
Probable negative	One test (Pastorex, culture, PCR or gram stain) failing to indicate bacteria in CSF	366	2%
Confirmed negative	Two or more tests (Pastorex, culture, PCR or gram stain) failing to indicate bacteria in CSF	183	0%

Table 2
Summary of line list data for the 19-week study period by district.

District	Population	Suspected meningitis cases	Confirmed Spn meningitis cases	Confirmed Nm meningitis cases	Epidemic threshold (suspected weekly cases 10 per 10^5) exceeded	Cumulative incidence per 10^5
Asunafo North	143,000	14	7	1	No	9.8
Asutifi North	60,800	1	0	0	No	1.6
Asutifi South	60,600	4	2	1	No	6.6
Atebubu-Amanten	121,000	12	3	0	No	9.9
Berekum	149,000	2	2	0	No	1.3
Dormaa East	58,300	6	1	0	No	10.3
Dormaa Municipal	129,000	27	7	1	No	21.0
Jaman South	106,000	7	5	7	No	6.6
Kintampo North	109,000	11	3	1	No	10.1
Pru	148,000	9	3	2	No	6.1
Sene East	69,400	5	1	0	No	7.2
Sunyani Municipal	141,000	28	9	0	No	19.8
Tano South	89,600	4	2	0	No	4.5
Techiman Municipal	169,000	77	10	4	No	45.5
Jaman North	95,200	364	39	2	Yes	382.3
Nkoranza South	116,000	100	24	6	Yes	86.4
Sene West	66,800	20	2	0	Yes	29.9
Tain	101,000	145	19	12	Yes	143.6
Techiman North	67,700	20	1	1	Yes	29.5
Wenchi	103,000	110	28	2	Yes	106.9

3. Results

Twenty of the 27 districts of the Brong-Ahafo Region were represented in the line list. The districts had a mean population size of 105,000. Over the 19-week study period, nine of these had cumulative suspected meningitis incidence greater than 20 suspected cases per 100,000; five had cumulative incidence greater than 40 per 100,000; four had cumulative incidence greater than 80 per 100,000, and three had cumulative incidence greater than 100 per 100,000. For predicting larger outbreaks of 60 suspected cases per 100,000 and greater, all thresholds had a sensitivity and negative predictive value of 100%, but a threshold of 10 per 100,000 per week had the best positive predictive values and specificity (Fig. 1).

Five districts (Jaman North, Nkoranza South, Tain, Techiman North, and Wenchi) crossed the epidemic threshold of 10 cases per 100,000 per week, three of which exceeded a cumulative incidence of 100 cases per 100,000 (Fig. 2).

Sixty-six percent of suspected bacterial meningitis cases in the five outbreak districts and 73% of confirmed pneumococcal meningitis cases occurred in 5- to 29-year-olds. Fig. 3 shows the age distribution of suspected and confirmed incidence of meningitis in the five districts triggering the epidemic threshold.

Vaccinating individuals between 5 and 29 years of age in the five eligible districts would have required approximately 284,000 doses of vaccine (Table 3). If a vaccination campaign had been implemented within two weeks of triggering the epidemic threshold of 10 suspected cases per 100,000 per week, an estimated number of 36 cases would have been prevented during the outbreak period, placing the number needed to vaccinate to prevent a case at 15,300. With a delay of four weeks, 20 cases might have been prevented, whereas immediate vaccination might have averted 61 cases.

Using a lower threshold of 3 cases per 100,000 per week prevents only a few more cases, but raises the number needed the vaccinate to prevent a case significantly because districts with much smaller outbreaks also trigger a response.

Using a stricter definition for bacteria negative CSFs results in a much higher estimate of the number of likely Spn meningitis cases (335 cases as opposed to 176 in the five outbreak districts) and a lower number needed to vaccinate to prevent a case (Table S1). With a delay of two weeks, 63 cases might have been prevented, placing the number needed to vaccinate at 8800, whereas immediate vaccination might have averted 113 cases, placing the number needed to vaccinate at 4800.

4. Discussion

An incidence threshold of 10 cases per 100,000 seems the most appropriate epidemic threshold for pneumococcal meningitis outbreaks given the limited data available. This threshold would also have been triggered in four of five previous likely outbreaks of pneumococcal meningitis identified in the WHO enhanced meningitis surveillance system (Solenzo, Burkina Faso, 2009; Goundi, Chad, 2009; Karangasso Vigue, Burkina Faso, 2011; Pama, Burkina Faso, 2011) [1]. No attempt was made to evaluate different microbiological criteria for defining a pneumococcal outbreak. In this case, a simple majority of confirmed cases due to Spn was required.

Excluding the sensitivity analysis, the number needed to vaccinate to prevent a case (NNV) is higher than the range of previous estimates for reactive meningococcal campaigns (3700–11,600 for 2–4 week lag) [15], suggesting that reactive vaccination for pneumococcal meningitis outbreaks may be less efficient in preventing cases. Whilst the number needed to vaccinate to prevent a death (NNVD) has not been estimated for reactive meningococcal campaigns, the NNVD is expected to be lower for reactive vaccination in pneumococcal outbreaks given the higher case-fatality rates typically associated with pneumococcal meningitis [18].

It is not certain how quickly immune response would build up after PCV13 in the targeted age groups, however, a clinical trial of naïve 10- to 18-year-olds showed high (>90%) responsiveness one month post-vaccination [17]. A conjugate vaccine like PCV13 would also have additional indirect benefits, decreasing carriage and transmission of vaccine-type serotypes where it is used, although realizing the full indirect benefits would take several months.

Serotype 1 was particularly dominant in this outbreak. Seven other studies in the meningitis belt have reported serotype distribution of pneumococcal meningitis cases, all in populations with no PCV use [3,6,18–22]. Overall, 45% were serotype 1. Kwambana-Adams 2016 reports a higher proportion of isolates belonging to serotype 1 (67% overall) in the Brong Ahafo outbreak than in the other studies [2]. Among the other studies, there are no

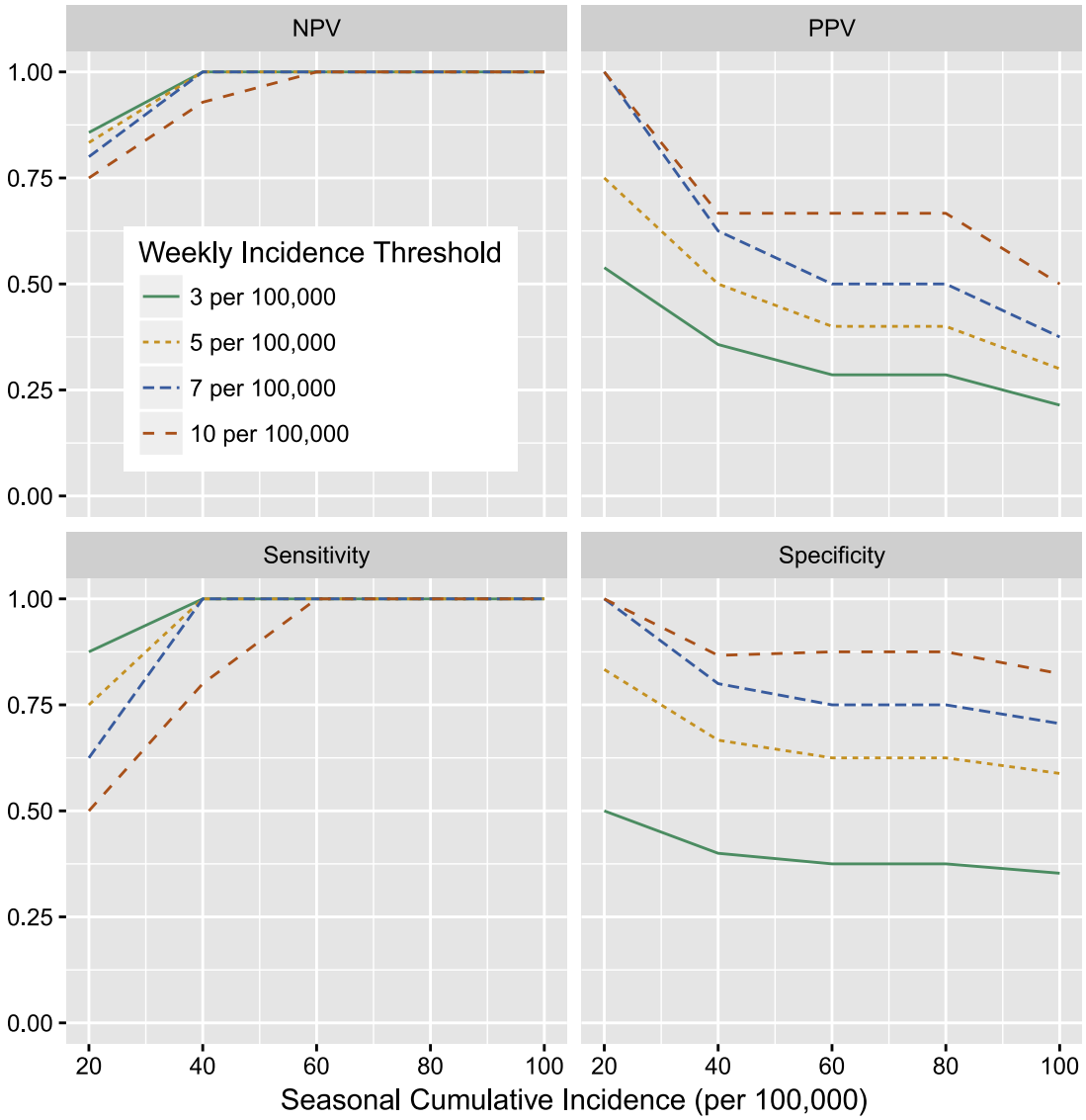

Fig. 1. Negative predictive value (NPV), positive predictive value (PPV), sensitivity, and specificity of various incidence thresholds (3, 5, 7, and 10 suspected cases per 100,000 per week) for predicting a range of sizes of outbreaks.

marked differences between settings described as "epidemic" or "outbreak" and endemic settings. There are no appropriate data available to support or contradict the hypothesis that outbreaks or clusters of disease tend to be caused by a single serotype because most serotyping data is published as aggregate data over many years.

This model is more conservative than the model used to evaluate reactive meningococcal vaccination [15]. Whereas the meningococcal model assumed all cases occurred in individuals under 30 years of age, this model estimates that only 70% of cases occur in the targeted age group. The meningococcal model also assumed that 79% of suspected cases were due to NmW. In addition, the surveillance system relies on a case definition of meningitis; immunization against Spn may prevent additional cases of pneumonia and septicaemia making these estimates conservative.

However, the predictions of this model are highly dependent on the age distribution of cases, the proportion of cases due to Spn, and the overall shape of the incidence curve over time. The data from the Brong-Ahafo outbreak show a particularly strong peak in the 15- to 29-year age group, similar to distributions reported from endemic situations [18]. By contrast, the distribution of incidence of Spn meningitis from Traore 2009 peaks sharply in infants but is otherwise fairly even across age groups despite a description in the discussion of "epidemic" patterns [3].

Because many cases had no associated laboratory data, we have chosen to model suspected Spn meningitis cases. As our sensitivity analysis has shown (Table S1), reactive vaccination may be more or less effective depending on underlying assumptions about the true proportion of suspected meningitis cases caused by *S. pneumoniae*. The case-fatality rates in each category support our classification system, with low rates in bacteria-negative cases, intermediate rates in untested cases, and high rates in Spn- and Nm-confirmed cases (Table 1).

These predictions are also dependent on how quickly the outbreak progresses. In this outbreak, 14% of suspected cases occurred within four weeks of triggering the epidemic threshold – in other words, 14% of suspected cases would be missed by a reactive response with a lag of two weeks. A higher proportion of suspected cases occurred in the first four weeks of past suspected pneumococcal meningitis outbreaks: 18% in Goundi, Chad in 2009, 28% in Karangasso Vigue, Burkina Faso in 2011, 21% in Pama, Burkina Faso in 2011 and 38% in Solenzo, Burkina Faso in 2009 [1].

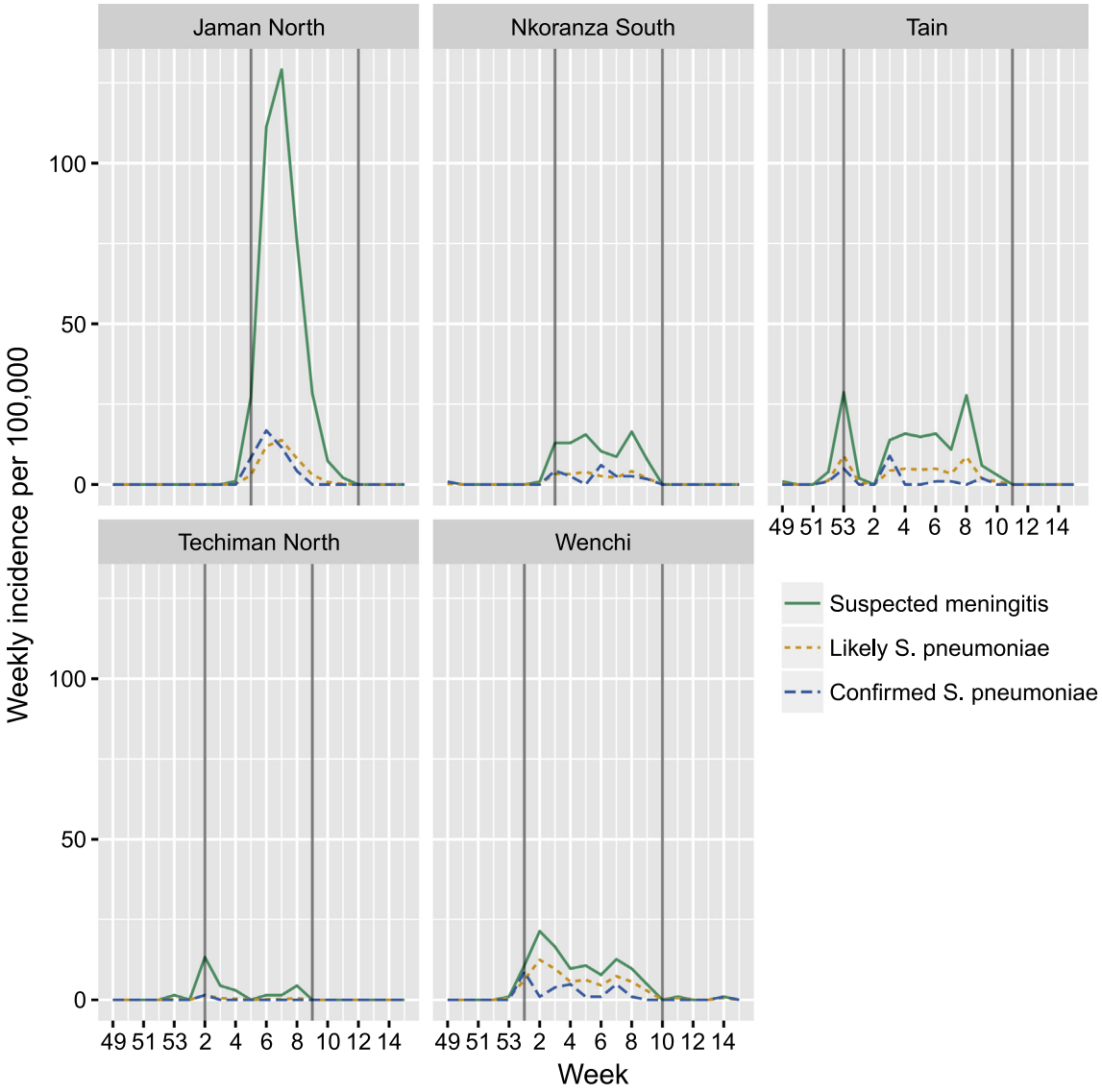

Fig. 2. Incidence of suspected meningitis, likely and confirmed pneumococcal meningitis in five districts crossing the epidemic threshold of 10 cases per 100,000. Grey vertical lines indicate beginning and end of outbreak period.

Our estimates, based on data from the Brong-Ahafo outbreak, suggest that reactive vaccination for pneumococcal meningitis would have prevented fewer cases per dose of vaccine than previous estimates for meningococcal meningitis reactive vaccination (a routine intervention in the African meningitis belt). As the size and duration of outbreaks are likely to vary by country and by year, data from future outbreaks are needed to refine these estimates.

It is clear that any reactive response must be timely in order for it to be effective. A particular challenge is ensuring rapid microbiological confirmation of the organism responsible for the outbreak and serotyping of pneumococcal isolates to determine if the outbreak is due to a vaccine-type strain. In Brong-Ahafo, serotyping facilities were initially not available locally and samples were sent to the MRC laboratory in The Gambia, leading to an interval of several weeks before results were available. A technical mission from MRC the Gambia provided support to establish serotyping capacity in Sunyani Hospital in Brong-Ahafo during the course of the outbreak. In addition, CDC established PCR capability at Tamali Zonal Public Health Laboratory during the outbreak, which serves Brong-Ahafo. If reactive vaccination for pneumococcal meningitis outbreaks were to be recommended by WHO, it will be important to ensure that other meningitis belt regions also establish and maintain serotyping capacity. Even if reactive vaccination for pneumococcal meningitis outbreaks is not recommended, building laboratory capacity in these regions will benefit health systems more broadly.

This study does not evaluate the potential impact of mass preventive vaccination, or of extending PCV coverage to older age groups through catch-up campaigns. WHO's Strategic Advisory Group of Experts (SAGE) on Immunization reviewed primary data on PCV vaccine schedules and their impact on carriage and disease, together with evidence from modelling studies on the impact of catch-up campaigns in October 2017 (http://www.who.int/immunization/policy/sage/en/). Further work may be warranted to quantify the impact of extending PCV to older ages (over 5 years) in preventive campaigns, but this is beyond the scope of this paper.

With the roll-out of PCV in the African meningitis belt, the risk of pneumococcal meningitis outbreaks and the need for subsequent reactive vaccination responses may recede as increasing numbers of birth cohorts are protected. The WHO is currently reviewing whether a different vaccination schedule with a subsequent booster dose would be more appropriate for this setting [12]. Meanwhile, this study provides the first evidence that

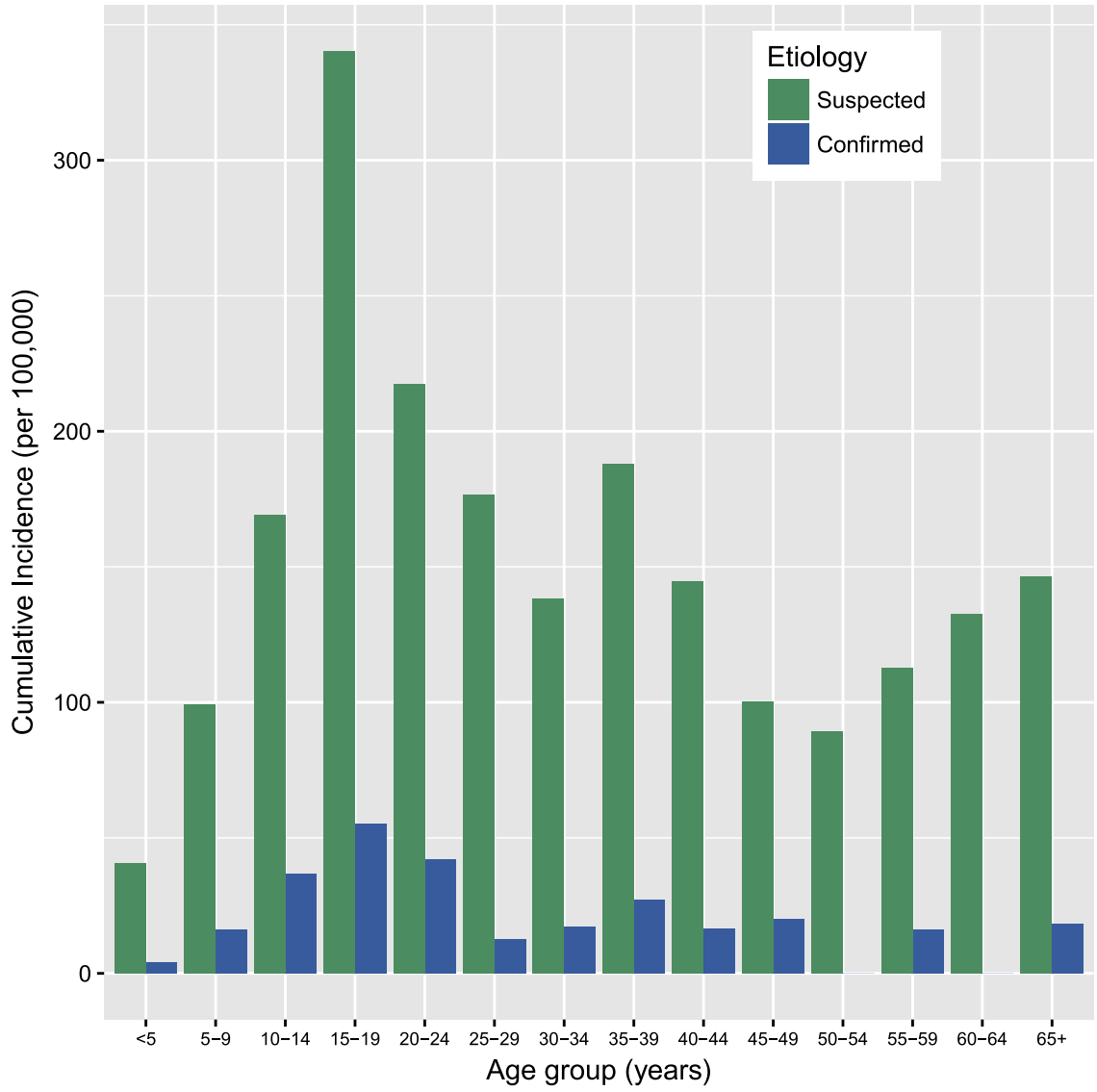

Fig. 3. Age distribution of suspected meningitis and confirmed pneumococcal meningitis incidence in five districts crossing the epidemic threshold of 10 cases per 100,000.

Table 3
Cases and deaths prevented by reactive vaccination with different lag time (weeks between crossing of incidence threshold and implementation of reactive vaccination campaign).

Incidence threshold	Lag in weeks	Cases prevented (% of total likely Spn [C_{Spn}] cases during outbreak)		Deaths prevented	Number needed to vaccinate to prevent a case	Number needed to vaccinate to prevent a death
10	0	61	35%	14	9100	39,100
10	2	36	21%	8	15,300	66,000
10	4	20	11%	5	27,800	120,000
3	0	63	32%	15	22,500	96,900
3	2	40	20%	9	35,300	152,000
3	4	23	12%	6	60,500	261,000

reactive pneumococcal vaccination could prevent cases and save lives during confirmed outbreaks. Additional work is needed to clarify the conditions warranting a response, and the logistical implications of supplying PCV13 for reactive vaccine campaigns.

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Conflict of interest

CLT reports personal fees from GlaxoSmithKline and Sanofi Pasteur, outside the submitted work. All other authors declare no competing interests. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2017.12.069.

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Meningococcal carriage by age in the African meningitis belt: a systematic review and meta-analysis

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Abstract

Meningococcal carriage dynamics drive patterns of invasive disease. The distribution of carriage by age has been well described in Europe, but not in the African meningitis belt, a region characterised by frequent epidemics of meningitis. We aimed to estimate the age-specific prevalence of meningococcal carriage by season in the African meningitis belt. We searched PubMed, Web of Science, the Cochrane Library and grey literature for papers reporting carriage of *Neisseria meningitidis* in defined age groups in the African meningitis belt. We used a mixed-effects logistic regression to model meningococcal carriage prevalence as a function of age, adjusting for season, location and year. Carriage prevalence increased from low prevalence in infants (0.595% in the rainy season, 95% CI 0.482–0.852%) to a broad peak at age 10 (1.94%, 95% CI 1.87–2.47%), then decreased in adolescence. The odds of carriage were significantly increased during the dry season (OR 1.5 95% CI 1.4–1.7) and during outbreaks (OR 6.7 95% CI 1.6–29). Meningococcal carriage in the African meningitis belt peaks at a younger age compared to Europe. This is consistent with contact studies in Africa, which show that children 10–14 years have the highest frequency of contacts. Targeting older children in Africa for conjugate vaccination may be effective in reducing meningococcal transmission.

Introduction

Most transmission of *Neisseria meningitidis* occurs amongst carriers; therefore vaccinating carriers is the only way to generate herd protection. Experience with conjugate vaccines has shown that with the correct age-specific strategy, such indirect effects make a profound contribution to disease control [1]. To this end, it is important to understand the distribution of meningococcal carriage to allow for efficient targeting of individuals who account for the most transmission. The age distribution of meningococcal carriers in industrialised countries has been described and synthesised; this showed that prevalence peaks around 19 years of age [2]. Patterns of carriage are however known to differ in the African meningitis belt, a region that experiences the highest burden of meningococcal disease in the world. Meningococcal carriage is a common occurrence compared to invasive disease, although the overall prevalence is highly variable, ranging from 0% to 30% [3,4]. Although the distribution of carriage prevalence by age also appears more variable in the African meningitis belt than in high-income countries, some studies have shown that carriage is most prevalent in children [3].

Studies of meningococcal carriage in the African meningitis belt have identified a number of risk factors apart from age. A multi-site cross-sectional study found increased odds of meningococcal carriage in rural areas *vs.* urban and higher prevalence in males [4]. Household crowding and pollution from tobacco and indoor kitchen facilities also increased the odds of carriage significantly [4]. The association between respiratory infection and meningococcal carriage remains unclear, but some studies indicate a positive relationship between carriage acquisition and symptoms of respiratory disease, like sore throat or rhinitis [5]. Localised epidemics of meningococcal meningitis occur frequently in the belt, but there is no clear relationship between epidemic status and the prevalence of carriage. One study found higher rates of serogroup W carriage in a district experiencing a group W epidemic compared to a neighbouring non-epidemic district, prompting speculation that it may be dominance of a strain rather than overall prevalence that links carriage and epidemics [6].

Season is an important risk factor for carriage in the African meningitis belt. Meningitis epidemics in the meningitis belt occur in the dry season and mathematical models of meningococcal transmission dynamics currently require substantial 'seasonal forcing' of transmission

to reproduce the observed patterns of disease [7]. One study found higher odds of carriage of capsular meningococci during the dry season; [4] this has not been demonstrated consistently but is compatible with the idea that the capsule protects the bacterium from drying during aerosol transmission. Carriage of unencapsulated strains does not appear to have any association with season [4].

Previous reviews of the literature on meningococcal carriage in Africa have not been systematic in nature and have not examined age-specific patterns in any quantitative way. The aim of this paper was to conduct a systematic literature review of meningococcal carriage prevalence by age and season in the African meningitis belt and to synthesise these data in order to inform future vaccination strategies.

Methods

Search and study selection

This paper was prepared in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) and PRISMA guidelines [8,9]. The literature searches were performed by one author (LVC) in January 2017 and updated in September 2017. PubMed, Web of Science, the Cochrane Library and the grey literature were searched for papers reporting carriage of *N. meningitidis* in defined age groups in locations within the African meningitis belt, using the following search terms: '('Neisseria meningitidis' OR 'N meningitidis' OR meningitis OR meningococcal OR meningococci OR meningococcus OR meningitidis) AND (carriage OR carrier OR carriers) AND (Africa OR 'meningitis belt' OR Gambia OR Senegal OR Guinea-Bissau OR Mauritania OR Guinea OR Ghana OR 'Burkina Faso' OR 'Upper Volta' OR 'Cote d'Ivoire' OR 'Ivory Coast' OR Togo OR Benin OR Nigeria OR Niger OR Chad OR Tchad OR Cameroon OR 'Central African Republic' OR Sudan OR 'South Sudan' OR Eritrea OR Ethiopia OR Uganda OR Kenya OR 'Democratic Republic of Congo OR Zaire)'.

Studies were eligible for inclusion if they reported pharyngeal carriage of all meningococcal serogroups in defined age groups in generalisable populations in the African meningitis belt. Longitudinal, cross-sectional and serial cross-sectional study designs were included. Studies reporting carriage rates among household contacts of Hajjis or other known carriers were excluded. Studies in both English and French were included in the systematic review. Two studies in Russian were excluded because abstracts could not be obtained. The reference lists of included papers were hand-searched to identify any papers that were missed by the electronic search.

Data extraction and classification

We contacted authors for additional information if studies reported age groups wider than 10 years and the median age was not reported or if the time period of the study was not reported. Where carriage prevalence was reported in age groups of range 10 years or less, we used the midpoint age for analysis. For open-ended age groups, we calculated a midpoint with an upper age limit of 60 years. Using additional data from the African Meningococcal Carriage Consortium cross-sectional studies, we divided the oldest age group previously reported as 30 plus years into two groups, 30–44 years and 45 plus years.

For papers that included results from several populations or studies, data were extracted only for observations meeting the inclusion criteria. Extracted data included the study location, time period, design, any mention of an outbreak or epidemic of meningitis coinciding with the study period, whether the study occurred before or after the MenAfriVac mass campaigns in the study region, use of random sampling, laboratory used to culture the pharyngeal swabs, time between sampling and plating, age range of the individuals, median age of individuals in each age group, number of individuals swabbed and the number of individuals positive for capsulated meningococcal carriage. We excluded individuals carrying capsule-null isolates from our definition of capsulated meningococcal carriage but isolates characterised as non-determinate or non-groupable were included.

Studies were assigned to the dry or rainy season on the basis of the month in which the study took place, defining the dry season as December–June and the rainy season as July–November. Additional data from the studies by Kristiansen and colleagues in Burkina Faso and Ethiopia were used to divide prevalence estimates from these studies into dry and rainy season measures.

Studies were classified as having used random sampling if this was specifically reported; otherwise 'no' was recorded.

Data were extracted independently by LVC and AK and differences were checked by CLT.

Data analysis

For the meta-analysis, we excluded data from age bands wider than 20 years. For longitudinal studies, only the first observation in the time series was used to avoid over-representing a particular population in the meta-analysis.

A natural cubic spline (a piecewise cubic polynomial function with linear tails) was used to model group median age [2,10]. The basis matrix for the spline was generated using the 'ns()' function in the R core package 'splines'. Boundary knots (points in the spline below and above which the function is defined to be linear) were placed at 0 and 30 years because of the low density of sampling in older age groups. The number of internal knots was selected by comparing the AIC of models with two and three internal knots, placing knots at appropriate quantiles (inner tertiles for two knots, inner quartiles for three knots. Optimal placement of these knots was determined by evaluating the AIC of models with every possible combination of knots drawn from the set of ages equidistant from every consecutive observed age between 0 and 30 years. Internal knots placed at 9.25, 9.75 and 28.5 years of age gave the best model fit.

We modelled season and outbreak status as a three-tiered fixed effect and a nested interaction term of location and year of swabbing as random effects. We used fixed effects for factors that had a constant effect in all studies and random effects for factors for which only a subset of all possible levels had been observed. We tried using the physical laboratory as a proxy for differences in ambient temperature, growth medium, swab type and other unreported factors which might affect the likelihood of isolating meningococci from a sample, but this did not improve model fit. Other factors that were considered but did not improve model fit included mass group A conjugate vaccination, country, decade, latitude, time to plating and study.

We started with a simple logistic regression because this is the traditional model for analysing prevalence data. However, when we found that a low proportion of observations fell within the bootstrapped 95% CI, we investigated three additional models

which are commonly used to capture overdispersion: an observation-level random effects model, a beta-binomial or hierarchical model and a zero-inflated binomial model [11]. We found that the simple logistic regression captured more of the variability in the data than the observation-level random effects model and provided a better fit than the beta-binomial and zero-inflated binomial models, so we used a logistic structure for our final model.

All candidate models allow overall carriage prevalence to vary but constrain the distribution of prevalence by age to be the same across all years and locations.

Models were fit using the lme4, spaMM and glmmADMB packages in R [12–15]. To generate confidence intervals for the model predictions and random effects, 10 000 iterations of bootstrapping with replacement were performed and bias-corrected 95% confidence intervals were calculated [16]. Profile confidence intervals for fixed effects parameters were calculated using the lme4 package [12]. We assessed model fit by AIC and by performing leave-one-out cross-validation, whereby the model is refit on the full dataset excluding a single observation and this new model is used to predict prevalence in the excluded observation. This prediction is then compared to the true value. To check the results of the spline model, we identified the age group with the highest carriage prevalence for each study measuring carriage in more than one age group and performed a one-way proportion test between this peak value and prevalence in all other age groups. To adjust for repeated significance testing, we used an upper *P*-value cut-off of 0.0005, yielding an overall confidence of >95%.

We checked our season definition against average monthly rainfall anomalies in each site using publicly available data from the National Oceanic and Atmospheric Administration (Fig. S1). In a sensitivity analysis, we excluded data from four sites with non-characteristic rainfall patterns. These sites all fell on the edges of the meningitis belt: Butajira, Ethiopia (2 sub-sites), Arba Minch, Ethiopia (4 sub-sites) and Kpalkpalgbeni, Bring-Ahafo District, Ghana.

For the visual presentation of the fixed-effects portion of the model, we adjusted the observed carriage prevalence ($P_{observed}$) to account for the random effects in the full model as follows: $P_{adjusted} = \exp(\log(P_{observed}) - \sigma_{Location} - \sigma_{Location\text{-}year})$, where $\sigma_{Location}$ and $\sigma_{Location\ -year}$ are the random effects intercept for location and year for a given observation.

To estimate the proportion of carriers that would be targeted in a mass vaccination campaign covering four age groups (0–15 years, 0–17 years, 0–19 years and 0–29 years) we assumed a population structure consistent with that of Niger in 2017 and used the fitted estimate of carriage prevalence for the rainy season (although results are consistent across seasons) [17]. We accounted for uncertainty in this estimate by simulating 100 000 draws from a uniform distribution with boundaries at the 2.5th and 97.5th percentile of the fitted prevalence, using these draws as the rates for a random binomial draw with population size corresponding to each single year age cohort in Niger 2017 and then taking the 2.5th and 97.5th percentiles of the proportion covered to yield a 95% confidence interval.

Assessment of study quality and heterogeneity

We assessed the role of study design by comparing a model with and without sampling procedure (random *vs.* non-random) and with and without time to plating of swabs as fixed-effect variables.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 23 relevant articles that reported unique studies of carriage by age in generalisable populations in the African meningitis belt representing eight countries: Burkina Faso, Chad, Ethiopia, Ghana, the Gambia, Mali, Nigeria and Niger. Eleven were cross-sectional studies; five serial cross-sectional, four longitudinal and three were vaccine trials (two polysaccharide and one conjugate vaccine). Twelve of 23 articles did not report randomisation in participant selection. Sixteen studies were eligible for inclusion in the meta-analysis (Table 1). Seven of these 16 did not report random sampling. Eighteen of 23 studies in the systematic review and 15 of 16 eligible for inclusion in the meta-analysis reported information on the serogroups or genogroups of the carriage isolates (Table 2). See Figure 1 and Tables S1 and S2 for further details of search and reasons for exclusion.

Systematic review

Longitudinal studies

Longitudinal studies reported high variation in carriage rates over time (1–35%), but no significant differences in carriage prevalence between age groups, probably because of smaller sample sizes [18–21]. Prevalence recorded around the time of meningococcal outbreaks was high in recent studies (2000s and 2010s), with two studies showing particularly high rates in ages 5–29 years (16–38%) [22–24]. Two early studies (1970s) of carriage during a single group A meningococcal outbreak found lower rates of carriage (2–5%) [25,26].

Studies of seasonal change

Most studies which specified months comprising the dry and rainy seasons placed the beginning of the dry season between November and January and the beginning of the rainy season between April and July. One study also included a Harmattan season (October–January) between the rainy and dry seasons [27]. Early studies documented the variability of carriage prevalence in the African meningitis belt but found little support for consistent differences in prevalence by season. A year-long study in Burkina Faso found a wide variation in carriage rates but no significant changes associated with the onset of the rainy season [21]. Two other studies found similarly variable results with no obvious seasonal patterns [27,28]. One study in rural northern Nigeria displayed remarkably stable prevalence over the year, with carriage ranging from 2.1% to 2.7% at four sampling intervals [28]. These early studies may have been limited by their relatively short duration or small sample sizes.

An 8-year longitudinal study of a cohort ($n \sim 300$) in Northern Ghana measured carriage twice annually, in April and November. Although this was not noted in associated publications, the average carriage rate in November (4.4%) was substantially lower than that in April (7.9%) [18]. This was the first study to produce evidence supporting the hypothesis that carriage prevalence increases during the dry season.

Table 1. Carriage studies included in meta-analysis. Summary of studies of meningococcal carriage by age in the African meningitis belt included in meta-analysis

Paper	Location	Study period	Study design	Study population	Ages
Burian *et al.*, 1974 [35]	Bamako, Mali	Jan–May 1970	Cross-sectional	School children, children seen at preventative care centers, contacts of cases	All ages
Blakebrough *et al.*, 1980[25]	Malumfashi, Nigeria	Dec 1977 to Jun 1978	Cross-sectional	School children	5–10
Blakebrough *et al.*, 1983[26]	Malumfashi, Nigeria	Jan–May 1978	Vaccine trial	School children (boys), both controls and polysaccharide vaccines	11–20
Leimkugel *et al.*, 2007[18]	Navrongo, Ghana	Apr 1998 to Nov 2005	Longitudinal	General	All ages
Amadou Hamidou *et al.*, 2006[19]	Niamey, Niger	Feb–May 2003	Longitudinal	School children	7–16
Yaro *et al.*, 2007 [20]	Bobo-Dioulasso, Burkina Faso	Feb–Jun 2003	Longitudinal	General	4–29
Forgor *et al.*, 2005 [23][a]	Kpalkpalgbeni, Ghana	Apr 2003 to Apr 2004	Serial cross-sectional	General	All ages
Mueller *et al.*, 2011[22]	Ouagadougou, Burkina Faso	Mar 2006	Cross-sectional	General	1–39
Trotter *et al.*, 2013 [36]	Bobo-Dioulasso, Burkina Faso	Mar 2008	Cross-sectional	General	0–59
Kristiansen *et al.*, 2011[29]	Bogodogo, Dande and Kaya, Burkina Faso	Feb–Nov 2009	Serial cross-sectional	General	1–29
Basta *et al.*, 2013 [37]	Bamako, Mali; Butajira, Ethiopia; Niakkar, Senegal; Say, Niger	Jun 2009 to Jan 2010	Cross-sectional	School children	5–15
MenAfriCar Consortium 2015 [4]	Bamako, Mali; Narena and Siby, Mali; Butajira, Ethiopia[a]; Fatick, Senegal; Niakkar, Senegal; Kassena-Nankana, Ghana; Navrongo, Ghana; Konduga, Nigeria; Maiduguri, Nigeria; Mandelia, Chad; N'Djamena, Chad; Say, Niger; Yantala, Niger	Apr 2010 to Jul 2012	Serial cross-sectional	General	All ages
Kristiansen *et al.*, 2013[30]	Bogodogo, Dande and Kaya, Burkina Faso	Oct 2010 to Nov 2011	Serial cross-sectional	General	1–29
Kristiansen *et al.*, 2014[33]	Bogodogo, Dande and Kaya, Burkina Faso	Oct–Nov 2012	Cross-sectional	General	1–29
Manigart *et al.*, 2016[38]	Fajikunda, the Gambia	Jul 2013	Cross-sectional	General	10–18
Bårnes *et al.*, 2016 [39][a]	Arba Minch, Ethiopia	Mar–Sep 2014	Cross-sectional	General	1–29

[a]Observations excluded in sensitivity analysis–climactic outlier sites.

A multi-site serial cross-sectional study in Burkina Faso measuring carriage four times annually in 2009 and 2011 found significantly higher carriage prevalence in dry season surveys than in rainy [29,30]. Finally, a serial cross-sectional study across seven countries of the meningitis belt found significantly elevated odds of carriage during the dry season as compared with the rainy (adjusted OR, 1.54; 95% CI, 1.37–1.75) [4].

Laboratory methods

All studies relied on culture for the initial identification of meningococcal isolates. Between one and ten colonies were selected for further testing, most commonly serogrouping. Fourteen of 23 studies (all published after 2000) reported using molecular methods for confirmation and further characterisation of culture isolates.

Meta-analysis

Data from 16 papers, comprising 114 331 individual swabs, were available for quantitative data synthesis.

The four model variants tested did not vary greatly in their parameter estimates and goodness of fit (Table S3). We selected the simple logistic regression model because the greatest proportion of observations fell within the 95% confidence interval of bootstrapped predictions and the leave-one-out cross-validation

Table 2. Meningococcal serogroup distribution. Summary of the serogroup distribution of *N. meningitidis* isolated from carriers in the African meningitis belt

			Serogroup distribution					
Study	Year of data collection	Prevalence of carriage	A	C	W	X	Y	NG
Burian 1974[35]	1970	144/2569 (5.6%)	19%	1%	…	9%	4%	56%
Sanborn 1971[40][a,d]	1971	179/311 (57.6%)	52%	…	…	…	…	…
Blakebrough 1980[25][d]	1977	7/130 (5.4%)	43%	…	…	…	…	…
Blakebrough 1983[26][d]	1978	4/168 (2.4%)	50%	…	…	…	…	…
Leimkugel 2007[18]	1998	14/300 (4.7%)	57%	…	7%	0%	29%	7%
Raghunathan 2006[6][a]	2002	203/899 (22.6%)	0%	1%	65%	6%	…	28%
Amadou-Hamidou 2006[19]	2003	38/287 (13.2%)	0%	…	34%	…	11%	55%
Forgor 2005[23][b,d]	2003	48/299 (16.1%)	…	…	71%	…	…	…
Yaro 2007[20]	2003	16/456 (3.5%)	…	…	50%	0%	0%	50%
Mueller 2011[22]	2006	129/615 (21%)	74%	…	…	…	26%	…
Sié 2008[24][a,d]	2006	24/180 (13%)	92%	…	…	…	…	…
Trotter 2013[36]	2008	12/1037 (1.2%)	…	…	25%	8%	42%	25%
Kristiansen 2011[29]	2009	809/20 326 (4%)	10%	0%	9%	11%	56%	13%
Kristiansen 2013[30]	2010	1643/25 520 (6.4%)	0%	0%	6%	75%	13%	5%
MenAfriCar Consortium 2015[4][b]	2010	896/48 405 (1.9%)	5%	3%	69%	2%	7%	11%
Kristiansen 2014[33]	2012	390/4964 (7.9%)	0%	6%	87%	8%	3%	2%
Manigart 2016[38][c]	2013	33/999 (3.3%)	0%	6%	33%	0%	9%	30%
Bårnes 2016[39][b]	2014	492/7479 (6.6%)	0%	1%	6%	14%	2%	76%
All meta-analysis	1970–2014	4703/114 331 (4.1%)	5%	1%	26%	31%	17%	17%
Pre-MenAfriVac	1970–2014	2637/73 202 (3.6%)	10%	2%	25%	9%	23%	27%
Post-MenAfriVac	2010–2012	2066/41 129 (5.0%)	<1%	<1%	27%	59%	9%	4%

[a]Excluded from meta-analysis.
[b]Climactic outliers excluded from meta-analysis in sensitivity analysis.
[c]Two group E and five group B carriers also reported.
[d]Percentages do not sum to 100 because full serogroup data not reported.

correlation was greatest for this model. This best-fitting model had season as a fixed effect and location and year as random effects.

The fixed effects parameters of the final model are shown in Table 3. The model suggests that meningococcal carriage prevalence in the African meningitis belt increases rapidly in childhood, peaks at 10 years of age (1.94% in the rainy season, 95% CI 1.87–2.47%) and gradually declines after this point (Fig. 2). In a country with the same population structure as Niger, our model estimates that 58% of carriers are under the age of 16 and 84% are under the age of 30 (Table 4). Odds of carriage were significantly increased for studies taking place during the dry season (1.5 95% CI 1.4–1.7) as compared with the rainy season and further increased for studies taking place during outbreaks (OR 6.7 95% CI 1.6–29), though the uncertainty in the latter estimate is high as limited data on carriage during outbreaks are available. No other risk factors were found to significantly impact the odds of carriage.

Predicted carriage prevalence by age is shown in Figure 2, incorporating only fixed effects.

One-way proportion testing between peak reported carriage prevalence and prevalence in all other age groups confirmed age-related trends, with four of 13 studies showing a peak in age groups containing 10 years of age (the peak age identified by the spline regression model) and the remaining nine showing no significant difference between peak prevalence and the prevalence in the age group containing 10 years of age (Table S4).

Predicted carriage prevalence was not significantly different when excluding data from sites that were climactic outliers (Table 3, Figure S3).

Location and year contributed to substantial variation in overall carriage rates. Random effects intercepts are given in Tables S5 and S6. Figure S2 shows model predictions including random effects. The variance for the location-year interaction intercept was greater than that for the location intercept (1.02 *vs.* 0.55). Neither location nor year alone was a consistent determinant of the location-year intercept (Table S6).

Shown in Figure 3, leave-one-out cross-validation predicted values were moderately correlated with true values (Pearson's rho 0.89). However, the median percent error for non-zero values was substantial, 34%. The model performed poorly at predicting observations of 0% carriage. More than half of all observations were outside the 95% confidence intervals for the model predictions (64%).

Discussion

We found that meningococcal carriage rates in the African meningitis belt were significantly higher in individuals aged 5–19 than

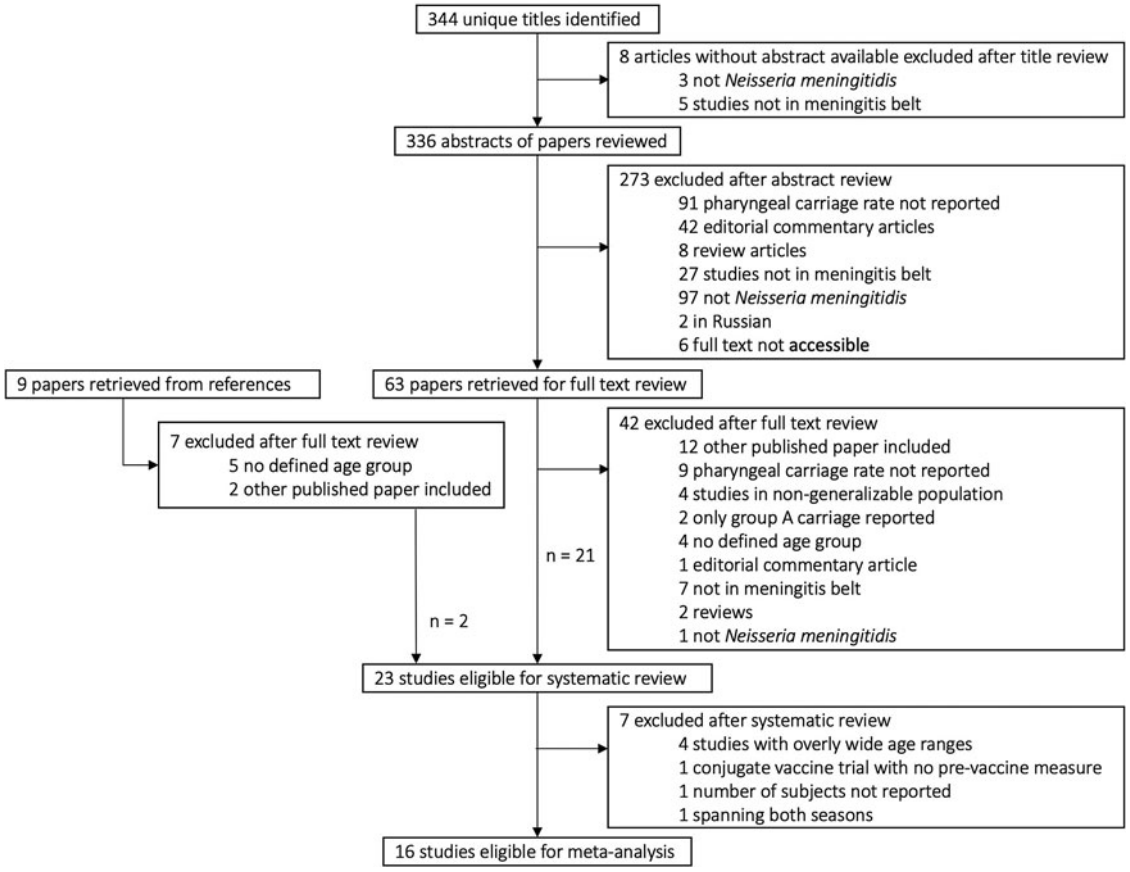

Fig. 1. Selection of studies on meningococcal carriage prevalence for systematic review and meta-analysis. For full details of all the papers that were reviewed, including reasons for exclusion, please contact the corresponding author.

Table 3. Fixed effects parameters. Predicted odds ratios and profile confidence intervals and median bootstrapped odds ratios and 95% bootstrapped confidence intervals for fixed effects parameters from fit on full dataset and on dataset excluding climactic outliers

	Full dataset		Excluding climactic outliers	
Factor	Odds ratio (95% profile CI)	Odds ratio (95% bootstrap CI)	Odds ratio (95% profile CI)	Odds ratio (95% bootstrap CI)
Natural cubic spline of age				
Spline I	3.4 (2.9–4.1)	3.5 (2.5–4.6)	3.6 (3–4.4)	3.7 (2.6–4.9)
Spline II	2 (1.6–2.4)	2 (1.5–2.9)	1.8 (1.4–2.2)	1.8 (1.3–2.6)
Spline III	5.2 (3.7–7.2)	4.9 (3–9.6)	4.9 (3.5–7.1)	4.7 (2.8–9.7)
Spline IV	0.79 (0.71–0.87)	0.79 (0.66–0.93)	0.7 (0.63–0.79)	0.71 (0.59–0.83)
Season				
Rainy	1.0	1.0	1.0	1.0
Dry	1.5 (1.4–1.7)	1.5 (1.3–1.8)	1.6 (1.5–1.8)	1.6 (1.3–1.9)
Outbreak	6.7 (1.6–29)	7.9 (3.9–8.3)	4.9 (0.81–31)	5.7 (1.3–6.4)

in age groups outside this range. A logistic regression showed that carriage prevalence increases from a minimum in infants to a broad peak in children centered at age 10 (1.94% in the rainy season, 95% CI 1.87–2.47%), then gradually decreases in later adolescence and adulthood. The trends in prevalence by age captured by the model are broadly consistent with contact studies in the sub-Saharan Africa, which find the highest intensity of contacts in 5–15-year-olds, especially close physical contacts and contacts with individuals outside of the household [41]. In the context of future strategies for use of the pentavalent meningococcal conjugate vaccine, this work shows that a substantial proportion of meningococcal carriers could be targeted while lowering the

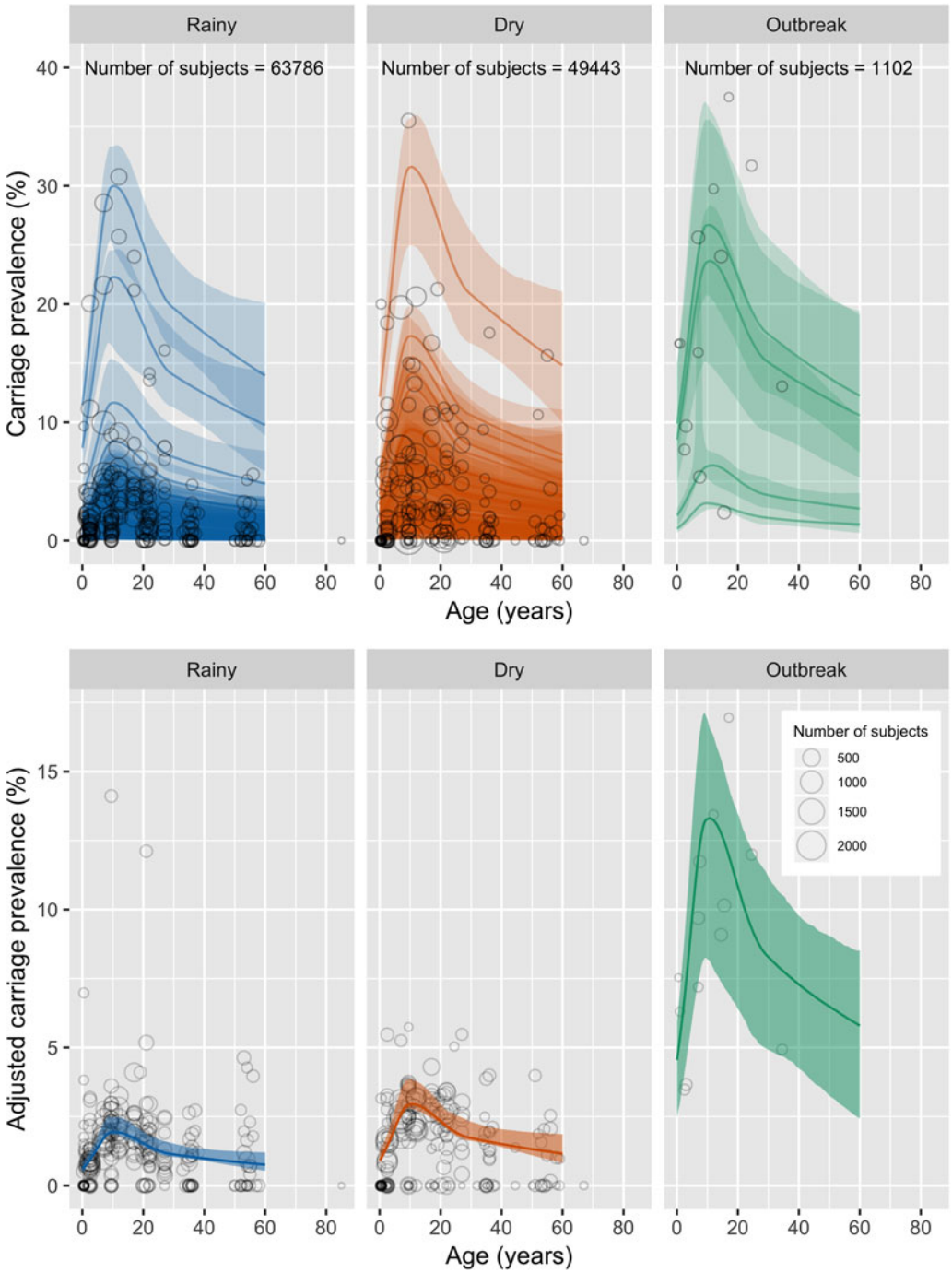

Fig. 2. Observed carriage prevalence measures and model predictions. Top panel: Circles show the data points included in the meta-analysis, with the larger circles representing a larger sample size. Solid line shows model predictions including random effects. Shaded ribbon shows 95% bias-corrected confidence intervals. Bottom panel: Circles show the data points included in the meta-analysis, with carriage prevalence adjusted for random effects intercept. Solid line shows model predictions excluding random effects. Shaded ribbon shows 95% bias-corrected confidence intervals. Dry season predictions are shown in red; rainy season in blue; outbreak in green.

upper threshold for vaccination from 29 years of age to 17 or 19 years of age. However, we note that 17% of carriers in the data that informed our model carried non-groupable strains, which would not be targeted by a pentavalent vaccine.

The dry season in the African meningitis belt is characterised by low humidity, high temperatures, increased wind speed and high levels of airborne dust. We found that the odds of carriage were significantly increased during the dry season and further increased during outbreaks, all of which occurred during the dry season. This is consistent with mathematical modelling which has shown that seasonal forcing in transmissibility of carriage is necessary to reproduce the extreme variability and scale of meningitis incidence characteristic of the African meningitis belt [7]. This finding is also consistent with in vivo studies in mice and in vitro studies of human neutrophils which have shown that exposure to dust is associated with

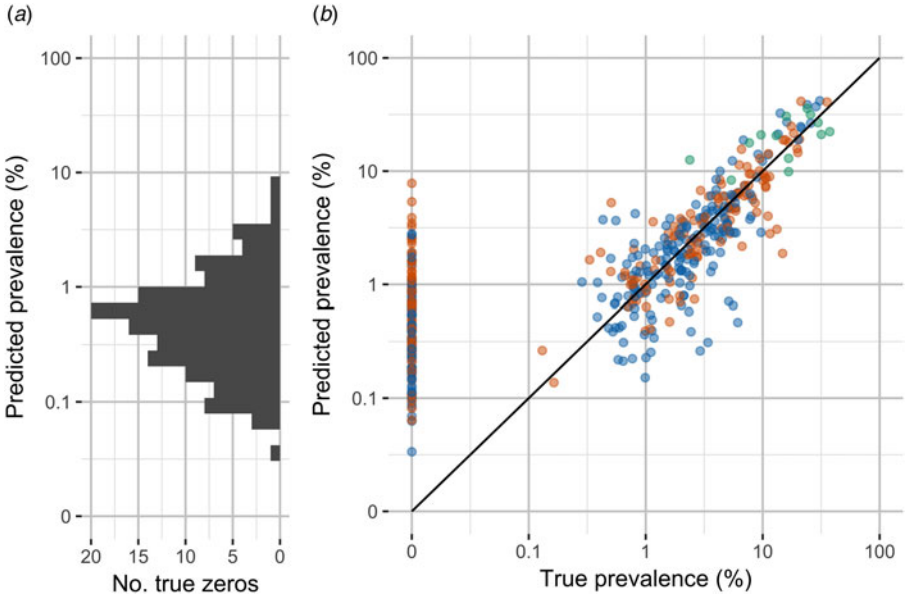

Fig. 3. Observed carriage prevalence and model predictions by leave-one-out cross-validation. (A) Distribution of model predictions for true zero observations. (B) True prevalence and prevalence predicted by leave-one-out cross-validation. Note the discontinuous scale to emphasise zero observations and the use of log scale for non-zero observations.

Table 4. Target age for vaccination. Proportion of carriers under 60 years of age directly targeted by vaccination of different age groups

Age group	Proportion of carriers (95% CI)	
Under 16 years	58%	(57–60%)
Under 18 years	64%	(63–65%)
Under 20 years	69%	(62–74%)
Under 30 years	84%	(82–84%)

reduced bacterial killing and increased bacterial load in the nasopharynx [31].

However, it is important to emphasise that the increased odds of carriage during the dry season and during outbreaks are not sufficient to fully account for the dramatic increase in disease incidence observed during these periods. There is evidence that individual susceptibility to invasive disease also increases during the dry season and during outbreaks [32].

Mass group A conjugate vaccination has no significant effect on overall carriage prevalence in the model. Serogroup A meningococci accounted for just 10% of all carriage isolates in pre-vaccine studies (Table 2), so it is not surprising that the model did not capture any change due to vaccine-related reductions in group A carriage. Carriage of group A meningococci did substantially decrease from 0.4% overall before mass campaigns to <0.005% overall after.

This model has some limitations. Cross-validation predictions are well correlated with true prevalence (Pearson's rho 0.89), but substantial variability in carriage prevalence remains unexplained, with fewer than half of observations falling within the 95% confidence intervals for model predictions.

The model is principally informed by two large serial cross-sectional studies carried out between 2009 and 2012, one based in Burkina Faso (50 810 subjects) [29,30,33] and the multi-country African Meningococcal Carriage Consortium study (48 405 subjects) [4]. These are both high-quality characteristic multi-site studies, but this dependence may mean that our model is more representative of recent epidemiological trends in the African meningitis belt.

Gender was not included in the model because this was not consistently reported, but the age distribution of carriage may be modified by gender because of differences in social behaviour [34]. A number of studies have also shown a higher prevalence of carriage in males overall, but this would not be expected to bias the results of this analysis unless the gender distribution of participants were substantially different between age groups [4,5].

Because of the sparseness of sampling in older age groups, a linear relationship between carriage prevalence and age above 30 years was assumed. As a result, carriage appears to decline steadily throughout middle and later adulthood. However, in reality, carriage may increase in the elderly as immunity wanes. Further study of this age group will be important as older people comprise an increasing proportion of the population in the African meningitis belt.

Despite these shortcomings, we conclude that older children in African meningitis tend to be the age group in which carriage is most prevalent. The odds of carriage are significantly higher during the dry season and during outbreaks and carriage of group A meningococci has substantially decreased in countries where mass MenAfriVac vaccination has been implemented. This meta-analysis may help to guide vaccination policy, both to maintain control of group A disease and in the implementation of affordable multivalent vaccines.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0950268819001134

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Conflict of interest. None.

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Risk factors for acquisition of meningococcal carriage in the African meningitis belt

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Abstract

OBJECTIVE To investigate potential risk factors for acquisition in seven countries of the meningitis belt.

METHODS Households were followed up every 2 weeks for 2 months, then monthly for a further 4 months. Pharyngeal swabs were collected from all available household members at each visit and questionnaires completed. Risks of acquisition over the whole study period and for each visit were analysed by a series of logistic regressions.

RESULTS Over the course of the study, acquisition was higher in: (i) 5-to 14-year olds, as compared with those 30 years or older (OR 3.6, 95% CI 1.4–9.9); (ii) smokers (OR 3.6, 95% CI 0.98–13); and (iii) those exposed to wood smoke at home (OR 2.6 95% CI 1.3–5.6). The risk of acquisition from one visit to the next was higher in those reporting a sore throat during the dry season (OR 3.7, 95% CI 2.0–6.7) and lower in those reporting antibiotic use (OR 0.17, 95% CI 0.03–0.56).

CONCLUSIONS Acquisition of meningococcal carriage peaked in school age children. Recent symptoms of sore throat during the dry season, but not during the rainy season, were associated with a higher risk of acquisition. Upper respiratory tract infections may be an important driver of epidemics in the meningitis belt.

keywords acquisition, risk factors, *Neisseria meningitidis*, Africa

Introduction

Epidemics of meningococcal meningitis occur periodically in the African Meningitis Belt, an area of sub-Saharan Africa stretching from Senegal in the west to Ethiopia in the east [1]. These epidemics are highly seasonal, with the majority of cases occurring during the dry season, predominantly in the first 5 months of the year [2]. Given that asymptomatic pharyngeal carriage of meningococci is relatively frequent (ranging from 3% to 30% of the population) [3] and because meningococcal acquisition only occasionally leads to invasive disease, one explanation for this striking seasonality is an increased risk of invasive disease in the dry season, due to mucosal damage from environmental factors such as low absolute humidity and dust [1, 4, 5]. Another hypothesis suggested by mathematical modelling is that higher rates of meningococcal transmission during the dry season,

*MenAfriCar Consortium members are in Appendix 1.

combined with population immunity, may be sufficient to explain epidemic patterns [6]. Although a review of carriage in the meningitis belt published in 2007 found no evidence to support a seasonal effect on carriage [3], more recent studies have found a higher prevalence of carriage in the dry season [7, 8].

Studies of carriage prevalence and acquisition will, therefore, lead to a better understanding of the epidemiology of meningococcal meningitis in the African meningitis belt. The African Meningococcal Carriage Consortium (MenAfriCar) undertook 20 cross-sectional carriage surveys in seven African meningitis belt countries from July 2010 to July 2012, involving the collection of over 48 000 pharyngeal swabs. These studies found a higher frequency of carriage in children aged 5 to 14 years, in the dry season and in rural populations [7]. During these surveys, households with at least one pharyngeal carrier of *N. meningitidis* were recruited for longitudinal studies [9].

Previous longitudinal studies in the meningitis belt have been undertaken mainly at the population level [10–12] and few have investigated the transmission and acquisition of carriage at an individual level [13, 14]. The aim of this MenAfriCar study was to investigate a comprehensive set of potential risk factors for the acquisition of carriage of *N. meningitidis* across the African meningitis belt.

Methods

Household surveys

Households included in this study were recruited during the course of cross-sectional surveys conducted in seven countries in the African meningitis belt (Chad, Ethiopia, Ghana, Mali, Niger, Nigeria and Senegal) in 2010, 2011 and 2012. Details of the survey methods employed have been published previously [7]. Longitudinal surveys were triggered by the identification of a putative carrier during a cross-sectional survey (Visit 0). This initial identification of carriers relied on conventional microbiology and was later confirmed via molecular methods at the University of Oxford. In some cases, molecular methods did not confirm the presence of meningococci, so 51 of 184 households recruited to the study did not have an index carrier.

Within 4 weeks of the identification of a carrier, all members of the putative carrier's household were invited to take part in further studies (Visit 1). The head of the household was asked about characteristics of the household, including numbers of rooms and bedrooms, sleeping arrangements, location of kitchen and cooking fuel, house construction, drinking water, sanitation and household assets such as vehicle ownership, livestock and electrical goods.

A pharyngeal swab sample was obtained from all members of a household who gave consent and a questionnaire completed which included questions on: smoking; social activities; symptoms of recent respiratory tract infection; socio-economic status and educational level; school attendance; travel history; recent medication including antibiotics; meningitis vaccination; and ethnic group. Carrier households were followed up 2-weekly for 2 months (Visits 2–5) and monthly for a further four months (Visits 5–9). At each follow-up visit, each household member was asked for a pharyngeal swab sample and to answer a short follow-up questionnaire on factors that might have changed since the previous visit, such as symptoms of a respiratory tract infection.

Laboratory methods

Pharyngeal swab samples, taken from the posterior pharynx and tonsillar fossa via the mouth, were plated directly onto Modified Thayer Martin agar plates in the field, taken to the laboratory within 6 h of collection and processed as previously described [9]. A sample of boiled suspensions of Gram-negative oxidase positive bacteria was sent to the University of Oxford for molecular analysis. Amplification and sequencing of the rplF gene was used to confirm the presence of, and to differentiate between, *Neisseria* species. Confirmed *N. meningitidis* were further characterised by genogroup (including capsule-null) and porA genosubtype.

Data management

Data were managed using the Teleform system version 10.4.1 (Autonomy, Cambridge, UK) with a separate database module linking the main study database with genetic laboratory results from the Oxford PubMLST.org/neisseria database (https://pubmlst.org/neisseria). Data from the longitudinal questionnaires were merged using a common person ID or census number, person matching was checked, any duplicate entries were removed and aberrant values excluded.

Statistical analysis

The genogroup-specific acquisition rates and 95% confidence intervals were calculated as Poisson rates, counting the number of acquisitions occurring in non-index carriers and the time at risk as the days between the first carriage-negative swab and the first positive swab. A series

of fixed-effects logistic regressions were used to identify significant risk factors for acquisition. In the first round of regressions, individual risk factors were included in a multi-variable logistic regression with the *a priori* variables sex, age group and country. In the second round, risk factors with $P < 0.1$ in round 1 were added to a single model with *a priori* variables. In the third round, risk factors with $P < 0.05$ in round 2 were retained in the multi-variable model. In the fourth round, all factors dropped in round 3 were added back in to the model one by one and all variables with $P < 0.05$ were retained, giving the final models. The study-long and visit-by-visit models were then run with household ID and both household and individual ID as random effects respectively, to account for clustering and factors that were no longer significant ($P \geq 0.05$) were dropped.

Acquisition was assessed over the full study period (study-long) and visit-by-visit. Individuals were defined as positive for study-long acquisition if they had a negative swab (no meningococci isolated) at visits 0 or 1 and a positive swab (any meningococci isolated) at any following visit. Individuals were defined as negative for study-long acquisition if they had a negative swab at visits 0 or 1 and no positive swab at any subsequent visit. Individuals with three or more missed visits in total were excluded, as the possibility of acquisition during this missed period could not be ruled out and individuals carrying at visits 0 or 1 were also excluded.

Individuals were defined as positive for visit-by-visit acquisition on a given visit if the individual had a positive swab at the current visit and a negative swab at the previous visit or carried a different strain at the previous visit and the strain was not previously carried during the study. Strains were assessed by genogroup and porA variable regions 1 and 2. Individuals were defined as negative for visit-by-visit acquisition on a given visit if the individual had a negative swab at the previous visit and a negative swab at the current visit. Individuals carrying an identical strain to that obtained at the previous visit and individuals who cleared carriage were excluded from the analysis. Tables S1 and S2 provide the classification of cases for study-long and visit-by-visit acquisition.

We defined the dry season as January to May and the rainy season as June to December. Because we found a significant association between sore throat and season and also previous studies have demonstrated an interaction between meningococcal carriage, upper respiratory tract infection and season, we also tested for interaction between sore throat and season in our final model and found that the model with an interaction term fitted better than the model with no interaction (Table S4).

Ethics

The study was approved by the ethics committee of the London School of Hygiene and Tropical Medicine and by the relevant ethical authorities in each African centre [9]. The head of the household or another responsible adult gave verbal informed consent for the household to be included in the study. Each individual recruited within that household gave written informed consent; for children under the age of 18 years a parent or guardian gave written consent and children aged over 12 years were additionally asked to give written assent.

Results

Acquisition over course of the study

Overall, 169/861 (20%) of the non-index carriers became pharyngeal carriers of a meningococcus at least once over the course of the study. A higher proportion of 5- to 14-year-olds acquired carriage than other age groups and a higher proportion of participants acquired carriage in Senegal, Niger, Ghana and Ethiopia relative to Chad and Mali (Table 1). A wide variation in acquisition rates was observed between countries. Genogroup W and capsule-null (cnl) meningococci accounted for the majority (83%) of acquisitions. The acquisition rates of genogroup W meningococci were 2.0% per month (95% CI 1.6–2.4) double that of cnl meningococci at 1.0% per month (95% CI 0.74–1.4). Genogroups A, C, Y and other genogroup (i.e. other than A, B, C, W, X, Y or cnl) acquisitions were uncommon and no genogroup B or X acquisitions were detected.

In the final multi-variable model, the highest odds of acquisition were amongst 5- to 14- year olds, with odds in all age groups under 30 years of age being significantly higher than the reference group of individuals 30 years and older (Table 1). Active smokers had higher odds of acquiring carriage than non-smokers living in households with no smokers, with a lower confidence bound just below 1 (OR 3.57 95% CI 0.98–12.99). Non-smokers living in households with smokers also had elevated odds of acquisition but the difference was not statistically significant. Wood was the ubiquitous cooking fuel, with 96% of the participants using this as cooking fuel; 56% of the participants had additional wood smoke exposure. Participants with household exposure to wood smoke (independent of using wood as cooking fuel) had higher odds of acquiring carriage than those without (OR 2.60 95% CI 1.26–5.59). Although this trend was not significant in the regression analysis, higher acquisition rates were observed in households

Table 1 Risk factors for *Neisseria meningitidis* acquisition over the full study period: single risk factor analysis and multi-variable model. Adjustment was made in both single and multi-variable analysis for age, country and sex

	Single risk factor analysis				Multi-variable model			
Factor	Total	Positive (%)	OR	95% CI	Total	Positive (%)	OR	95% CI
Age								
30 plus					205	11.7	1	
Under 5					91	28.6	3.12	(1.27, 8.05)
5–14					108	23.1	3.62	(1.42, 9.93)
15–29					161	21.1	2.38	(1.22, 4.76)
Country								
Chad					54	5.6	1	
Ethiopia					64	26.6	7.65	(1.81, 44.4)
Ghana					74	23	6.77	(1.52, 40.1)
Mali					157	5.7	0.532	(0.110, 3.22)
Niger					206	28.6	10.0	(2.53, 57.3)
Senegal					10	40	13.3	(1.23, 159)
Sex								
Female					326	17.5	1	
Male					239	21.8	1.00	(0.585, 1.71)
Exposure to wood smoke in house (apart from use in cooking)*								
No	372	20.2	1		261	19.2	1	
Yes	478	19.0	2.74	(1.76, 4.32)	304	19.4	2.60	(1.26, 5.59)
Tobacco exposure*								
None	234	14.1	1		230	13.5	1	
Passive (secondhand) smoke	312	22.8	1.92	(0.965, 3.77)	312	22.8	1.92	(0.823, 4.55)
Active smoker	23	30.4	3.75	(1.23, 10.8)	23	30.4	3.57	(0.978, 13.0)§
Any sore throat reported*								
No	651	17.8	1					
Yes	208	25.5	1.66	(1.09, 2.53)				
Any runny nose reported*								
No	184	20.7	1					
Yes	675	19.4	1.57	(0.995, 2.51)				
Use gas as primary cooking fuel*								
No	832	20.0	1					
Yes	25	12.0	0.311	(0.0664, 1.03)				
Completion of primary school (amongst over 17 years)*								
No	269	18.2	1					
Yes	99	11.1	0.381	(0.170, 0.793)				
Household member completed secondary school*								
No	444	22.3	1					
Yes	415	16.9	0.670	(0.455, 0.983)				
More than 2 participants per room*								
No	484	14.5	1					
Yes	375	26.4	1.44	(0.996, 2.10)				
Attending primary school (ages 5–17)								
No	52	25	1					
Yes	254	23.2	0.721	(0.325, 1.65)				
Regular social meetings								
None	202	20.3	1					
1–2 per week	68	16.2	0.916	(0.404, 1.96)				
3–4 per week	48	8.3	0.531	(0.141, 1.61)				
5–7 per week	52	5.8	0.356	(0.0793, 1.14)				
Index carrier in household								
No	259	12.0	1					
Yes	600	23.0	1.32	(0.826, 2.16)				

Table 1 (*Continued*)

	Single risk factor analysis				Multi-variable model			
Factor	Total	Positive (%)	OR	95% CI	Total	Positive (%)	OR	95% CI
Use wood as primary cooking fuel								
No	31	12.9	1					
Yes	828	19.9	1.02	(0.340, 3.83)				
Indoor kitchen								
No	660	16.4	1					
Yes	199	30.7	1.28	(0.838, 1.94)				

NB Total number of individuals may not sum to 861 in every case because of missing values.
*P-value less than 0.1 in single risk factor analysis.
§P-value less than 0.05.

with an indoor kitchen and in households which used wood as the primary cooking fuel than in those who did not.

Visit-specific acquisition analysis

Participants who said they had a sore throat since the previous visit during the dry season were significantly more likely (OR 3.67 95% CI 1.95–6.65) to have acquired carriage in that time period than those who did not have a sore throat in the rainy season (Table 2). Those who reported taking antibiotics since the previous visit were significantly less likely (OR 0.169 95% CI 0.0271–0.564) to have acquired carriage.

Discussion

This longitudinal study found a higher risk of acquisition amongst individuals who reported a sore throat since the previous visit, but only during the dry season. An association between an upper respiratory tract infection and meningococcal carriage has been reported previously [14]. A sore throat could be due to an initial inflammation of the pharynx from meningococcal colonisation or could be caused by a concurrent unrelated infection that predisposes an individual to acquisition [15]. If the latter is true, upper respiratory tract infections in combination with dust and low humidity may be an important driver for the high risk of meningitis epidemics in the dry season. This hypothesis is supported by a recent study indicating an association between upper respiratory tract infection (defined as otitis, severe sore throat and rhinopharyngitis) and meningitis outbreaks in Burkina Faso [16]. Such upper respiratory tract infections could plausibly increase both the risk of acquisition and the risk of invasion after acquisition.

The 5 to 14-year-old age group had the highest acquisition rate. The highest prevalence of carriage in cross-sectional MenAfriCar studies and in Burkina Faso in 2009 was similarly highest in 5 to 14-year olds [7, 17]. An overall acquisition rate of 2.4% (95% CI 1.6–4.0%) per month was estimated from this same study using a hidden Markov model [9]. There were no significant differences reported by age group, but data were subdivided by control and index households and there was no adjustment for other risk factors.

Additional factors linked to acquisition of meningococci over the course of this study were smoking tobacco and exposure to wood smoke. Smoking, passive exposure to smoke and to smokers has been shown to convey a high risk of carriage and invasive disease in high-income countries [18–21]. Exposure to cigarette smoke has also been linked to the risk of carriage in the meningitis belt [7, 14]. The higher risk of acquisition from smoke exposure in this study suggests a direct risk from smoke itself, potentially from interference with mucosal immunity, as exposure to wood smoke was an independent risk factor. Exposure to smoke from wood fires has also been shown as a risk factor for meningococcal meningitis in northern Ghana [22]. Although use of wood as primary cooking fuel was not found to be a significant risk factor, this could be explained by the fact that nearly all study participants relied on wood as primary fuel or that some households used outdoor kitchens, thus moderating the degree of exposure.

Strengths of this study are the multi-centre design across seven countries of the meningitis belt conducted at the same time, including a mix of urban and rural populations with a broad age range, the use of standardised field and laboratory protocols and a large sample size. Measuring acquisition rather than carriage ensures that

Table 2 Risk factors for visit-by-visit *Neisseria meningitidis* acquisition: single risk factor analysis and multi-variable model. Adjustment was made *a priori* in both single and multi-variable analysis for age, country and sex

	Single risk factor analysis (plus *a priori*)				Multi-variable model			
Factor	Total	Positive (%)	OR	95% CI	Total	Positive (%)	OR	95% CI
Age								
30 plus					1504	1.8	1	
Under 5					1539	3.4	1.99	(1.22, 3.32)
5–14					2129	4.2	2.76	(1.75, 4.48)
15–29					1239	3	1.83	(1.08, 3.15)
Country								
Chad					990	0.6	1	
Ethiopia					564	4.6	7.54	(2.59, 24.5)
Ghana					828	3.5	5.7	(1.96, 18.6)
Mali					1574	0.9	1.51	(0.483, 5.13)
Niger					2281	5.2	11.5	(4.53, 34.5)
Senegal					174	7.5	14.2	(3.6, 60.7)
Sex								
Female					3405	2.9	1	
Male					3006	3.6	1.23	(0.907, 1.68)
Antibiotic taken*								
No	6592	3.5	1		6150	3.3	1	
Yes	261	0.8	0.197	(0.0323, 0.623)	261	0.8	0.169	(0.0271, 0.564)
Interaction term*								
No sore throat, rainy	2643	3.3	1		2643	3.3	1	
No sore throat, dry	3481	2.8	0.88	(0.651, 1.19)	3481	2.8	0.844	(0.617, 1.16)
Sore throat, rainy	123	2.4	0.906	(0.218, 2.52)	123	2.4	0.82	(0.192, 2.39)
Sore throat, dry	164	11	3.72	(2.09, 6.34)	164	11	3.67	(1.95, 6.65)
Sore throat*								
No	6566	3.3	1					
Yes	287	7.3	2.64	(1.58, 4.19)				
Season								
Rainy: June to December	1944	3.1	1					
Dry: January to May	4467	3.3	1.07	(0.78, 1.47)				
Meningitis vaccination								
No	5743	3.7	1					
Yes	1110	2	1.54	(0.899, 2.55)				
Attendance at social event								
No	3319	4.4	1					
Yes	3534	2.5	0.851	(0.63, 1.14)				
Travel greater than one hour								
No	6055	3.6	1					
Yes	798	2	0.955	(0.538, 1.58)				
Cough								
No	5163	3.6	1					
Yes	1690	3	0.955	(0.682, 1.31)				
Runny nose								
No	4634	3.8	1					
Yes	2219	2.6	0.961	(0.689, 1.32)				

*P-value less than 0.1 in single risk factor analysis.

the risk factors identified in this study are not biased by factors associated with longer carriage duration. A comprehensive range of risk factors was included, so that important confounding factors are unlikely to have been missed; however, the sampling of carriers and non-carriers was not random and we would expect some misclassification of carriage status from the known low sensitivity of pharyngeal swabbing.

Both the acquisition of meningococci found in this longitudinal study and prevalence of carriage in the

MenAfriCar cross-sectional studies varied considerably by country. Although laboratory methods were standardised across centres, differences in laboratory techniques could still have contributed to some of the differences observed. As most meningococcal acquisitions were either genogroup W or capsule-null and outside epidemics, it cannot be assumed that risk factors for acquisition of other genogroups or during epidemics would be the same as those found in this study [23].

It was surprising that some risk factors such as household crowding that have long been known to raise the risk of carriage and disease [7, 13, 24, 25] were not associated in this study with acquisition. Crowding was measured here by numbers sharing a bedroom or bedmat and by numbers of people per room in the household. It is possible that crowded living conditions are so prevalent across the meningitis belt countries that any effect of crowding on acquisition is not detectable. A study in rural Gambia did not find any differences in crowding between compounds with and without cases of meningococcal meningitis during an epidemic [26].

Reported vaccination was clustered in particular time periods and countries corresponding to the introduction of group A conjugate vaccine. Vaccination was not found to be protective against carriage acquisition. However, we would not expect a group A conjugate vaccine to have a significant impact on carriage in this study as very few group A carriers were detected.

We were not able to draw any conclusions regarding the relationship between carriage acquisition and disease incidence because none of the study sites reported an outbreak of meningitis during the follow-up period.

This study involved multiple countries and examined an exhaustive set of household and individual risk factors for meningococcal acquisition. The importance of identifying these risk factors is that acquisition is a necessary prerequisite for invasive disease. Acquisition studies also play a potential role in vaccine evaluation. Of particular interest for countries of the African meningitis belt is the finding that symptoms of upper respiratory tract infection are linked to risk of acquisition, but only in the dry season. The evidence is mounting that such infections are an important factor behind the risk of epidemics in the meningitis belt.

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Appendix 1

Institutions and individual members of the MenAfriCar consortium who contributed to this study. Armauer Hansen Research Institute, Addis Ababa, Ethiopia: Oumer Ali, Abraham Aseffa (PI), Ahmed Bedru, Tsehaynesh Lema, Tesfaye Moti, Yenenesh Tekletsion, Alemayehu Worku, Haimanot Guebre Xabher (deceased), Lawrence Yamuah. Centre de Recherche Médicale et Sanitaire (CERMES), Niamey, Niger (Member of the International Network of Pasteur Institutes): Rahamatou Moustapha Boukary, Jean-Marc Collard (PI), Ibrahim Dan Dano, Ibrahim Habiboulaye, Bassira Issaka, Jean-François Jusot, Sani Ousmane, Issoufa Rabe. Centre de Support en Santé International (CSSI), N'Djamena, Chad: Doumagoum Moto Daugla (PI), Jean Pierre Gami, Kadidja Gamougam, Lodoum Mbainadji, Nathan Naibei, Maxime Narbé, Jacques Toralta. Centre pour les Vaccins en Développement, Bamako, Mali: Abdoulaye Berthe, Kanny Diallo, Mahamadou Keita, Uma Onwuchekwa, Samba O. Sow (PI), Boubou Tamboura, Awa Traore, Alou Toure. Centers for Disease Control, Atlanta, USA: Tom Clark, Leonard Mayer. Department of Community Medicine, University of Maiduguri, Maiduguri, Nigeria: Mary Amodu, Omeiza Beida, Galadima Gadzama, Babatunji Omotara (PI), Zailani Sambo, Shuaibu Yahya. Faculty of Infectious Disease, London School of Hygiene & Tropical Medicine, London, UK: Daniel Chandramohan, Brian M. Greenwood (PI), Musa Hassan-King, Olivier Manigart, Maria Nascimento, James M. Stuart, Arouna Woukeu. Princeton University, USA: Nicole E. Basta. Public Health England Vaccine

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Case definition for study-long acquisition.

Table S2. Case definition for visit-by-visit acquisition.

Table S3. Odds of sore throat adjusting for age, country, sex and season.

Table S4. Likelihood ratio test comparing visit-by-visit model with and without term of interaction between season and sore throat.

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SUPPLEMENT ARTICLE

Spatiotemporal Analysis of Serogroup C Meningococcal Meningitis Spread in Niger and Nigeria and Implications for Epidemic Response

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Background. After the re-emergence of serogroup C meningococcal meningitis (MM) in Nigeria and Niger, we aimed to re-evaluate the vaccination policy used to respond to outbreaks of MM in the African meningitis belt by investigating alternative strategies using a lower incidence threshold and information about neighboring districts.

Methods. We used data on suspected and laboratory-confirmed cases in Niger and Nigeria from 2013 to 2017. We calculated global and local Moran's I-statistics to identify spatial clustering of districts with high MM incidence. We used a Pinner model to estimate the impact of vaccination campaigns occurring between 2015 and 2017 and to evaluate the impact of 3 alternative district-level vaccination strategies, compared with that currently used.

Results. We found significant clustering of high incidence districts in every year, with local clusters around Tambuwal, Nigeria in 2013 and 2014, Niamey, Niger in 2016, and in Sokoto and Zamfara States in Nigeria in 2017. We estimate that the vaccination campaigns implemented in 2015, 2016, and 2017 prevented 6% of MM cases. Using the current strategy but with high coverage (85%) and timely distribution (4 weeks), these campaigns could have prevented 10% of cases. This strategy required the fewest doses of vaccine to prevent a case. None of the alternative strategies we evaluated were more efficient, but they would have prevented the occurrence of more cases overall.

Conclusions. Although we observed significant spatial clustering in MM in Nigeria and Niger between 2013 and 2017, there is no strong evidence to support a change in methods for epidemic response in terms of lowering the intervention threshold or targeting neighboring districts for reactive vaccination.

Keywords. epidemic response; meningitis; Niger; Nigeria; vaccine.

Since guidelines were first issued by the World Health Organization (WHO) in 1995, reactive vaccination policy in the African meningitis belt has evolved in response to changes in disease burden and continuing insights from research. The first set of guidelines proposed an incidence threshold indicating high epidemic risk at 15 or more suspected cases of meningitis per 100 000 population per week over a period of 2 weeks [1]. This was updated in 2000 to recommend a lower threshold of 10 suspected cases per 100 000 per week for high-risk districts and to emphasize the importance of surveillance at a district level, because outbreaks of meningitis tend to occur at a fine spatial scale and can be missed when surveillance is carried out more coarsely [2]. A recommendation was also made for vaccination of districts in alert (exceeding incidence of 5 suspected cases per 100 000 per week) and neighboring an epidemic district. With the introduction of group A meningococcal conjugate vaccine in the meningitis belt in 2010 and subsequent reduction in the burden of group A meningococcal meningitis, these thresholds were re-evaluated, focusing on *Neisseria meningitidis* (Nm) serogroup W outbreaks [3]. This research informed the next iteration of WHO guidelines, which maintained the epidemic threshold of 10 suspected cases per 100 000 per week but emphasized the importance of surveillance in populations smaller than 100 000 persons and minimizing delay between triggering of the incidence threshold and intervention. The guidelines also lowered the alert threshold to 3 suspected cases per 100 000 per week and relaxed the recommendation for vaccination in neighboring districts to allow for more flexibility [4].

Prior studies of meningitis patterns in Niger have demonstrated significant spatial heterogeneity and strong interannual

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and intradistrict variation in meningitis incidence, and authors have suggested that surveillance on finer spatial scales may improve the timeliness and targeting of epidemic response [5–7]. In particular, these studies find that performing outbreak detection on the subdistrict level and response on the district level is more efficient than traditional detection at the district level. In light of the recent emergence and continued epidemics of serogroup C meningococcal meningitis in Nigeria and Niger, we aimed to re-evaluate the reactive vaccination policy used to respond to seasonal outbreaks of meningococcal meningitis in the African meningitis belt and investigated alternative strategies. Although subdistrict-level data are not widely available, we wanted to investigate whether targeting neighbors at the district level might allow for more efficient use of vaccine. We also wanted to extend the scope of these earlier studies by including data from Nigeria in our analysis, and considering the full time period from the emergence of the outbreak strain in 2013 [8].

METHODS

Surveillance Data

We used surveillance data on suspected cases of meningitis from the enhanced district-level surveillance system established in 2003 [9]. A suspected case is defined as any person with sudden onset of fever (>38.5°C rectal or 38.0°C axillary) and any one of the following signs: neck stiffness, flaccid neck (infants), bulging fontanelle (infants), convulsion, or other meningeal signs. Weekly district-level counts of suspected cases are collated nationally and then reported to the WHO Inter-Country Support Team (WHO-IST) for West Africa. We used data from Niger and Nigeria during the period from 2013 to 2017, when serogroup C was dominant. We used the district-level population sizes reported by each country to WHO-IST, which are updated annually.

We used national-level annual data on confirmed cases of meningitis to estimate the overall proportion of cases due to serogroup C and preventable by vaccination (Table 1). Cerebrospinal fluid (CSF) samples are tested by national reference laboratories using polymerase chain reaction, culture, or latex agglutination, and these results are collated by WHO-IST [10]. Because of the lack of microbiological data for Nigeria in 2016, we assumed the etiological proportions were the same as in Niger 2016 for the purposes of the model. We also used anonymized line list data, which includes the age of cases and more detailed laboratory confirmation data for Niger 2015 to 2017 and Nigeria 2017, to evaluate the accuracy of some of our model assumptions.

Maps

We matched districts to their locations on district-level maps obtained from WHO using place names. Where no match was found between the map names and a surveillance database place name, we used the GeoNames database to situate the unknown place name within a known district [11]. Large districts that divided into 2 or more smaller districts during the study period (2013–2017) were kept as a single district to allow for tracking of vaccine coverage over time and to avoid introducing bias by sudden population changes (Supplementary Table S1). We defined neighbors as those districts sharing a border with the focal district. This definition of neighboring districts included those across national borders.

Cluster Detection

We tested for nonrandom spatial distribution of annual cumulative incidence using the Global Moran's I statistic for each year from 2013 to 2017 [12]. Measures of spatial autocorrelation can be highly dependent on the imposed spatial structure, ie, what is considered a neighbor and how each neighbor is weighted [13]. For this reason, we calculated Moran's global I statistic in R using the spdep package with 3 different weighting structures—by simple contiguity, great circle distance (within 50 km of centroid), and taking the 5 nearest neighbors, with distance again calculated by great circle centroid-to-centroid (Supplementary Table S2). For the distance-based weight, we evaluated distances between 20 and 100 kilometers. Fifty kilometers was chosen

Table 1. Confirmed and Suspected Cases of Meningitis and Estimated Proportion of Suspected Cases That Could Have Been Prevented by C, ACW, and ACWY Vaccines Between 2013 and 2017 in Niger and Nigeria[a]

Year	Country	Suspected Meningitis Cases	Total Confirmed Nm	A	C	X	Y	W	Covered by C	Covered by ACW	Covered by ACWY
2013	Niger	311	11	0	0	0	0	11	0%	100%	100%
	Nigeria	871	10	3	7	0	0	0	70%	100%	100%
2014	Niger	315	24	0	8	0	0	16	33%	100%	100%
	Nigeria	1175	38	0	38	0	0	0	100%	100%	100%
2015	Niger	7978	1436	0	1183	1	0	206	82%	97%	97%
	Nigeria	2655	20	0	20	0	0	0	100%	100%	100%
2016	Niger	1976	357	0	312	15	0	25	87%	94%	94%
	Nigeria	831	…	…	22	…	…	…	…	…	…
2017	Niger	3387	1073	0	848	220	0	4	79%	79%	79%
	Nigeria	9918	18	1	14	0	0	1	78%	89%	89%

Abbreviations: Nm, *Neisseria meningitidis*.

[a]A, C, X, Y, W columns may not add up to total confirmed Nm due to nontypeable isolates.

because it maximized spatial effects in most years. All districts meeting neighbor criterion were weighted equally. The significance of these values was determined by rank within 999 Monte Carlo permutations.

Because all weighting methods detected significant positive spatial autocorrelation of similar magnitude in each year, we continued by using only contiguity weights for our analysis of local clusters. We calculated Anselin's local Moran's I to locate clusters of districts with high incidence or outlier districts with higher incidence than neighbors [5, 14]. We used the spdep package in R and GeoDa software to calculate local Moran's I statistics for each district in each year. In GeoDa, we used a permutation approach with 99 999 permutations to generate pseudo *P* values. We then compared these to the analytical results from the spdep packages. We used an overall alpha of 0.05 and a Bonferroni adjustment for repeated testing. Because the analytical *P* values and the pseudo *P* values gave inconsistent results, we reported only the clusters found significant by both methods (Supplementary Table S3, Figure 1).

Definitions

We refer to the raw data of weekly suspected cases as observed suspected cases (OSCs), and we refer to cases expected in the

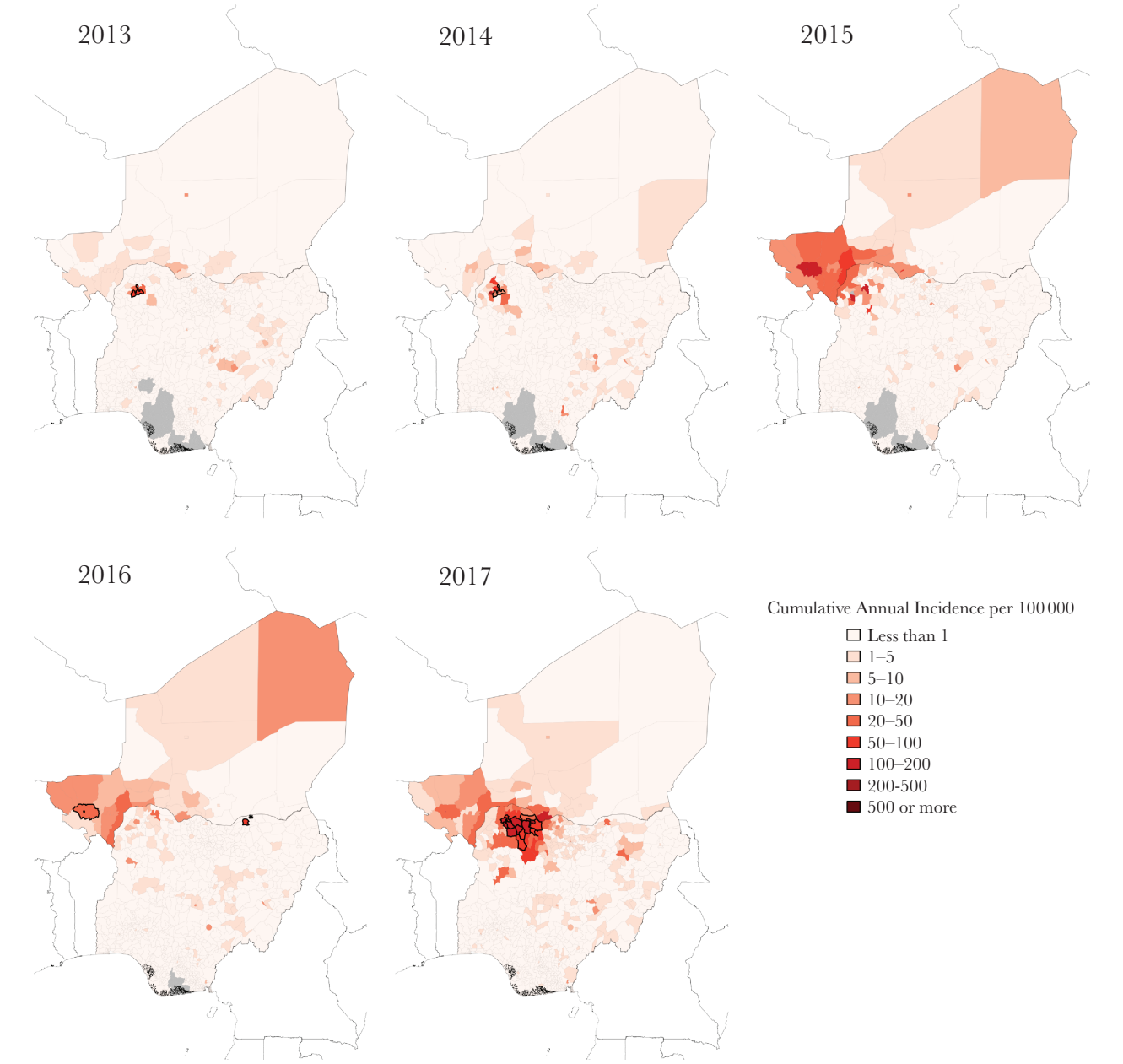

Figure 1. Cumulative annual district-level incidence of suspected cases of meningitis in Niger and Nigeria 2013 to 2017. Centers of significant clusters of high incidence by Anselin's local Moran's I outlined in black. High-incidence outlier in 2016 indicated with asterisk. Gray areas represent districts for which no data are reported.

absence of the vaccination campaigns taking place in selected districts in 2015, 2016, and 2017 as modeled suspected cases. Epidemic and alert incidence thresholds are consistent with current WHO guidelines, with alert defined as more than 3 suspected cases per 100 000 population per week or more than 2 cases total per week for districts with less than 30 000 population and epidemic with as more than 10 suspected cases per 100 000 population per week or more than 5 cases total per week or a doubling of cases in a 2-week period for districts with less than 30 000 population [4]. We define a district-level meningitis outbreak period where Nm is the dominant cause of meningitis as the period in which incidence of OSCs exceeds the alert incidence threshold.

Estimating Cases in the Absence of Intervention

Reactive vaccination campaigns occurred in 2015, 2016, and 2017 in 56 districts in response to NmC outbreaks using polysaccharide vaccine, monovalent C conjugate vaccine, and quadrivalent ACWY conjugate vaccine. To model suspected cases of meningitis in the absence of vaccination, we made the following assumptions: (1) 80% of suspected cases during the outbreak period are due to Nm; (2) 20% of cases outside the outbreak period are due to Nm; (3) the serogroup distribution is proportional to national annual proportions; (4) there is a delay of 6 weeks between triggering of the epidemic threshold and protection from vaccination (Table 2). Where no threshold was triggered but vaccination still took place, we made a best guess for the timing of the intervention based on neighboring districts. For polysaccharide vaccine, we further assumed the following: (1) campaigns target 2- to 29-year-olds, who make up 70% of the population and 90% of cases [15, 16]; (2) 80% vaccine efficacy against serogroups A, C, and W [17]; and (3) protection lasts for 104 weeks (approximately 2 years) [18]. This type of model has been used by many authors in the past to estimate the impact of reactive vaccination for meningitis outbreaks [3, 19, 20]. More importantly, it assumes no impact of the vaccine on carriage and thus transmission of meningococci.

For the monovalent C conjugate vaccine, we used output from a dynamic model to approximate herd effects, assuming 85% vaccine efficacy against serogroup C meningitis, an average of 5 years duration of protection, and coverage levels calculated from reported population size and vaccine use [21, 22]. For the quadrivalent conjugate vaccine, we used output from the same dynamic model to approximate herd effects, assuming 98% coverage of 2- to 15-year-olds (reflecting the actual coverage in Ouallam), 85% vaccine efficacy against serogroups A, C, W, and Y, and an average 5 years duration of protection [23].

Vaccine coverage is calculated using the district-level population reported in surveillance data, assuming the targeted population is 2- to 29-year-olds, representing 70% of total population, and the number of doses of vaccine released by the International Coordinating Group on Vaccine Provision or population vaccinated as reported in the Weekly Epidemiological Record where available [24–26]. For all coverage calculations, we assumed 10% vaccine wastage.

Modeling New Vaccination Strategies

We then modeled uniform application of the current strategy and 3 alternative reactive vaccination strategies, making the same assumptions as described above (Table 2). Under the current strategy, mass vaccination takes place on a district level where the weekly incidence of suspected cases exceeds the epidemic threshold and the causative serogroup can be identified. We drop this etiological confirmation requirement for modeling because weekly district-level laboratory data were not available. In alternative strategy A, vaccination takes place when the alert threshold is exceeded. In strategy B, all neighboring districts that have not received vaccine in the last 5 or 2 years for conjugate and polysaccharide vaccine, respectively, are targeted in addition to the district exceeding the epidemic threshold. In strategy C, only those neighboring districts in alert are targeted in addition to the focal district in epidemic. To compare these strategies, we modeled use of a trivalent polysaccharide vaccine, making the following assumptions: (1) campaigns target 2- to 29-year-olds with 85% coverage, who make up 70% of the population and 90% of cases [15, 16]; (2) 80% vaccine efficacy against serogroups A, C, and W [17]; (3) protection lasts for 104 weeks (approximately 2 years) [18]. We model delays between triggering a vaccine response and onset of vaccine protection as 4, 6, and 8 weeks, effectively giving 2, 4, and 6 weeks

Table 2. Summary of Model Assumptions

Model	Coverage	Vaccine Efficacy	Serogroups Covered	Duration of Protection	Delay	Herd Effects	Population Targeted
Polysaccharide vaccination (2015–2017)	Calculated from ICG data	80%	A, C, W	2 years	6 weeks	No	2–29 years; 70% of population
Monovalent conjugate C vaccination (2017)	Calculated from ICG data	85%	C	5 years (average)	6 weeks	Yes	1–19 years
Quadrivalent conjugate vaccination (2015)	Calculated from ICG data	85%	A, C, W, Y	5 years (average)	6 weeks	Yes	2–15 years
Theoretical polysaccharide vaccination	85%	80%	A, C, W	2 years	4–8 weeks	No	2–29 years; 70% of population

Abbreviations: ICG, International Coordinating Group.

for implementation and 2 weeks for vaccine protection to take effect after delivery [17].

Analysis of Model Results

We evaluated the performance of the different strategies and vaccine types by calculating the cases averted, doses of vaccine required to prevent a case (NNV), and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each strategy for predicting outbreaks defined by different cumulative annual incidences (from 100 cases per 100 000 to 20 cases per 100 000).

RESULTS

Spatial and Temporal Characterization

Outbreak activity was first observed in northern Nigeria in 2013 and continued in 2014 (Figures 1 and 2). In 2015, activity spread to the southwestern region of Niger, including the urban area of Niamey. Fewer outbreaks were observed in 2016, followed by relatively high case counts in Niger and the highest case counts in Nigeria thus far in 2017. We detected 20 district-years with high incidence and positive spatial autocorrelation (ie, centers of clusters of high incidence), 46 districts neighboring these clusters, and 1 district with high incidence and negative spatial autocorrelation, meaning it was an outlier from its neighbors). Tambuwal LGA in Sokoto State in Nigeria, where the group C outbreak strain was first identified, was detected as the center of high incidence clusters in 2013 and 2014, but it did not pass the weekly epidemic incidence threshold (WIT10) of 10 cases per 100 000 in 2014 and did not exceed a cumulative annual incidence of 100 suspected cases per 100 000 in either year (CAI100) [8]. Of the neighboring districts, 2 and 4 districts, respectively surpassed the WIT10 in 2013 and 2014 and none exceeded the CAI100. No significant clusters were detected in 2015. High incidence clustered around Niamey in Niger in 2016. Only 1 district, Niamey I, exceeded the WIT10, and none exceeded the CAI100 (although Niamey I came close with 96 cases per 100 000). There was also a spatial outlier of high incidence identified in Nguru LGA in Yobe State in north-central Nigeria. In 2017, 2 large clusters were detected in Sokoto State and Zamfara State in Nigeria. All 15 of the center districts and 16 of the 21 neighboring districts surpassed WIT10 between weeks 10 and 18. Nine of the center districts in these clusters and 2 neighboring districts exceeded the CAI100. Supplementary Table S3 gives full details of all clusters detected.

Impact of Reactive Campaigns

Reactive vaccination campaigns were conducted in 2015, 2016, and 2017 in 60 districts in response to NmC outbreaks using polysaccharide vaccine, monovalent C conjugate vaccine, and quadrivalent ACWY conjugate vaccine (Supplementary Table S4). Our model estimates that these campaigns prevented 1100 of 19 000 (6%) cases of meningococcal meningitis overall during the period 2015 to 2017 (270 of 10 000 [3%] cases in Nigeria and 830 of 9000 [9%] cases in Niger).

Modeling Alternative Reactive Vaccination Strategies

The current strategy required fewest interventions with 63 districts requiring 11 million doses of polysaccharide vaccine between 2013 and 2017, followed by alternative strategy C, which would have targeted an additional 21 districts with 5 million

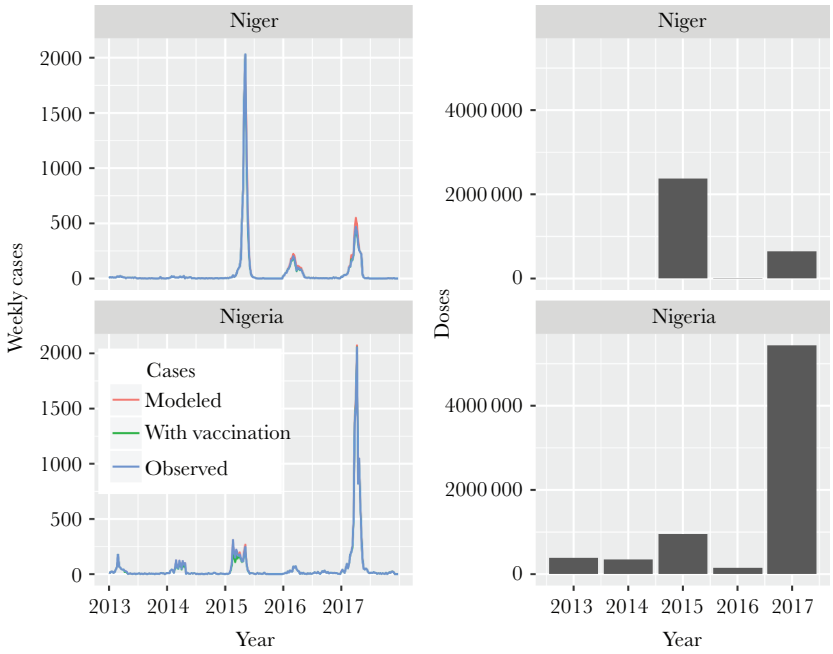

Figure 2. Observed and modeled weekly case counts, annual cases averted by reactive vaccination, and doses vaccine delivered in Niger and Nigeria 2013 to 2017.

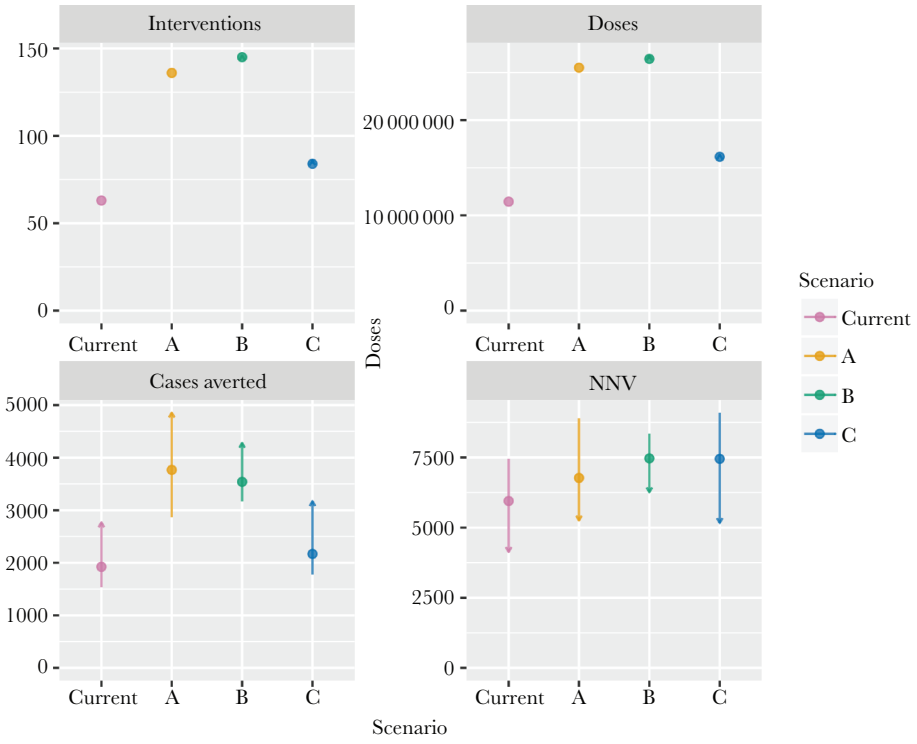

Figure 3. Number of interventions (individual districts vaccinated), doses, proportion of total cases averted, and number needed to vaccinate to prevent a case over the period 2013–2017 for different reactive vaccination strategies using polysaccharide ACW vaccine. Points show estimates for 4-week delays, lines show 2- and 6-week delays, with arrow heads indicating shorter delays.

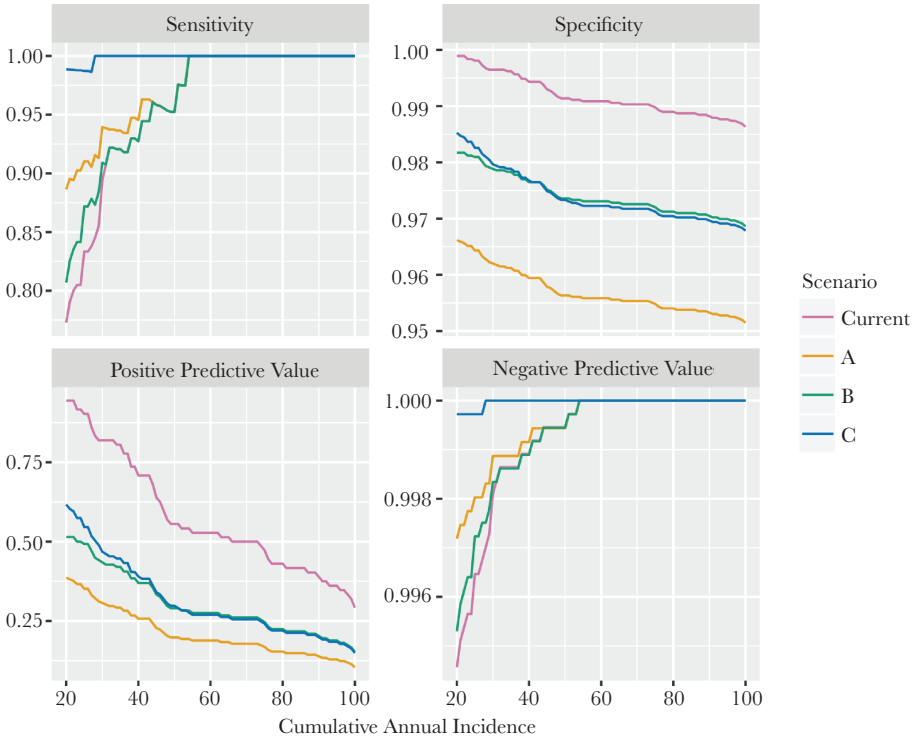

Figure 4. Sensitivity, specificity, positive predictive value, and negative predictive value of different targeting strategies for predicting cumulative annual incidence between 20 and 100 suspected cases per 100 000.

additional doses (Figure 3). Strategies A and B would have required targeting 73 and 82 additional districts, respectively, requiring an additional 14 and 15 million doses of polysaccharide vaccine.

Strategy C had the greatest sensitivity in predicting small outbreaks, whereas the current strategy had the least (Figure 4). Sensitivity was comparable across all strategies for large outbreaks. The current strategy had the highest PPV at any cumulative incidence threshold, followed by strategy C. Specificity and NPV were similar across all strategies. Strategies A and B prevented the most cases, 19% and 18% of all meningococcal meningitis cases, followed by strategy C (11%) and the current strategy (10%).

With shorter delays of 2 weeks, A prevented the most cases (25%); with longer delays of 6 weeks, B prevented the most cases (16%). Across all strategies, interventions with delays of 2 weeks prevented between 1.4 and 1.8 times as many cases those with delays of 6 weeks. Shortening the delay by 2 weeks while maintaining the current strategy would have prevented 14% of cases, close to the proportion prevented by strategies A and B while requiring no additional vaccine. No strategy outperformed the current strategy in terms of NNV, but A was the second most efficient use of vaccine, with an NNV of 6800 compared with the current strategy at 5900.

DISCUSSION

We found significant clustering of high incidence districts in every year, with local clusters occurring around Tambuwal LGA in Nigeria in 2013 and 2014, around Niamey, Niger in 2016, and 2 around Sokoto and Zamfara States in Nigeria in 2017. The locations of these local clusters are consistent with areas of elevated incidence. No significant local cluster was identified in 2015 although incidence was high in Niamey and Tillaberi Regions, perhaps because the distribution of incidence was more even in space.

Our modeling analyses provide no strong evidence to support a change in the methods currently used for predicting and targeting outbreaks. The current weekly incidence threshold of 10 suspected cases per 100 000 is highly specific and sensitive to large outbreaks. Shortening delays between outbreak detection and vaccination offers a substantial benefit. These 2 results are consistent with previous findings regarding group W outbreak response [3]. Although the absolute values in NNV may differ slightly between this and previous studies, adjustment for differing assumptions about coverage and vaccine efficacy can largely account for these differences [6, 27]. However, we note that the majority of districts were larger than 100 000 population, which is not consistent with WHO recommendations. Previous studies have demonstrated that surveillance at finer spatial scales may allow for more efficient and earlier use of vaccine where it is needed [7, 28].

This study also highlights the substantial difference between the number of doses of vaccine required to intervene as per WHO policy (approximately 11 million) and the number of doses that were made available and used in reactive vaccination campaigns between 2013 and 2017 (approximately 4 million) [29]. Although some of this shortfall can be explained by the necessity of dropping the etiological confirmation requirement in our model, it is clear that vaccine scarcity had an impact on decisions about where to carry out reactive vaccination and for which age groups. Although data from Nigeria on laboratory-confirmed cases of meningitis were lacking, one study confirmed our assumption that NmC was the predominant cause of meningitis in Nigeria, with 172 of 173 Nm isolates being from serogroup C [30].

Informed by expert opinion, our model assumes that 80% of suspected meningitis cases occurring during outbreaks are caused by Nm, with just 20% of suspected cases caused by Nm outside of outbreak periods. Line list data from Niger between 2015 and 2017 and Nigeria in 2015 suggests that only 27% of suspected cases occurring during outbreaks are confirmed as meningococcal meningitis, with a similar proportion occurring outside of outbreak periods (Supplementary Table S5). A majority of CSFs test negative for common bacterial pathogens both during and outside of outbreak periods. It is possible that this is driven by antibiotic administration before taking CSF, sample degradation, and the low sensitivity of latex agglutination tests and culture methods compared with polymerase chain reaction-based methods [31–34]. However, we cannot exclude the possibility that there may be substantial clinical misclassification of suspected meningitis cases.

CONCLUSIONS

The epidemiological behavior of meningococcal meningitis in the African meningitis belt is notoriously difficult to predict. Our results will only apply to future epidemiological situations insofar as the spatiotemporal distribution and magnitude of group C meningitis outbreaks remain approximately the same. There is a high degree of uncertainty about which epidemiological characteristics may be considered typical given the strain's recent emergence. In any case, it is important to maintain high-quality surveillance throughout the meningitis belt, striving especially to improve laboratory diagnostics in outbreak settings.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Appendix B

Appendix to Chapter 2

Table B.1 Age distribution of confirmed *S. pneumoniae* meningitis.

Publication	Year	Age group	Confirmed cases	Percent of total
Emele 2000 [112]	1987 to 1992	Under 1 year	6	14%
		1 to 4 years	17	40%
		5 to 9 years	14	33%
		10 to 14 years	1	2%
		15 to 19 years	1	2%
		20 years plus	4	9%
Traore 2009 [62]	2002 to 2006	Under 1 year	57	23%
		1 year	15	6%
		2 to 4 years	21	8%
		5 to 9 years	36	15%
		10 to 14 years	23	9%
		15 to 19 years	21	8%
		20 to 29 years	18	7%
		30 to 39 years	25	10%
		40 to 49 years	18	8%
		50 to 59 years	6	2%
		60 years plus	6	2%
Gessner 2012 [111]	2007 to 2009	Under 1 year	47	17%
		1 to 4 years	25	9%
		5 to 14 years	93	33%
		15 to 49 years	96	34%
		50 years plus	19	7%
Karou 2012 [110]	2007 to 2010	Under 5 years	18	26%
		6 to 12 years	22	32%
		13 to 19 years	11	16%
		20 to 39 years	8	12%
		40 to 55 years	9	13%
Chaibou 2014 [108]	2007 to 2011	Under 1 year	103	23%
		1 year	37	8%
		2 to 5 years	35	8%
		6 to 15 years	143	32%
		16 to 30 years	69	15%
		31 to 60 years	49	11%
		61 plus years	12	3%
Kambire 2016 [32]	2011 to 2013	Under 1 year	276	18%
		1 year	65	4%
		2 to 4 years	137	9%
		5 to 9 years	312	20%
		10 to 14 years	287	19%
		15 to 29 years	253	17%
		30 plus years	198	13%
Kwambana-Adams 2016[21]	2015 to 2016	Under 1 year*	2	2%
		1 to 4 years*	3	4%
		5 to 14 years	30	35%
		15 to 29 years	31	36%
		30 to 59 years	16	19%
		60 years plus	3	4%
Mihret 2016 [64]	2015 to 2016	Under 4 years §	6	33%
		5 to 12 years	4	22%
		13 to 19 years	1	6%
		20 to 29 years	4	22%
		30 to 39 years	0	0%
		40 years plus	3	17%

*PCV13 used in routine EPI since 2012. §PCV10 used in routine EPI since 2011.

Table B.2 Case-fatality rates of confirmed *S. pneumoniae* meningitis.

Publication	Year	Age group	Case-fatality rate
Campagne 1999 [59]	1981 to 1996 †	Under 1 year	58%
		1 to 4 years	57%
		5 to 9 years	16%
		10 to 14 years	35%
		15 to 19 years	62%
		20 to 29 years	58%
		30 to 39 years	20%
		40 plus years	60%
		Overall	53% (n=340)
Campbell 2004 [60]	2002 to 2003	Under 1 year	26%
		1 to 4 years	9%
		5 to 15 years	31%
		Overall	23% (n=47)
Leimkugel 2005 [61]	1998 to 2003	All ages	44% (n=117)
Traore 2009 [62]	2002 to 2006	Under 1 year	52% (n=79)
		1 to 4 years	50% (n=58)
		5 to 14 years	45% (n=80)
		15 plus years	44% (n=145)
		Overall	47% (n=363)
Mueller 2012 [63]	2007 to 2009	All ages	40% (n=155)
Kambire 2016 [32] ‡	2011 to 2013	Under 2 years	32% (n=301)
		2 to 4 years	18% (n=123)
		5 to 9 years	25% (n=275)
		10 to 14 years	23% (n=252)
		15 to 29 years	23% (n=228)
		30 to 64 years	31% (n=143)
		65 years plus	54% (n=26)
		Overall	26% (n=1348)
Kwambana-Adams 2016[21] ‡	2015 to 2016	Under 2 years*	33% (n=3)
		2 to 4 years*	0% (n=3)
		5 to 9 years	33% (n=12)
		10 to 14 years	36% (n=22)
		15 to 29 years	20% (n=50)
		30 to 64 years	38% (n=26)
		65 years plus	0% (n=3)
		Overall	28% (n=119)
Mihret 2016 [64]	2012 to 2013	All ages §	17% (n=18)
Moisi 2017 [65]	2010 to 2013	All ages	35% (n=78)

†Data from 11 non-meningococcal epidemic years. ‡Calculated from data. *PCV13 used in routine EPI since 2012. §PCV10 used in routine EPI since 2011.

Table B.3 Serotype distribution of confirmed *S. pneumoniae* meningitis.

Publication	Year	Age group	PCV13 vaccine-type isolates	ST1 isolates
Campbell 2004 [60]	2002 to 2003	Under 16 years	30 of 38 (79%)	1 of 38 (3%)
Leimkugel 2005 [61]	1998 to 2003	Under 1 year	2 of 2 (100%)	0 of 2 (0%)
		1 to 4 years	4 of 4 (100%)	2 of 4 (50%)
		5 to 14 years	7 of 29 (24%)	4 of 29 (14%)
		15 to 29 years	11 of 12 (92%)	11 of 12 (92%)
		30 to 59 years	12 of 14 (86%)	11 of 14 (79%)
		60 years plus	6 of 9 (67%)	5 of 9 (56%)
Traore 2009 [62]	2002 to 2006	Under 5 years	12 of 18 (67%)	3 of 18 (17%)
		5 to 65 years	23 of 30 (77%)	18 of 30 (60%)
Gessner 2012 [111]	2007 to 2009	Under 5 years	32 of 60 (53%)	11 of 60 (18%)
		5 to 9 years	26 of 32 (81%)	22 of 32 (69%)
		10 to 14 years	24 of 27 (89%)	24 of 27 (89%)
		15 to 19 years	18 of 24 (75%)	17 of 24 (71%)
		20 to 24 years	6 of 7 (86%)	5 of 7 (71%)
		25 to 29 years	9 of 12 (75%)	6 of 12 (50%)
		30 to 34 years	7 of 8 (88%)	6 of 8 (75%)
		35 to 39 years	3 of 6 (50%)	3 of 6 (50%)
		40 to 44 years	4 of 7 (57%)	2 of 7 (29%)
		45 to 49 years	7 of 10 (70%)	5 of 10 (50%)
		50 years plus	7 of 11 (64%)	5 of 11 (45%)
Collard 2013 [109]	2003 to 2011	Under 2 years	147 of 244 (60%)	17 of 244 (7%)
		2 years plus	449 of 633 (71%)	376 of 633 (59%)
Kambire 2016 [32]	2011 to 2013	Under 2 years	156 of 236 (66%)	28 of 236 (12%)
		2 to 4 years	51 of 79 (65%)	22 of 79 (28%)
		5 to 9 years	168 of 221 (76%)	127 of 221 (57%)
		10 to 14 years	156 of 199 (78%)	121 of 199 (61%)
		15 to 29 years	128 of 174 (74%)	109 of 174 (63%)
		30 to 64 years	67 of 107 (63%)	51 of 107 (48%)
		65 years plus	11 of 20 (55%)	6 of 20 (30%)
Kwambana-Adams 2016[21]	2015 to 2016	Under 1 year*	0 of 2 (0%)	0 of 2 (0%)
		1 to 4 years*	1 of 2 (50%)	1 of 2 (50%)
		5 to 14 years	9 of 10 (90%)	8 of 10 (80%)
		15 to 29 years	12 of 14 (86%)	12 of 14 (86%)
		30 to 59 years	6 of 10 (60%)	5 of 10 (50%)
		60 years plus	1 of 1 (100%)	0 of 1 (0%)
Moisi 2017 [65]	2010 to 2013	Under 5 years	12 of 12 (100%)	1 of 12 (8%)
		5 years plus	42 of 56 (75%)	32 of 56 (57%)

*PCV13 used in routine EPI since 2012.

Table B.4 Annual incidence of confirmed *S. pneumoniae* meningitis per 100,000.

Publication	Year	Age group	Annual incidence
Campagne 1999 [59]	1981 to 1996*	Under 1 year	150
		1 to 4 years	10
		5 to 9 years	6
		10 to 14 years	7
		15 to 19 years	9
		20 to 29 years	5
		30 to 39 years	3
		40 plus years	8
Campbell 2004 [60]	2002 to 2003	Under 1 year	43
		1 to 4 years	6
		5 to 15 years	3
Leimkugel 2005 [61]	1998 to 2003	Under 1 year	43
		1 to 4 years	19
		5 to 14 years	26
		15 to 29 years	18
		30 to 59 years	15
		60 years plus	23
Traore 2009 [62]	2002 to 2006	Under 3 months	60
		3 to 5 months	134
		6 to 11 months	57
		1 year	29
		2 to 4 years	14
		5 to 9 years	13
		10 to 14 years	10
		15 to 19 years	11
		20 to 29 years	6
		30 to 39 years	14
		40 to 49 years	19
		50 to 59 years	8
		60 years plus	8
Mueller 2012 [63]	2007 to 2009	Under 6 months	58
		6 to 11 months	43
		1 to 4 years	5
		5 to 9 years	11
		10 to 14 years	9
		15 to 19 years	15
		20 to 29 years	6
		30 to 39 years	6
		40 years plus	4
Kambire 2016 [32]	2011	Under 1 year	31
		1 to 4 years	7
		5 to 9 years	9
		10 to 14 years	10
		15 plus years	4
	2012	Under 1 year	33
		1 to 4 years	7
		5 to 9 years	8
		10 to 14 years	7
		15 plus years	3
	2013	Under 1 year	17
		1 to 4 years	3
		5 to 9 years	4
		10 to 14 years	5
		15 plus years	2

*Data from 11 non-meningococcal epidemic years.

Appendix C

Appendix to Chapter 5

Table C.1 Summary of studies of meningococcal carriage by age in the African meningitis belt included in meta-analysis. *Observations excluded in sensitivity analysis climactic outlier sites.

Paper	Location	Study period	Study design	Study population	Ages
Burian 1974[166]	Bamako, Mali	Jan to May 1970	Cross-sectional	School children, children seen at preventative care centers, contacts of cases	All ages
Blakebrough 1980[181]	Malumfashi, Nigeria	Dec 1977 to Jun 1978	Cross-sectional	School children	5 to 10
Blakebrough 1983[182]	Malumfashi, Nigeria	Jan to May 1978	Vaccine trial	School children (boys), both controls and polysaccharide vaccinees	11 to 20
Leimkugel 2007[169]	Navrongo, Ghana	Apr 1998 to Nov 2005	Longitudinal	General	All ages
Amadou 2006[177]	Niamey, Niger	Feb to May 2003	Longitudinal	School children	7 to 16
Yaro 2007[178]	Bobo-Dioulasso, Burkina Faso	Feb to Jun 2003	Longitudinal	General	4 to 29
Forgor 2005[167]*	Kpalkpalgbeni, Ghana	Apr 2003 to Apr 2004	Serial cross-sectional	General	All ages
Mueller 2011[170]	Ouagadougou, Burkina Faso	Mar 2006	Cross-sectional	General	1 to 39
Trotter 2013[171]	Bobo-Dioulasso, Burkina Faso	Mar 2008	Cross-sectional	General	0 to 59
Kristiansen 2011[41]	Bogodogo, Dande, and Kaya, Burkina Faso	Feb to Nov 2009	Serial cross-sectional	General	1 to 29
Basta 2013[231]	Bamako, Mali Butajira, Ethiopia Niakkar, Senegal Say, Niger	Jun 2009 to Jan 2010	Cross-sectional	School children	5 to 15
MenAfriCar 2015[40]	Bamako, Narena, and Siby, Mali Butajira, Ethiopia* Fatick and Niakkar, Senegal Kassena-Nankana and Navrongo, Ghana Konduga and Maiduguri, Nigeria Mandelia and N'Djamena, Chad Say and Yantala, Niger	Apr 2010 to Jul 2012	Serial cross-sectional	General	All ages
Kristiansen 2013[168]	Bogodogo, Dande, and Kaya, Burkina Faso	Oct 2010 to Nov 2011	Serial cross-sectional	General	1 to 29
Kristiansen 2014[73]	Bogodogo, Dande, and Kaya, Burkina Faso	Oct to Nov 2012	Cross-sectional	General	1 to 29
Manigart 2016[185]	Fajikunda, the Gambia	Jul 2013	Cross-sectional	General	10 to 18
Barnes 2016[165]*	Arba Minch, Ethiopia	Mar to Sep 2014	Cross-sectional	General	1 to 29

Table C.2 Summary of carriage studies included in systematic review. *Climactic outlier observations excluded in sensitivity analysis.

Paper	Location	Study period	Study design	Study population	Random sample	Laboratory methods	Ages
Burian 1974[166]	Bamako, Mali	Jan to May 1970	Cross-sectional	School children, children seen at preventative care centers, contacts of cases	No	Culture	All ages
Sanborn 1971	Northern Nigeria	Feb to Mar 1971	Vaccine trial	Both polysaccharide vaccinees & controls (vaccine had no impact on carriage)	No	Culture	5 to 15
Etienne 1973	Bobo-Dioulasso, Burkina Faso	Feb 1972 to Feb 1973	Longitudinal	General	No	Culture	All ages
Blakebrough 1982	Malumfashi, Nigeria	Apr 1976 to Oct 1977	Cross-sectional	School children	No	Culture	4 to 16
Blakebrough 1980[181]	Malumfashi, Nigeria	Dec 1977 to Jun 1978	Cross-sectional	School children	No	Culture	5 to 10
Blakebrough 1983[182]	Malumfashi, Nigeria	Jan to May 1978	Vaccine trial	School children (boys), both controls & polysaccharide vaccinees	Yes	Culture	11 to 20
Emele 1999	Sokoto, Nigeria	Nov 1990 to Mar 1992	Serial cross-sectional	General	No	Culture	1 to 19
Leimkugel 2007[169]	Navrongo, Ghana	Apr 1998 to Nov 2005	Longitudinal	General	Yes	Culture with PCR confirmation	All ages
MacLennan 2000	Senegal & the Gambia		Vaccine trial	Children receiving conjugate vaccine	No	Culture with PCR confirmation	5
Raghunathan 2006[155]	Dedougou & Yako, Burkina Faso	May 2002	Cross-sectional	General	Yes	Culture	5 to 25
Amadou 2006[177]	Niamey, Niger	Feb to May 2003	Longitudinal	School children	No	Culture	7 to 16
Yaro 2007[178]	Bobo-Dioulasso, Burkina Faso	Feb to Jun 2003	Longitudinal	General	Yes	Culture with PCR confirmation	4 to 29
Forgor 2005[167]	Kpalkpalgbeni, Ghana	Apr 2003 to Apr 2004	Serial cross-sectional	General	No	Culture with PCR confirmation	All ages
Mueller 2011[170]	Ouagadougou, Burkina Faso	Mar 2006	Cross-sectional	General	Yes	Culture with PCR confirmation	1 to 39
Sie 2008[180]	Nouna Health District, Burkina Faso	May 2006	Cross-sectional	General	Yes	Culture with PCR confirmation	All ages
Trotter 2013[171]	Bobo-Dioulasso, Burkina Faso	Mar 2008	Cross-sectional	General	Yes	Culture with PCR confirmation	0 to 59
Kristiansen 2011[41]	Bogodogo, Dande & Kaya, Burkina Faso	Feb to Nov 2009	Serial cross-sectional	General	Yes		1 to 29
Basta 2013[231]	Bamako, Mali Butajira, Ethiopia Niakkar, Senegal Say, Niger	Jun 2009 to Jan 2010	Cross-sectional	School children	No	Culture with PCR confirmation	5 to 15

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Table C.2 – *Continued from previous page*

Paper	Location	Study period	Study design	Study population	Random sample	Laboratory methods	Ages
MenAfriCar 2015[40]	Bamako, Narena & Siby, Mali Butajira, Ethiopia* Fatick & Niakkar, Senegal Kassena-Nankana & Navrongo, Ghana Konduga & Maiduguri, Nigeria Mandelia & N'Djamena, Chad Say & Yantala, Niger	Apr 2010 to Jul 2012	Serial cross-sectional	General	Yes	Culture with PCR confirmation	All ages
Kristiansen 2013[168]	Bogodogo, Dande & Kaya, Burkina Faso	Oct 2010 to Nov 2011	Serial cross-sectional	General	Yes	Culture with PCR confirmation	1 to 29
Kristiansen 2014[73]	Bogodogo, Dande & Kaya, Burkina Faso	Oct to Nov 2012	Cross-sectional	General	Yes	Culture with PCR confirmation	1 to 29
Manigart 2016[185]	Fajikunda, the Gambia	Jul 2013	Cross-sectional	General	No	Culture with PCR confirmation	10 to 18
Barnes 2016[165]	Arba Minch, Ethiopia	Mar to Sep 2014	Cross-sectional	General	No	Culture with PCR confirmation	1 to 29

Table C.3 Details of studies excluded from meta-analysis.

Paper	Reason for exclusion	Study population	Location	Time period	Age	Positive	Sampled	Prevalence (%)
Sanborn 1972[184]	Wide age range	Polysaccharide vaccinees and controls	Northern Nigeria	Feb 1971	5 to 15	179	311	57.6
Etienne 1973[179]	Wide age range	General	Bobo-Dioulasso, Burkina Faso	Feb 1972	0 to 14	13	63	20.4
					15 plus	11	32	34.2
Blakebrough 1982[13]	Wide age range	School children	Malumfashi, Nigeria	Apr 1976	4 to 16	8	107	7.5
				Aug 1976		7	104	6.7
				Oct 1977		53	631	8.4
Raghunathan 2006[155]	Wide age range	Non-epidemic district	Dedougou, Burkina Faso	May 2002	5 to 25	75	439	17.1
		Epidemic district	Yako, Burkina Faso			128	460	27.8
Emele 1999[183]	Both seasons	General	Sokoto, Nigeria	Nov 1990	1 to 4	8	95	8.4
				to Mar	5 to 9	23	270	8.5
				1992	10 to 14	13	303	4.3
					15 to 19	1	58	1.7
MacLennan 2000[232]	Conjugate vaccine	Children receiving conjugate vaccine	Senegal & the Gambia	1997	5	43	510	8.4
Sie 2008[180]	No sample size	General	Nouna Health District, Burkina Faso	May 2006	1 to 4	7		
					5 to 9	5		
					10 to 14	4		
					15 to 19	2		
					20 to 29	4		
					30 to 39	0		
					40 plus	1		

Table C.4 Summary of model variants. * Akaike's information criterion. §Leave-one-out cross-validation predictions and true observations correlation (Pearson's rho and 95% confidence interval). ‡Profile confidence intervals non-convergent.

Model type	Fixed effects odds ratios (95% CI)						AIC*	Log-likelihood	LOOCV §
	Natural cubic spline of age				Season				
	I	II	III	IV	Dry	Outbreak			
Simple logistic	3.4	2.0	5.2	0.79	1.5	6.7	2081.3	-1031.6	0.890
	(2.9-4.0)	(1.7-2.4)	(3.7-7.2)	(0.71-0.87)	(1.4-1.7)	(1.6-27)			(0.869-0.908)
Observation-level random effects	3.9	1.9	4.4	0.81	1.4	6.6	1997.2	-988.6	0.890
	(3.0-5.1)	(1.4-2.5)	(2.6-7.7)	(0.7-0.94)	(1.2-1.6)	(1.6-27)			(0.869-0.907)
Beta-binomial hierarchical	3.4‡	2.0‡	5.2‡	0.78‡	1.5‡	6.9‡	2082.8	-1041.9	0.896
									(0.876-0.912)
Poisson	3.0	1.9	4.4	0.80	1.5	5.9	2061.0	-1021.5	0.934
	(2.6-3.6)	(1.6-2.3)	(3.2-6.1)	(0.73-0.89)	(1.4-1.6)	(1.5-23)			(0.921-0.945)
Negative binomial	3.5	1.8	4.0	0.83	1.4	5.8	1999.5	-989.8	0.957
	(2.7-4.5)	(1.4-2.3)	(2.4-6.5)	(0.72-0.95)	(1.2-1.6)	(1.5-23)			(0.949-0.964)

Table C.5 Carriage rates by study and age group. *Age group containing 10 years of age.

Paper (Sample size)	Age group	Number of individuals	Carriage prevalence	Lower prevalence than peak (p-value < 0.0005)
Barnes 2016[165]	1-4 years	1575	4.7%	***
(n = 7479)	5-9 years	2766	6.7%	
	10-14 years*	1674	6.3%	
	15-19 years	490	9.8%	Peak
	20-24 years	332	8.4%	
	25-29 years	642	7.9%	
Burian 1974[166]	Under 1 year	60	6.7%	
(n = 2569)	1-4 years	173	11.6%	
	5-9 years	1191	5.6%	
	10-14 years*	881	4.3%	
	15-19 years	136	5.9%	
	20-29 years	68	5.9%	
	30-39 years	38	5.3%	
	40-49 years	15	0%	
	Over 50 years	7	14.3%	Peak
Emele 1999	1-4 years	95	8.4%	
(n = 726)	5-9 years	270	8.5%	Peak
	10-14 years*	303	4.3%	
	15-19 years	58	1.7%	
Etienne 1973	0-14 years*	63	20.6%	
(n = 95)	15 plus years	32	34.4%	Peak
Forgor 2005[167]	Under 1 year	6	16.7%	
(n = 299)	1-4 years	78	7.7%	
	5-9 years	44	15.9%	
	10-14 years*	37	29.7%	
	15-19 years	24	37.5%	Peak
	20-39 years	93	14.0%	
	40 plus years	17	5.9%	
Kristiansen 2011[41]	1-4 years	4588	2.3%	***
(n = 20326)	5-9 years	5496	4.3%	
	10-14 years*	3732	5.1%	Peak
	15-19 years	2810	4.9%	
	20-24 years	2080	4.1%	
	25-29 years	1620	3.4%	
Kristiansen 2013[168]	1-4 years	6258	4.4%	***
(n = 25520)	5-9 years	6987	8.7%	
	10-14 years*	4883	8.9%	Peak
	15-19 years	3159	6.3%	***
	20-24 years	2369	3.3%	***
	25-29 years	1864	2.7%	***
Kristiansen 2014[73]	1-4 years	1221	5.2%	***
(n = 4964)	5-9 years	1438	11.2%	Peak
	10-14 years*	896	9.7%	
	15-19 years	565	8.0%	
	20-24 years	455	5.1%	***
	25-29 years	389	2.8%	***
Leimkugel 2007[169]	Under 5	40	5.0%	
(n = 300)	5-9 years	43	7.0%	
	10-14 years*	45	4.4%	
	15-19 years	34	2.9%	
	20-29 years	27	11.1%	Peak
	30-39 years	31	3.2%	
	40-49 years	33	3.0%	
	50 plus years	47	2.1%	

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Table C.5 – *Continued from previous page*

Paper (Sample size)	Age group	Number of individuals	Carriage prevalence	Lower prevalence than peak (p-value < 0.0005)
MenAfriCar 2015[40]	Under 1 year	2195	1.2%	***
(n = 48404)	1-4 years	8817	1.4%	***
	5-14 years*	13105	2.7%	Peak
	15-29 years	12407	1.9%	***
	30-44 years	6575	1.3%	***
	45 plus years	5305	1.5%	***
Mueller 2011[170]	1 year	30	16.7%	
(n = 615)	2-4 years	124	9.7%	***
	5-9 years	156	25.6%	
	10-19 years*	154	24.0%	
	20-29 years	82	31.7%	Peak
	30-39 years	69	13.0%	
Trotter 2013[171]	0-0.5 years	56	0%	
(n = 1037)	0.5-1 years	53	0%	
	1-4 years	120	0.8%	
	5-9 years	120	2.5%	
	10-14 years*	115	0%	
	15-19 years	118	0%	
	20-24 years	118	0.8%	
	25-29 years	115	2.6%	
	30-39 years	110	0.9%	
	40 plus years	112	2.7%	Peak
Yaro 2007[178]	4-14 years*	224	4.5%	Peak
(n = 456)	15-29 years	232	2.6%	

1

Table C.6 Random effects intercepts for location term.

Location	Intercept
Bobo-Dioulasso, Burkina Faso	-0.14
Bogodogo, Burkina Faso	0.13
Dande, Burkina Faso	0.81
Kaya, Burkina Faso	1.16
Secteur 15, Burkina Faso	0.34
Mandelia, Chad	-0.8
N'Djamena, Chad	-0.59
Arba Minch, Ethiopia	0.4
Butajira (rural), Ethiopia	-0.02
Butajira (urban), Ethiopia	-0.31
Kassena-Nankana (town), Ghana	0.34
Kassena-Nankana District, Ghana	0.28
Kpalkpalgbeni, Brong-Ahafo, Ghana	0.28
Navrongo, Ghana	-0.32
Bamako, Mali	-0.11
Bamako and Koulikoro, Mali	0.26
Narena and Siby, Mali	-0.6
Niamey, Niger	0.53
Say, Niger	-0.05
Yantala, Niger	0.33
Konduga, Nigeria	-1.22
Maiduguri, Nigeria	-0.46
Malumfashi, Kaduna State, Nigeria	-0.58
Fatick, Senegal	0.25
Niakkar, Senegal	0.45
Fajikunda, The Gambia	0.19

Table C.7 Random effects intercepts for location-year interaction term.

Location	Year 1970	1977	1978	1998	2003	2006	2008	2009	2010	2011	2012	2013	2014
Bobo-Dioulasso, Burkina Faso	...	...	...	...	0.34	...	-0.60	...	...	...	...	...	...
Bogodogo, Burkina Faso	...	...	...	...	...	...	...	-0.22	0.47	-0.36	0.35	...	...
Dande, Burkina Faso	...	...	...	...	...	...	...	-0.11	0.07	-0.25	1.81	...	...
Kaya, Burkina Faso	...	...	...	...	...	...	...	0.01	1.87	0.70	-0.40	...	...
Secteur 15, Burkina Faso	...	...	...	...	...	0.63	...	...	...	...	...	...	...
Mandelia, Chad	...	...	...	...	...	...	...	...	0.01	0.51	-2.01	...	...
N'Djamena, Chad	...	...	...	...	...	...	...	...	-0.18	-0.25	-0.67	...	...
Arba Minch, Ethiopia	...	...	...	...	...	...	...	...	...	...	...	...	0.75
Butajira (rural), Ethiopia	...	...	...	...	...	...	...	...	0.42	0.45	-0.90	...	...
Butajira (urban), Ethiopia	...	...	...	...	...	...	...	0.04	0.5	-0.23	-0.88	...	...
Kassena-Nankana, Ghana	...	...	...	...	...	...	...	...	-0.9	1.14	0.41	...	...
Kassena-Nankana District, Ghana	...	...	...	0.52	...	...	...	...	...	...	...	...	...
Kpalkpalgbeni, Brong-Ahafo, Ghana	...	...	...	...	0.52	...	...	...	...	...	...	...	...
Navrongo, Ghana	...	...	...	...	...	...	...	...	-1.49	-0.61	1.49	...	...
Bamako, Mali	...	...	...	...	...	...	...	1.74	-1.32	-0.02	-0.60	...	...
Bamako and Koulikoro, Mali	0.49	...	...	...	...	...	...	...	...	...	...	...	...
Narena and Siby, Mali	...	...	...	...	...	...	...	...	-0.94	-0.52	0.35	...	...
Niamey, Niger	...	...	...	...	1.00	...	...	...	...	...	...	...	...
Say, Niger	...	...	...	...	...	...	...	-0.19	-0.18	0.70	-0.42	...	...
Yantala, Niger	...	...	...	...	...	...	...	...	0.65	0.73	-0.76	...	...
Konduga, Nigeria	...	...	...	...	...	...	...	...	-1.08	-1.19	...	...	...
Maiduguri, Nigeria	...	...	...	...	...	...	...	...	-0.86	...	...	...	...
Malumfashi, Kaduna State, Nigeria	...	-0.20	-0.87	...	...	...	...	...	...	...	...	...	...
Fatick, Senegal	...	...	...	...	...	...	...	...	-0.33	-0.7	1.49	...	...
Niakkar, Senegal	...	...	...	...	...	...	...	-0.99	-0.27	-0.11	2.21	...	...
Fajikunda, The Gambia	...	...	...	...	...	...	...	...	...	...	...	0.35	...

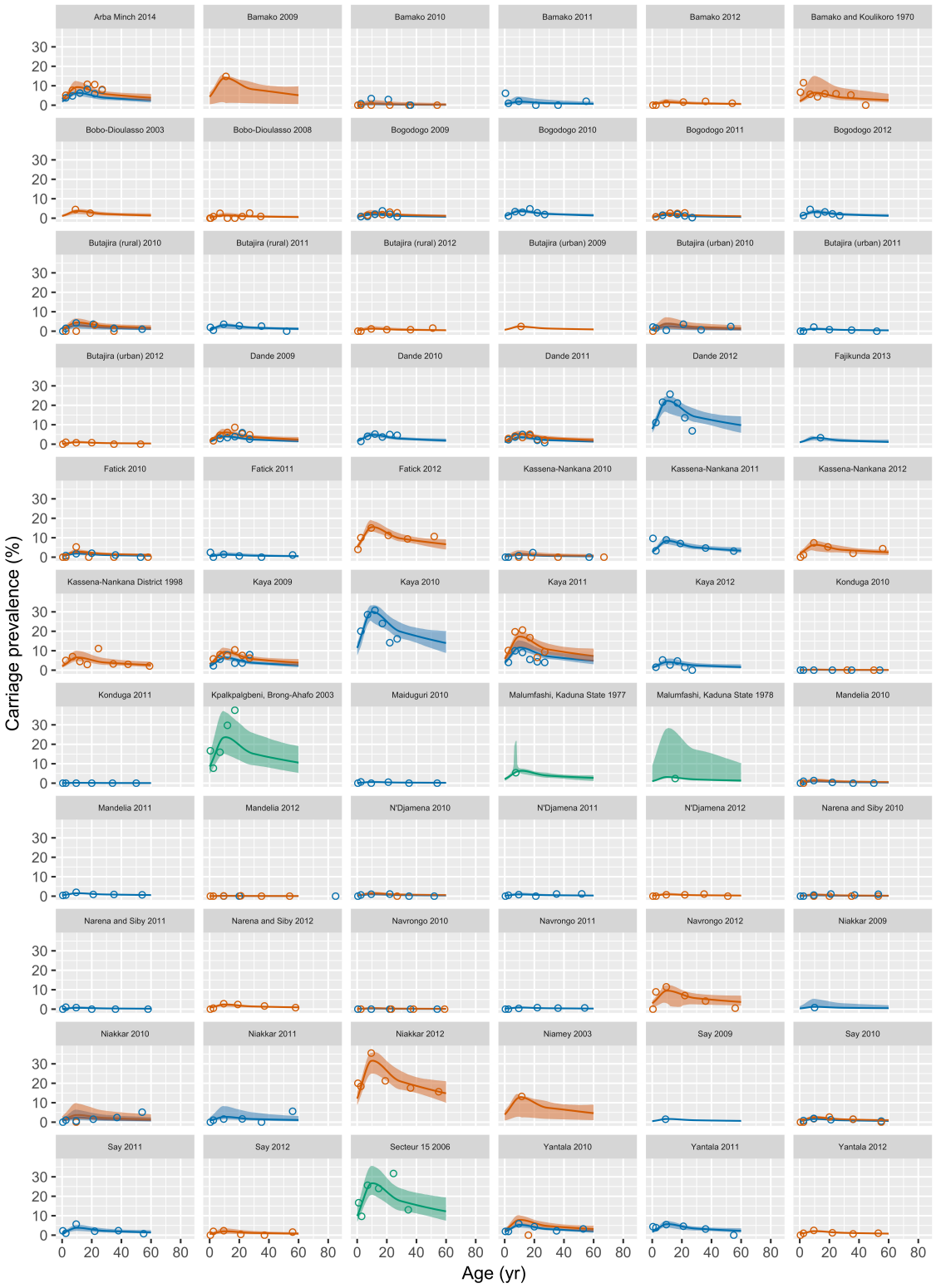

Fig. C.1 Carriage prevalence by age (circles), median bootstrap predictions including random effects (line) and bias-corrected 95% confidence intervals (ribbon) by location and year. Dry season predictions shown in red; rainy season in blue; outbreak periods in green. Note the change in scale.

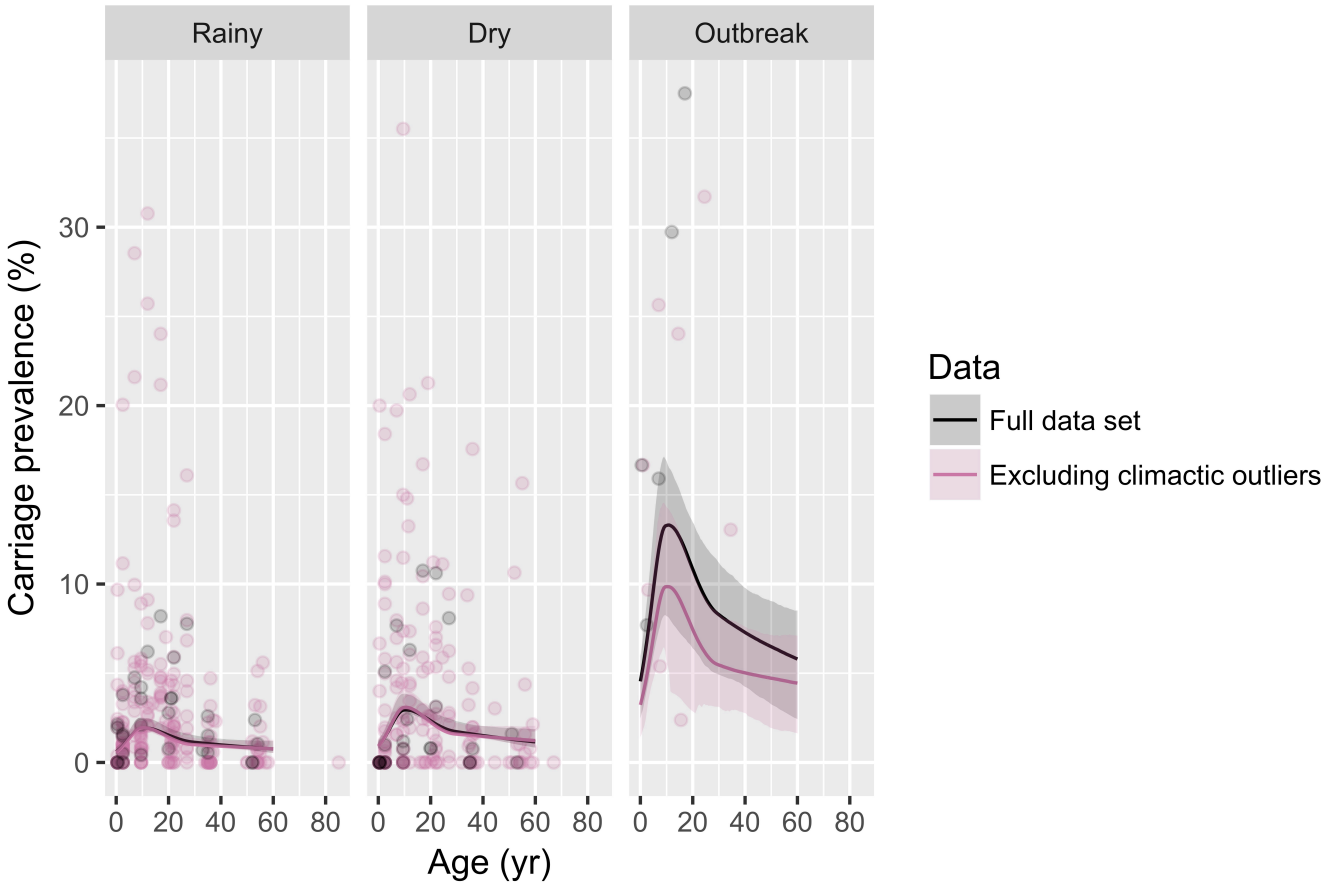

Fig. C.2 Comparison of model fit (fixed effects) on the full data set (pink and black points) and excluding climactic outliers (pink points only). Carriage prevalence by age (circles), median bootstrap predictions (line) and bias-corrected 95% confidence intervals (ribbon) by epidemiological category.

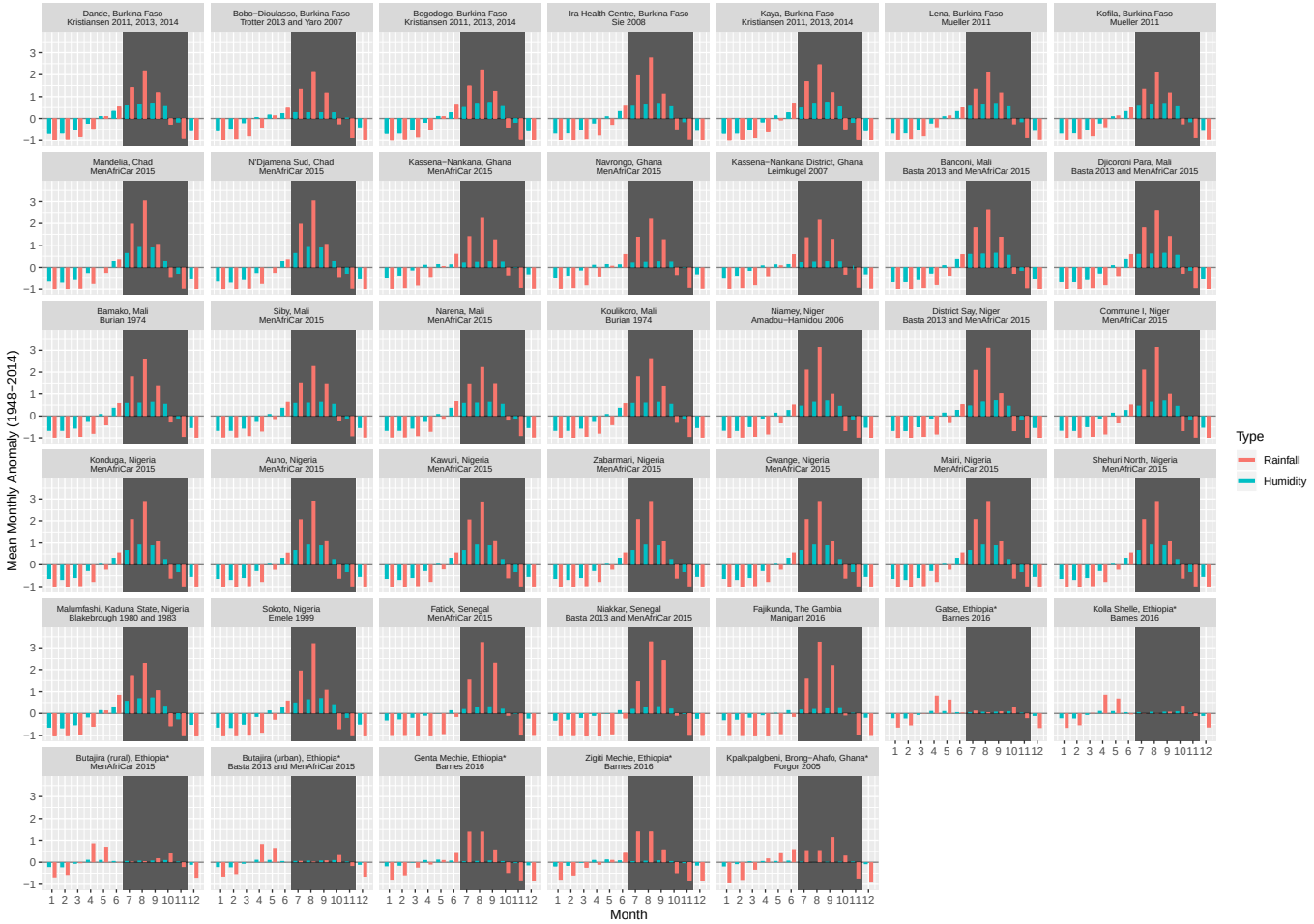

Fig. C.3 Rainfall and relative humidity monthly anomalies at study sites compared with model definition of rainy season (black shading). Climactic outliers at bottom, marked with asterisk.

Appendix D

Appendix to Chapter 7

Table D.1 District names in surveillance and map data sets.

Country	Region	District (surveillance)	District (map)	Year
Niger	Agadez	Aderbissanat	Tchirozerine	2016-2017
Niger	Agadez	Iferouane	Arlit	2017
Niger	Agadez	Ingall	Tchirozerine	2017
Niger	Diffa	Bosso	Diffa	2017
Niger	Diffa	Goudoumaria	Maine Soroa	2017
Niger	Diffa	N'gourti	N'guigmi	2017
Niger	Dosso	Dioundiou	Gaya	2016-2017
Niger	Dosso	Falmeye	Boboye	2017
Niger	Dosso	Tibiri	Guidam-roumdji	2016-2017
Niger	Maradi	Bermo	Dakoro	2017
Niger	Maradi	Gazaoua	Tessaoua	2017
Niger	Maradi	Guidan-Roumdji	Guidam-roumdji	2013-2017
Niger	Niamey	Niamey II	Niamey I	2015-2017
Niger	Niamey	Niamey III	Niamey II	2015-2017
Niger	Niamey	Niamey IV	Niamey II	2015-2017
Niger	Niamey	Niamey V	Niamey III	2015-2017
Niger	Tahoua	Bagaroua	Illela	2017
Niger	Tahoua	Malbaza	Birni N'konni	2016-2017
Niger	Tahoua	Tahoua Commune	Tahoua	2017
Niger	Tahoua	Tahoua Dept	Tahoua	2016-2017
Niger	Tahoua	Tassara	Tchintabaraden	2017
Niger	Tahoua	Tillia	Tchintabaraden	2017
Niger	Tillaberi	Abala	Filingue	2017
Niger	Tillaberi	Ayorou	Tera	2017
Niger	Tillaberi	Balleyara	Filingue	2017
Niger	Tillaberi	Banibangou	Ouallam	2016-2017
Niger	Tillaberi	Bankilare	Tera	2017
Niger	Tillaberi	Gotheye	Tillaberi	2017
Niger	Tillaberi	Torodi	Say	2017
Niger	Zinder	Belbedji	Tanout	2017
Niger	Zinder	Damagaram T	Mirriah	2017
Niger	Zinder	Takeita	Mirriah	2017
Nigeria	Adamawa	Lamurde	Larmurde	2013-2015
Nigeria	Adamawa	Toungo	Teungo	2013-2015
Nigeria	Benue	Buruku	Bukuru	2013
Nigeria	Benue	Makurdi	Markurdi	2013-2017
Nigeria	Benue	Ogbdibo	Ogbadibo	2013
Nigeria	Benue	Otukpo	Oturkpo	2013

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Table D.1 – *Continued from previous page*

Country	Region	District (surveillance)	District (map)	Year
Nigeria	Gombe	Shongom	Shomgom	2013-2015
Nigeria	Imo	Ezinihitte Mbaise	Ezinihitte	2013-2015
Nigeria	Imo	Mbaitoli	Mbatoli	2013-2015
Nigeria	Imo	Onuimo	Unuimo	2013-2015
Nigeria	Jigawa	Birniwa	Biriniwa	2013-2015
Nigeria	Jigawa	Kiri-Kasamma	Kiri Kasama	2013-2015
Nigeria	Jigawa	Sule-Tankarkar	Sule Tankakar	2013-2015
Nigeria	Kaduna	Kubau	Kuban	2013-2015
Nigeria	Kano	Ungogo	Ungongo	2013-2015
Nigeria	Katsina	Jibya	Jibia	2013-2015
Nigeria	Katsina	Maiaduwa	Mai'Adua	2013-2015
Nigeria	Katsina	Malunfashi	Malumfashi	2013
Nigeria	Kebbi	Aliero	Aleiro	2013-2015
Nigeria	Kebbi	Arewa	Arewa Dandi	2013-2015
Nigeria	Kebbi	Danko Wasagu	Wasagu/Danko	2013-2015
Nigeria	Kebbi	Koko Bese	Koko/Besse	2013-2015
Nigeria	Kwara	Patigi	Pategi	2013-2015
Nigeria	Nasarawa	N/Eggon	Nasarawa Egon	2013-2015
Nigeria	Niger	Minna	Chanchaga	2013-2015
Nigeria	Niger	Munya	Muya	2013-2015
Nigeria	Oyo	Ogbomoso North	Ogbomosho North	2013-2015
Nigeria	Oyo	Ogbomoso South	Ogbomosho South	2013-2015
Nigeria	Oyo	Oorelope	Orelope	2013-2015
Nigeria	Taraba	K/Lamido	Karim Lamido	2013
Nigeria	Yobe	Bade	Barde	2013
Nigeria	Yobe	Bursari	Borsari	2013-2015
Nigeria	Yobe	Tarmuwa	Tarmua	2013-2015
Nigeria	Zamfara	Birnin Magaji	Birnin Magaji/Kiyaw	2013-2015
Nigeria	Zamfara	Birnin Magaji/Kiyawa	Birnin Magaji/Kiyaw	2016-2017

Table D.2 Significant clusters and outliers of high district-level incidence (per 100,000 population) detected by Anselin's local Moran's I-statistic. Epidemic incidence threshold (ET) at 10 cases per 100,000 per week. * indicates districts which also fall in the primary Kulldorff spatio-temporal cluster centred on Augie, Nigeria.

Year	District	Region	Country	Cluster centre, cluster or outlier?	Population	Week crossing ET	Cumulative annual incidence
2013	Tambuwal	Sokoto	Nigeria	Cluster centre	276637	8	87
2013	Kebbe	Sokoto	Nigeria	Cluster	153314		0
2013	Shagari	Sokoto	Nigeria	Cluster	192368	9	46
2013	Yabo	Sokoto	Nigeria	Cluster	141449		1
2013	Aliero	Kebbi	Nigeria	Cluster	81692		20
2013	Argungu	Kebbi	Nigeria	Cluster	242059		2
2013	Augie	Kebbi	Nigeria	Cluster	145231		0
2013	Gwandu	Kebbi	Nigeria	Cluster	187000	9	35
2013	Jega	Kebbi	Nigeria	Cluster	239419		0
2013	Gummi	Zamfara	Nigeria	Cluster	254996		1
2014	Tambuwal	Sokoto	Nigeria	Cluster centre	284936		15
2014	Kebbe	Sokoto	Nigeria	Cluster	157913		0
2014	Shagari	Sokoto	Nigeria	Cluster	198139	8	12
2014	Yabo	Sokoto	Nigeria	Cluster	145692		2
2014	Aliero	Kebbi	Nigeria	Cluster	84224	4	261
2014	Argungu	Kebbi	Nigeria	Cluster	249563		8
2014	Augie	Kebbi	Nigeria	Cluster	149734	12	55
2014	Gwandu	Kebbi	Nigeria	Cluster	192797	12	73

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Table D.2 – *Continued from previous page*

Year	District	Region	Country	Cluster centre, cluster or outlier?	Population	Week crossing ET	Cumulative annual ncidence
2014	Jega	Kebbi	Nigeria	Cluster	246841		22
2014	Gummi	Zamfara	Nigeria	Cluster	263156		30
2016	Kollo		Niger	Cluster centre	511496		28
2016	Niamey I		Niger	Cluster centre	503655	8	96
2016	Niamey III		Niger	Cluster centre	145801		23
2016	Boboye		Niger	Cluster	385387		7
2016	Filingue		Niger	Cluster	613430		6
2016	Niamey II		Niger	Cluster	482426		50
2016	Ouallam		Niger	Cluster	431800		16
2016	Say		Niger	Cluster	393721		4
2016	Tera		Niger	Cluster	727727		11
2016	Tillaberi		Niger	Cluster	312550		10
2016	Nguru	Yobe	Nigeria	Outlier	212481		51
2017	Bodinga	Sokoto	Nigeria	Cluster centre*	242803	12	135
2017	Dange-Shuni	Sokoto	Nigeria	Cluster centre*	269297	13	188
2017	Isa	Sokoto	Nigeria	Cluster centre*	202241	14	35
2017	Kware	Sokoto	Nigeria	Cluster centre*	185348	17	76
2017	Rabah	Sokoto	Nigeria	Cluster centre*	206479	11	127
2017	Sokoto North	Sokoto	Nigeria	Cluster centre*	322313	14	168
2017	Sokoto South	Sokoto	Nigeria	Cluster centre*	269807	14	144
2017	Tureta	Sokoto	Nigeria	Cluster centre*	94640	12	192
2017	Wamako	Sokoto	Nigeria	Cluster centre*	248635	14	146
2017	Anka	Zamfara	Nigeria	Cluster centre*	201197	12	65
2017	Bakura	Zamfara	Nigeria	Cluster centre*	264300	12	108
2017	Kaura Namoda	Zamfara	Nigeria	Cluster centre*	397878	13	97
2017	Maradun	Zamfara	Nigeria	Cluster centre*	298163	13	116
2017	Talata Mafara	Zamfara	Nigeria	Cluster centre*	304281	13	99
2017	Zurmi	Zamfara	Nigeria	Cluster centre*	415512	13	89
2017	Binji	Sokoto	Nigeria	Cluster*	145382	16	27
2017	Goronyo	Sokoto	Nigeria	Cluster*	252340	14	58
2017	Gwadabawa	Sokoto	Nigeria	Cluster*	320254	14	76
2017	Sabon Birni	Sokoto	Nigeria	Cluster*	287366		11
2017	Shagari	Sokoto	Nigeria	Cluster*	216512		7
2017	Silame	Sokoto	Nigeria	Cluster*	144484	14	27
2017	Tangaza	Sokoto	Nigeria	Cluster*	157599	18	26
2017	Wurno	Sokoto	Nigeria	Cluster*	224671	16	81
2017	Yabo	Sokoto	Nigeria	Cluster*	159202	15	46
2017	Birnin Magaji/Kiyaw	Zamfara	Nigeria	Cluster*	252583	13	95
2017	Bukkuyum	Zamfara	Nigeria	Cluster*	299268	17	33
2017	Bungudu	Zamfara	Nigeria	Cluster*	364718	15	37
2017	Gummi	Zamfara	Nigeria	Cluster*	289236	14	45
2017	Gusau	Zamfara	Nigeria	Cluster*	541825	13	93
2017	Maru	Zamfara	Nigeria	Cluster*	412773	13	99
2017	Shinkafi	Zamfara	Nigeria	Cluster*	191820	12	236
2017	Batsari	Katsina	Nigeria	Cluster	289274		29
2017	Jibia	Katsina	Nigeria	Cluster	234971	10	43
2017	Sandamu	Katsina	Nigeria	Cluster	190037		2
2017	Guidam-Roumdji		Niger	Cluster*	966372		31
2017	Madarounfa		Niger	Cluster*	548890	16	115

Table D.3 Vaccine use in reactive vaccination campaigns. Coverage data used in modelling cases in the absence of intervention. No data indicates districts where no specific coverage data were found other than a description of "full" or "partial" coverage.

District	Country	Year	Population	Vaccine type	Doses	Coverage	No data
Dogon-Doutchi	Niger	2015	385897	ACW PS	256622	95%	*
Dosso	Niger	2015	519638	ACW PS	345559	95%	*
Filingue	Niger	2015	594689	ACW PS	208141	50%	*
Illela	Niger	2015	468833	ACW PS	311774	95%	*
Kollo	Niger	2015	495869	ACW PS	329753	95%	*
Niamey I	Niger	2015	224212	ACW PS	149101	95%	*
Niamey II	Niger	2015	263583	ACW PS	175283	95%	*
Niamey III	Niger	2015	174202	ACW PS	115844	95%	*
Niamey IV	Niger	2015	293033	ACW PS	194867	95%	*
Niamey V	Niger	2015	141209	ACW PS	93904	95%	*
Ouallam	Niger	2015	419980	ACYW conjugate	279287	90%	
Aliero	Nigeria	2015	86835	ACW PS	30392	50%	*
Bunza	Nigeria	2015	159869	ACW PS	66222	59%	
Gudu	Nigeria	2015	124663	ACW PS	82901	95%	*
Jega	Nigeria	2015	254493	ACW PS	81975	46%	
Maiyama	Nigeria	2015	231241	ACW PS	21316	13%	
Shagari	Nigeria	2015	204083	ACW PS	51700	36%	
Zuru	Nigeria	2015	217896	ACW PS	144901	95%	*
Niamey II	Niger	2016	272153	ACW PS	180982	95%	*
Goronyo	Nigeria	2016	244991	ACW PS	162919	95%	*
Birni N'Konni	Niger	2017	374442	ACW PS	131055	50%	*
Dioundiou	Niger	2017	132321	ACW PS	87993	95%	*
Tibiri	Niger	2017	325948	ACW PS	114082	50%	*
Kollo	Niger	2017	560762	ACW PS	196267	50%	*
Madarounfa	Niger	2017	548890	ACW PS	365012	95%	*
Niamey II	Niger	2017	289437	ACW PS	192476	95%	*
Niamey III	Niger	2017	191289	ACW PS	66951	50%	*
Niamey IV	Niger	2017	321775	ACW PS	112621	50%	*
Anka	Nigeria	2017	201197	ACW PS	29172	21%	
Bakura	Nigeria	2017	264300	ACW PS	19210	10%	
Batagarawa	Nigeria	2017	255495	ACW PS	6775	4%	
Batsari	Nigeria	2017	289274	ACW PS	12177	6%	
Birnin Magaji/Kiyawa	Nigeria	2017	252583	ACW PS	55254	31%	
Bukkuyum	Nigeria	2017	299268	ACW PS	199013	95%	*
Bungudu	Nigeria	2017	364718	ACW PS	22165	9%	
Damaturu	Nigeria	2017	128498	ACW PS	38802	43%	
Faskari	Nigeria	2017	271358	ACW PS	6876	4%	
Fika	Nigeria	2017	199863	ACW PS	58811	42%	
Fune	Nigeria	2017	439100	ACW PS	14509	5%	
Funtua	Nigeria	2017	312243	ACW PS	5535	3%	
Gada	Nigeria	2017	343660	ACW PS	18786	8%	
Gujba	Nigeria	2017	189925	ACW PS	24676	19%	
Gummi	Nigeria	2017	289236	ACW PS	19070	9%	
Gusau	Nigeria	2017	541825	ACW PS	89030	23%	
Jibia	Nigeria	2017	234971	ACW PS	12545	8%	
Katsina	Nigeria	2017	440822	ACW PS	164	0%	
Kaura Namoda	Nigeria	2017	397878	ACW PS	125123	45%	
Malumfashi	Nigeria	2017	253204	ACW PS	1991	1%	
Maradun	Nigeria	2017	298163	ACW PS	14121	7%	
Maru	Nigeria	2017	412773	ACW PS	59443	21%	
Shinkafi	Nigeria	2017	191820	ACW PS	37904	28%	
Talata Mafara	Nigeria	2017	304281	ACW PS	42096	20%	
Tsafe	Nigeria	2017	376159	ACW PS	60874	23%	

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Table D.3 – *Continued from previous page*

District	Country	Year	Population	Vaccine type	Doses	Coverage	No data
Zurmi	Nigeria	2017	415512	ACW PS	23591	8%	
Bodinga	Nigeria	2017	242803	C conjugate	124450	73%	
Dange-Shuni	Nigeria	2017	269297	C conjugate	125037	66%	
Goronyo	Nigeria	2017	252340	C conjugate	36414	21%	
Gwadabawa	Nigeria	2017	320254	C conjugate	31485	14%	
Isa	Nigeria	2017	202241	C conjugate	42708	30%	
Rabah	Nigeria	2017	206479	C conjugate	97388	67%	
Sokoto North	Nigeria	2017	322313	C conjugate	154669	69%	
Sokoto South	Nigeria	2017	269807	C conjugate	133854	71%	
Tureta	Nigeria	2017	94640	C conjugate	47625	72%	