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Case-carrier ratio for meningococci in the African meningitis belt: A systematic review and standardized data analysis.

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Abstract

Background: The epidemiology of meningococcal meningitis is particular in the African meningitis belt. It is characterized by ubiquitous hyperendemic incidence in the early dry season and irregular localized epidemics at the height of the dry season that could spread over an entire region and result in large scale epidemics. Factors causing epidemics remain hypothetic. The case-carrier ratio is considered an ecological proxy for the risk of meningitis given asymptomatic pharyngeal infection by meningococci (carriage).

Objective: To provide best evidence on how meningococcal serogroup A case-carrier ratio varies according to season and epidemiologic situation and relates its variations to the occurrence of localized meningococcal meningitis epidemics in the African meningitis belt.

Methods: We conducted a systematic review of the literature to identify studies documenting both prevalence of meningococcal carriage and meningococcal meningitis incidence by serogroup in the African meningitis belt. We estimated the case-carrier ratio for each CCOU documented in eligible studies according to different epidemiologic situation and season. Meta-analysis was performed on carriage, incidence and case-carrier ratios using a random effect model.

Results: Significantly lower N.mA carriage prevalence was observed during endemicity and hyperendemicity compared to epidemics 0.43% (95%CI, 0.15%–0.86%); 0.44% (95%CI, 0.16%–0.86%) and 14.7% (95%CI, 9.4%–20.8%) respectively. No increase was observed between endemic to hyperendemic situation. There was a 33-fold increase in serogroup A carriage from hyperendemic to epidemics situation (from 0.44% (95%CI, 0.16%–0.86%) to 14.7% (95%CI, 9.4%–20.8%)). Monthly Incidence rates per 100,000 inhabitants were 0.2 (95%CI, 0.007–0.6); 2.6 (95%CI, 0.5–5.3) and 340 (95%CI, 183–545) for endemicity, hyperendemicity and epidemics respectively. In endemic situations, the CCR was $0.0x10^{-2}$ (95%CI, $0.0x10^{-2}$–$0.1x10^{-2}$); in hyperendemic situations $0.3x10^{-2}$ (95%CI, $0.1x10^{-2}$–$0.9x10^{-2}$) and in epidemic situations $2.2x10^{-2}$ (95%CI, $1.4x10^{-2}$–$3.4\ x10^{-2}$). The increase at each transition was therefore estimated as at least 3-fold between endemicity and hyperendemicity, and 7-fold between hyperendemicity and epidemics.

Conclusion: Systematic increase in meningococci carriage prevalence appears to be a necessary but not sufficient factor to trigger epidemics incidence in the meningitis belt. Increased individual risk of meningitis given asymptomatic carriage of a virulent meningococcus appears to contribute to the occurrence of epidemics. Due to absence of serogroup A cases during endemic periods in all studies of this systematic review, we could not quantify precisely the increase of the CCR between endemic and hyperendemic situation. This increase may be more important than that at the transition from hyperendemic to epidemic situation. More studies documenting carriage and incidence simultaneously are needed. And epidemic risk

factors that can cause a surge in carriage prevalence and increase risk of invasive disease given carriage. Viral infections are candidates.

Keywords: meningitis; meningococci; meningococcal; African meningitis belt;

Résumé

Contexte: La méningite à méningocoques présente une épidémiologie particulière dans la ceinture africaine de la méningite. Elle est caractérisée par une hyper endémicité ubiquitaire en début de saison sèche and des épidémies localisées survenant de manière irrégulière à hauteur de la saison sèche. Ces épidémies localisées peuvent affecter une ou des régions entières résultant en de grandes épidémies. Les facteurs causant ces épidémies demeurent hypothétiques. Le ratio cas porteur est considéré comme un proxy écologique du risque de méningite étant donné l'infection pharyngée asymptomatique par les méningocoques (portage asymptomatique).

Objectif: Apporter une évidence sur l'évolution du ratio cas-porteur selon la saison et d'une situation épidémiologique à l'autre et lier les variations observées à la survenue des épidémies localisées dans la ceinture africaine de la méningite.

Méthodes: Nous avions effectué une revue systématique de la littérature pour identifier les études qui documentent la prévalence du portage et l'incidence des cas confirmés de méningite par sérogoup du méningocoque. Nous avions ensuite estimé le ratio-cas porteur pour chaque couple d'observation Cas-Porteur publié dans les articles selon la saison et le contexte épidémiologique de la méningite à méningocoques. Une méta-analyse des données extraites et des ratios cas-porteur estimés à été réaliser en utilisant un model d'effets aléatoires « random effect model ». Le ratio cas porteur était considérer comme une approximation du risque de méningite étant donné le portage asymptomatique d'une souche virulente de méningocoque.

Résultats: Des taux de portage de N.mA très faibles étaient observés pendant les situations endémiques et hyper endémique comparées aux situations épidémiques 0.43% (95%CI, 0.15%–0.86%) ; 0.44% (95%CI, 0.16%–0.86%) et 14.7% (95%CI, 9.4%–20.8%) respectivement. Le portage n'a relativement pas augmenté entre l'endémicité et l'hyper endémicité. Une augmentation de 33 fois était observée pour le portage du sérogroup A entre la situation hyperendemic à celle épidémique (de 0.44% (95%CI, 0.16%–0.86%) à 14.7% (95%CI, 9.4%–20.8%)). Les incidences mensuelles pour 100000 habitants étaient de 0.2 (95%CI, 0.007–0.6); 2.6 (95%CI, 0.5–5.3) et 340 (95%CI, 183–545) en période d'endémicité, d'hyper endémicité et d'épidémie respectivement. En situation endémique, le ratio cas-porteur étaient de $0.0x10^{-2}$ (95%CI, $0.0x10^{-2}$–$0.1x10^{-2}$) ; en situation hyper endémique $0.3x10^{-2}$ (95%CI $0.1x10^{-2}$–$0.9x10^{-2}$) et en situations épidémiques $2.2x10^{-2}$ (95%CI, $1.4x10^{-2}$–$3.4x10^{-2}$). L'augmentation du ratio cas-porteur à chaque transition épidémiologique était en conséquence d'au moins 3 fois entre l'endémicité et l'hyper endémicité et de 7 fois entre l'hyper endémicité et les épidémies.

Conclusion : L'augmentation systématique du taux de portage des méningocoques apparait comme un facteur nécessaire mais non suffisant pour déclencher les épidémies de méningite à méningocoques dans la ceinture de la méningite. L'augmentation du risque individuel de développer la méningite étant donné le portage asymptomatique apparait également comme un facteur contribuant à la survenue d'épidémies localisées de méningite à méningocoques dans la ceinture africaine de de la méningite. En raison de l'absence de cas de méningites due au sérogroup A en période d'endémicité dans les études incluses dans cette revue, nous ne saurions quantifier avec précision l'augmentation du ratio cas-porteur entre la situation endémique et celle hyperendemic. Cette augmentation pourrait être plus importante que celle observée au cours de la transition entre les situations hyper endémique et épidémique. De nouvelles études documentant simultanément le portage et l'incidence ainsi que l'identification des facteurs de risques favorisant l'augmentation du portage et du risque de méningite étant donné le portage asymptomatique sont requis. Les infections virales sont des facteurs potentiels.

Mots Clés : Méningite ; méningocoques, ceinture Africaine de la méningite.

Abbreviations

AMI	African Medicus Index
CCOU	Case-Carrier Observation Unit
CCOU_id	Case-Carrier Observation Identification number
CCR	Case Carrier Ratio
MeSH	Medical Subject Headings
N.m A	Neisseria meningitidis serogroup A
N.m	Neisseria meningitidis
WHO	World Health Organization

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1. Introduction

1.1. Meningococcal meningitis.

Meningococcal meningitis is a serious infection of the thin lining that surrounds the brain and spinal cord caused by *Neisseria meningitidis*. The infection can lead to severe brain damages and is fatal despite treatment in 10% of cases. Common clinical manifestation includes stiff neck, high fever, and sensitivity to light, confusion, headaches and vomiting. Early diagnosis and treatment are critical to survive the disease. Even with early diagnosis of the disease and the start of adequate treatment 5 to 10% of patients die within 24-28 hours after symptoms onset and disease may result in brain damage, hearing loss, or a learning disability in 10% to 20% of survivors [1]. A less common but often fatal form of meningococcal disease is septicemia.

The meningococcal infection mainly takes place through repeated and close contacts with respiratory droplets of infected people. The infection leads to a period of asymptomatic carriage during which meningococci colonize the nasopharynx [2] and after which some people may clear the infection. The duration of nasopharyngeal asymptomatic carriage may be of hours to several months [3] and may vary according to population and settings. Asymptomatic carriers contribute largely to the spread of the infection. Although there remains gaps in our knowledge on the carriage dynamic, it was suggested that up to 5-10% of a population may be asymptomatic carriers [4]. The rate may be higher in epidemic context [1][5] but is also influenced by age, contact with a case and endemicity [5]. A great variability have been observed in carriage rates according to age and settings [2][5]. In European countries and countries with a similar epidemiological pattern of meningococcal disease, estimated carriage rate increased through childhood from 4.5 % in infants to peak of 23.7% in 19-year olds and subsequently decreased in adulthood to 7.8% in 50-year olds[2]. In African countries and particularly in area where the disease is endemic, reported carriage rates of meningococci range from 3% to over 30% [5].

Based on the immunochemistry of the capsular polysaccharide quoting the meningococcus, Branham and Vedros, identified in 1953 and 1987 respectively, 13 serogroups. Of these serogroups, six (A, B, C, W135, X and Y) have been reported as having epidemics potential with marked difference in geographic distribution and virulence [6]. Large-scale epidemics are mainly caused by serogroup A in the meningitis belt, although serogroups W135 and C have also been implicated in epidemics. Limited outbreaks and sporadic cases of the disease are more commonly caused by serogroups B and C and less frequently by other serogroups [7][8][9].

1.2. Study context and justification.

As opposed to the northern hemisphere's temperate zone (Europe and USA) where sporadic cases occur, meningococcal meningitis is a real public health concern[4] in Africa, primarily in a delimitated area stretching from Senegal in the West to Ethiopia in the East (figure.1). The area was first described and called "the *meningitis belt"* by Lapeyssonie in 1963 [10] and has been updated by A. Molesworth et al in 2002 [11].

Nearly 200,000 cases were reported in 1996 [12] and attack rates as high as 1:10 of population were reported during first epidemics meningococcal meningitis in West Africa [3]. Between 1998 and 2002, countries within the meningitis belt reported more than 224,000 new cases of meningococcal meningitis[13]. About 3000 to 10,000 deaths mainly among children under 15 years old are recorded annually according to intensity of epidemics [14]. In the 2009 epidemic season, 88199 suspected cases of meningitis including 5352 deaths were reported to WHO from 14 African countries [1].

The highest burden of meningococcal meningitis in the meningitis belt is due the particular epidemiology of the disease. It consists of seasonal hyperendemic incidence in the dry season and meningococcal meningitis epidemics. Epidemics nearly always occur at the height of the dry season and subside during the rainy season, only to break out again in the same or adjacent area the following dry season [15][16]. Epidemics can occur as localized epidemics in individual health center area or epidemic waves which affect entire regions at irregular intervals of about 5-12 years[14][7][17].

Due to its association with the dry season, climatic factors (rainfall, wind speed, dust load, and air humidity) are discussed as primary factors for hyperendemicity, but factor leading to epidemics remain hypothetic[18]. In a recent conceptual model, Mueller & Gessner suggested that the systematic transition from endemic incidence during the rainy season towards hyperendemic incidence during the dry season is due to increased risk of invasion given asymptomatic carriage [18]. This asymptomatic infection of the nasopharynx, lasting for hours or months, is supposed to be a quasi-obligatory step toward invasive disease. Furthermore, the transition from hyperendemic incidence towards epidemic incidence during the dry season should be due to an increase in the carriage prevalence or acquisition. Thus, they hypothesized that factors causing localized epidemics would have their impact primarily via the increased risk to acquire carriage, rather than via increased susceptibility to meningitis given carriage. The evaluation of this hypothesis and their model is crucial, as control strategies of meningococcal meningitis, including vaccination strategies, could be designed or better targeted based on this model.

A methodological approach to evaluate the variation of strain invasiveness and host susceptibility and their relation with the epidemiology of the disease is the estimation of the case-carrier ratio across multiple populations depending on season and epidemiological situation. The case-carrier ratio is considered an ecological proxy for the risk of disease given asymptomatic carriage of the causal infectious agent. It is estimated by combining meningitis cases data with asymptomatic carriers' data or incidence and prevalence estimates and therefore requires data from studies evaluating both simultaneously. Some research groups have conducted such studies in the past and during recent years, however, to our knowledge, no standardized and meta-analysis has been performed on such data to date.

This review aimed to retrieve and compile in a systematic way all relevant data from studies on meningococcal carriage and meningococcal meningitis surveillance that can be used to estimate meningococci case-carrier ratios for the African meningitis belt in order to test the hypothesis stated above.

1.3. Objectives of the study

1.3.1. Main objective.

To provide best evidence on how meningococcal case-carrier ratio varies according to season and epidemiologic situation in the African meningitis belt.

1.3.2. Specific objectives:

- To identify existing serogroup-specific data on meningococcal carriage and concomitant meningococcal meningitis incidence within the meningitis belt through a systematic review.
- To estimate summary case-carrier ratios specific for epidemiologic situations (endemic, hyperendemic, epidemic) and seasons (dry and wet).
- To quantify variations of the case-carrier ratio between epidemiologic situations and seasons and relate the magnitude of variations to the epidemiology of meningococcal meningitis.

2. Methods

Methods of the analysis and inclusion criteria were specified in advanced and documented in a protocol.

2.1. Eligibility criteria.

Studies were eligible for inclusion if they fulfilled the following eligibility criteria:

Outcomes of interest: Studies documenting both pharyngeal meningococcal carriage and meningococcal meningitis incidence or cases by serogroups.

Time and place: Studies published from 1963 onward and conducted in any country of the African meningitis belt as defined by Lapeyssonie in 1963 [10] and updated by A. Molesworth et al in 2002[11]. We chose to include studies from 1963 because it is well recognized that the epidemiology of meningitis in Africa has been described for the first time by the French medical epidemiologist Lapeyssonie in 1963 after a long trip across the continent. Therefore it appears to be consistent to look at publications from 1963 even though the distinction between *N.meningitidis* and *N. lactamica* was not made until 1969. The Gambia was included in this review, although it is not clear whether it is part of the meningitis belt.

Study Participants: Studies reporting to the general population (eg: population of a village, city, district) with defined age range of participants. Studies targeting children and/or young adults attending schools (eg: high-school children, primary school children…) were also eligible for inclusion provided that school attendance in this age group or population is common.

Study Design. Studies with cross-sectional and longitudinal studies were eligible for inclusion.

2.2. Exclusion Criteria

- Studies not documenting both meningococcal meningitis incidence and carriage.
- Studies documenting meningococcal carriage but not meningitis incidence and for which attempts to obtain incidence data (same targeted population and time) has failed.
- Studies conducted outside the African meningitis belt (except the Gambia).it is still unclear whether the Gambia is in the meningitis belt.
- Studies including only contacts of meningitis cases in the carriage evaluation.
- Studies targeting specific population groups such as prisoners, military camps etc…
- Studies with full text in language other than English and French

2.3. Information sources:

Studies were identified by searching electronic databases, scanning reference lists of relevant articles, and contacting research groups working or who were known to have conducted research projects in the meningitis belt to identify any relevant unpublished manuscript or ongoing study. No limit of language where applied for the search. The electronic search was applied to MEDLINE® with Full Text (1962 – Present) and Academic Search™ Complete (1887-Present) via EBSCOhost research platform. The African Index Medicus (AIM) an international Regional data base to African health literature and information sources was also searched. Last search was run on February 2012

2.4. Electronic Search

We used combination of medical subject headings (MeSH) terms, text words and synonyms terms to search the databases. Three sets of MeSH terms and text words were defined. 1) terms and text words to search for the first outcome of interest (meningococcal meningitis); 2) terms and text words to search for the second outcome of interest (nasopharyngeal carriage) and 3) terms to search for the geographic location of interest (countries of the meningitis belt). The following search terms (with wildcards when necessary were combined using standard Boolean operators.

(mening or mening* meningitis or cerebrospinal meningitis or Neisseria meningitis or acute meningitis or bacterial meningitis or epidemic mening*) and (mening* carri* or asymptomatic carri* or coloni?ation or neisseria colonisation carri* prevalence or pharyngeal coloni?ation or asymptomatic infection* or subclinical infection*) and (Africa or African meningitis belt or meningitis belt or Africa south of the Sahara or sub-Saharan Africa or Burkina Faso or Upper Volta or Niger or Mali or Togo or Ghana or Côte d'Ivoire or Ivory Coast or Senegal or Chad or Ethiopia or Sudan or Benin or Nigeria or Cameroun or The Gambia or Gambia)*.

We used an iterative process to generate the final search equation for retrieving the maximum possible relevant paper in electronic databases and search terms were refined and updated as databases searches evolved and we discovered new wording of the same key terms. A 'search diary' detailing the names of the databases searched, the Keywords used, the search equation and results is provided in table1-a in appendix (eg: for Medline). Titles and abstracts of studies to be considered for retrieval were recorded on Mendeley desktop along with details of references. (Mendeley desktop is a reference management application).

2.5. Electronic search in Medline with full text:

Table 1 summarized search terms, equations and the number of hits generated for Medline with full text. The iterative process conducting to the final search equation is provided in table 1-a

Table1: Final search equation for Medline with full text via Ebscohost research platform.

Final equation with search terms	Results
(("SH" Meningitis, Meningococcal AND TI (Meningitis, Meningococcal, Serogroup Y) OR TI (Serogroup Y, Meningococcal Meningitis) OR TI (Meningococcal Meningitis, Serogroup Y) OR TI (Meningitis, Meningococcal, Serogroup C) OR TI (Serogroup C Meningococcal Meningitis) OR TI (Meningococcal Meningitis, Serogroup C)) OR ("SH" Meningitis, Meningococcal AND TI (Meningitis, Meningococcal, Serogroup B) OR TI (Serogroup B Meningococcal Meningitis) OR TI (Meningococcal Meningitis, Serogroup B)) OR ("SH" Meningitis, Meningococcal AND TI (Meningitis, Meningococcal, Serogroup A) OR TI (Serogroup A Meningococcal Meningitis) OR TI (Meningococcal Meningitis, Serogroup A)) OR ("SH" Meningitis, Meningococcal AND TI (Meningococcal Meningitis, Serogroup W 135) OR TI (Serogroup W-135, Meningococcal Meningitis) OR TI (Serogroup W 135)) OR ("SH" Meningitis, Meningococcal AND TI (Meningitis, Meningococcal, Serogroup X) OR TI (Serogroup X Meningococcal Meningitis) OR TI (Meningococcal Meningitis, Serogroup X)) OR ("SH" Meningitis, Meningococcal AND AB (Meningitis, Meningococcal, Serogroup X) OR AB (Serogroup X Meningococcal Meningitis) OR AB (Meningococcal Meningitis, Serogroup X)) OR ("SH" Meningitis, Meningococcal AND AB (Meningitis, Meningococcal) OR AB (Meningococcal Meningitis) OR AB (Neisseria meningitis) OR AB (Meningitis, Cerebrospinal) OR AB (Acute meningitis) OR AB (Epidemic meningitis) OR AB (Meningitis, Meningococcic)) OR ("SH" Meningitis, Meningococcal AND TI (Meningitis, Meningococcal) OR TI (Meningococcal Meningitis) OR TI (Neisseria meningitis) OR TI (Meningitis, Cerebrospinal) OR TI (Acute meningitis) OR TI (Epidemic meningitis) OR TI (Meningitis, Meningococcic)) OR ("SH" Meningitis, Meningococcal AND AB (Meningitis, Meningococcal, Serogroup Y) OR AB (Serogroup Y, Meningococcal Meningitis) OR AB (Meningococcal Meningitis, Serogroup Y) OR AB (Meningitis, Meningococcal, Serogroup C) OR AB (Serogroup C Meningococcal Meningitis) OR AB (Meningococcal Meningitis, Serogroup C)) OR ("SH" Meningitis, Meningococcal AND AB (Meningococcal Meningitis, Serogroup W 135) OR AB (Serogroup W-135, Meningococcal Meningitis) OR AB (Serogroup W 135)) OR ("SH" Meningitis, Meningococcal AND AB (Meningitis, Meningococcal, Serogroup A) OR AB (Serogroup A Meningococcal Meningitis) OR AB (Meningococcal Meningitis, Serogroup A)) OR ("SH" Meningitis, Meningococcal AND AB (Meningitis, Meningococcal, Serogroup B) OR AB (Serogroup B Meningococcal Meningitis) OR AB (Meningococcal Meningitis, Serogroup B))) AND (MH Africa/ OR MH African meningitis belt/ OR MH meningitis belt/ OR MH Africa south of the Sahara/ OR MH sub-Saharan Africa / OR MH Burkina Faso/ OR MH Niger/ OR Niamey/ OR MH Mali/ OR MH Togo/ OR MH Ghana/ OR MH Côte d'Ivoire/ OR MH Ivory Coast/ OR MH Senegal/ OR MH Chad/ OR MH Ethiopia/ OR MH Sudan/ OR MH Benin/ OR MH Nigeria/ OR MH Cameroun/ OR MH The Gambia/ OR MH Gambia/)	Hits = 298

2.6. Study selection

By screening the title and abstract presented in electronic databases, articles that were irrelevant were excluded in the early stages of the search, whilst the decision to exclude or include other articles were only made once the full article has been read and inclusion criteria applied. In the African Medicus Index abstract were not available for all articles. When attempt to retrieve the abstract of the article failed, decision about relevance of the article where made based on the title only. The full text of articles considered relevant after screening of title and abstract were retrieved. Articles were read in full and inclusion criteria described above were applied. At this stage any articles that failed to meet the inclusion criteria were excluded. Articles eligible for inclusion were then scrutinize to identify those for which additional information are needed from authors. When such articles where identify authors were contacted and data collection sheets and questionnaire were sent to collect additional data or information important for the quantitative summary synthesis and meta-analysis. Eligible studies for which we failed to contact authors or to find information needed elsewhere were not included in meta-analysis. The number of articles included and excluded at the various stages of selection of articles as well as reasons for exclusion was documented. Assessment of study eligibility and inclusion of studies in Meta analysis were performed by one reviewer. Steps for selection of studies are summarized in figure 2.

2.7. Data extraction

We developed a data extraction sheet, pilot tested it on two randomly selected studies from the list of included studies and the data sheet was refined accordingly. Data were extracted by only one reviewer. Some data were extracted from graphs using the software “Graph Extract v2.5.” Authors of all the articles eligible for inclusion in the meta-analysis (except one whose contacts were not retrieved) were contacted and agreed to provide additional information and data on their studies, if available and to confirm data extracted from graphs. They were sent tables and questionnaires to fill (sample data collection tools are provided in figure 9 of the appendix). Additional data requested were in general age specific meningococcal colonization and disease rates and meningitis cases notification data if available.

2.8. Data items.

Information were extracted from each study on (1) characteristics of the study (Main author year of the study/publication, Inclusion criteria, Follow up or sampling time point of the carriage study, carriage study sample size, size of population covered by meningitis

surveillance, settings, epidemiologic context, and local season (2) characteristics of participants and target population (age range, type of population “general population or children and young adults”, meningococcal vaccination status of the target population within the three years preceding onset of study, (3) information about vaccine used (type of vaccine and coverage rate); (4) the outcomes of interest (N.m meningitis serogroup specific number of cases or incidence corresponding to the month of the carriage survey, N.m meningitis serogroup specific number or carriers or carriage prevalence. Age specific numbers or rates were extracted as well when reported by authors.

When information is missing or unclear for a given variable and could not be retrieved from authors, particularly information about the epidemiologic context of the study, reasonable assumptions were made when possible. We classed studies as conducted during an epidemic (due to serogroup A), if this was stated in the paper based on suspected and confirmed cases. Assumptions were then made only when no epidemic was reported and the authors did describe the context of the study in an implicit way. For example authors always stated whether their study was conducted in the dry season known as “ the meningitis season “ when meningitis hyperendemicity is ubiquitous or during the rainy/wet season when meningitis is considered endemic with no or sporadic cases. So when no epidemic is reported by the authors and studies were conducted in the dry season, we reported “hyperendemic” as epidemiological context. These assumptions were valid as they are in relation with observed patterns of the meningitis in the meningitis belt and are well documented in almost every article on the meningitis belt[3][19]. For studies conducted in the rainy or wet season we reported “endemic context”. For studies not reporting monthly meningoccocal meningitis cases or incidence the average monthly number of cases were considered. The clearly distinct magnitude of incidence rates in studies classed as endemic vs. hyperendemic (Figure10) validates this approach.

2.9. Risk of bias in individual studies.

To explore validity and variability in results of eligible studies we assessed their methodological quality using a critical appraisal form (see appendix). Methodological aspects assed were, the sampling design of the carriage survey, swabbing techniques, whether swabs were plated immediately on transport system on site after they were taking, microbiological and bacterial identification protocol, validity of diagnostic criteria for diseased, reporting of inclusion criteria for participants and number of exclusion or refusal before study onset, reporting of a meningococcal vaccination status of the study population and type of vaccine used.

2.10. Summary measures:

The case – carrier ratio CCR was the primary summary measure of interest in this review. CCR and 95% confidence intervals were estimated using data reported for each Case-carrier observation units reported on our primary outcomes (meningitis cases and meningococcal carriers). The case carrier ratio was estimated as (n_cases/n_population) / (n_carriers / n_sample) where n_cases is the number of confirmed cases of N.m meningitis in the target population surveillance, n_population is the population targeted by surveillance, n_carriers is the number of asymptomatic carriers in a sample of healthy residents of the population and n_sample the sample size of carriage survey. Using Delta method [37], the natural logarithm of variance of the CCR was estimated by (n_population – n_cases) / (n_population*n_cases) + (n_sample – n_carriers) / (n_carriers*n_sample). Haldane's continuity correction was used for hyperendemic context when there are no carriers found but cases identified.[20]

2.11. Meta-analysis of estimated case-carrier ratios

Statistical units were "Cases and Carriers Observation Units" (CCOU) reported in studies. For example, a publication reporting carriage and incidence data for 3 different carriage sampling time points based on the same study protocol contributed 3 CCOU that were reported to the study in meta-analysis. The meta-analysis was performed using fixed- and random-effects model. Pooled prevalence and incidence were also estimated with 95% confidence intervals according to epidemiologic context using commands for meta-analysis of proportions. We used the method proposed by Higgins et al. [38] to quantify inconsistency (the percentage of total variation across CCOUs due to heterogeneity) of the case carrier ratio across CCOUs. This measure of inconsistency termed (I^2) has the advantage of not being inherently dependent on the numbers of CCOUs and is accompanied with significance level. I^2=50% to 90 % were considered substantial heterogeneity and I^2 <50% were considered moderate or "reasonable" inconsistency. Analyses were done in Stata version 11.2.

3. Results.

3.1. Study selection.

The search of Medline with full text, Academic Search Complete and African Medicus Index databases provided a total of 367 citations (February 2012). Of these, 342 were discarded because after reviewing the title and abstract it appeared that these papers clearly did not meet the criteria. They reported meningococcal vaccine efficacy trial, epidemics incidence, serological studies, and evaluation of diagnostic test, pneumococcal meningitis incidence, weekly epidemiological reports and some studies not conducted in the meningitis belt. The full

text was retrieved and examined in more detail for 25 of the 26 remaining articles. It appeared that 14 did not meet the inclusion criteria as described. 11 studies met the criteria for inclusion in the review. No additional study that met the criteria for inclusion where identified by checking the references of located relevant papers. Of the 11 eligible studies, one was excluded because it was a pilot study on a convenient sample of 90 school children attending a primary school close to a research centre [21] Another study was excluded because we were not able to contact the authors to get additional relevant information[22]. Lastly 3 additional studies[23][24][25] were excluded from the meta-analysis of case-carrier ratios because relevant incidence data requested from contacted research groups were not available yet. One additional unpublished relevant study (C.Trotter et al.) was obtained from the study group resulting in a total of 6 studies included in the meta-analysis. The 6 studies were conducted in Ghana [17][26],Burkina-Faso[19][24][25], and the Gambia[26]. They contributed for a total of 18 CCOU in the meta-analysis. Flow diagram of study selection is provided in figure 2.

3.2. Study characteristics.

One longitudinal survey and eight cross sectional studies were selected for inclusion in the review. They were published in English. The longitudinal survey was conducted from 1998 to 2005 and contributed for 10 out of 18 CCOUs in the meta-analysis of the case carrier ratio. Summary characteristics of included studies and CCOUs they contributed in the review are outlined in Appendix Table 4.

3.3. Risk of bias within included studies.

Figure 3 summarizes the results of the assessment of methodological quality of studies included in the review. Results for the methodological quality assessment for each study are outlined in appendix table 2.

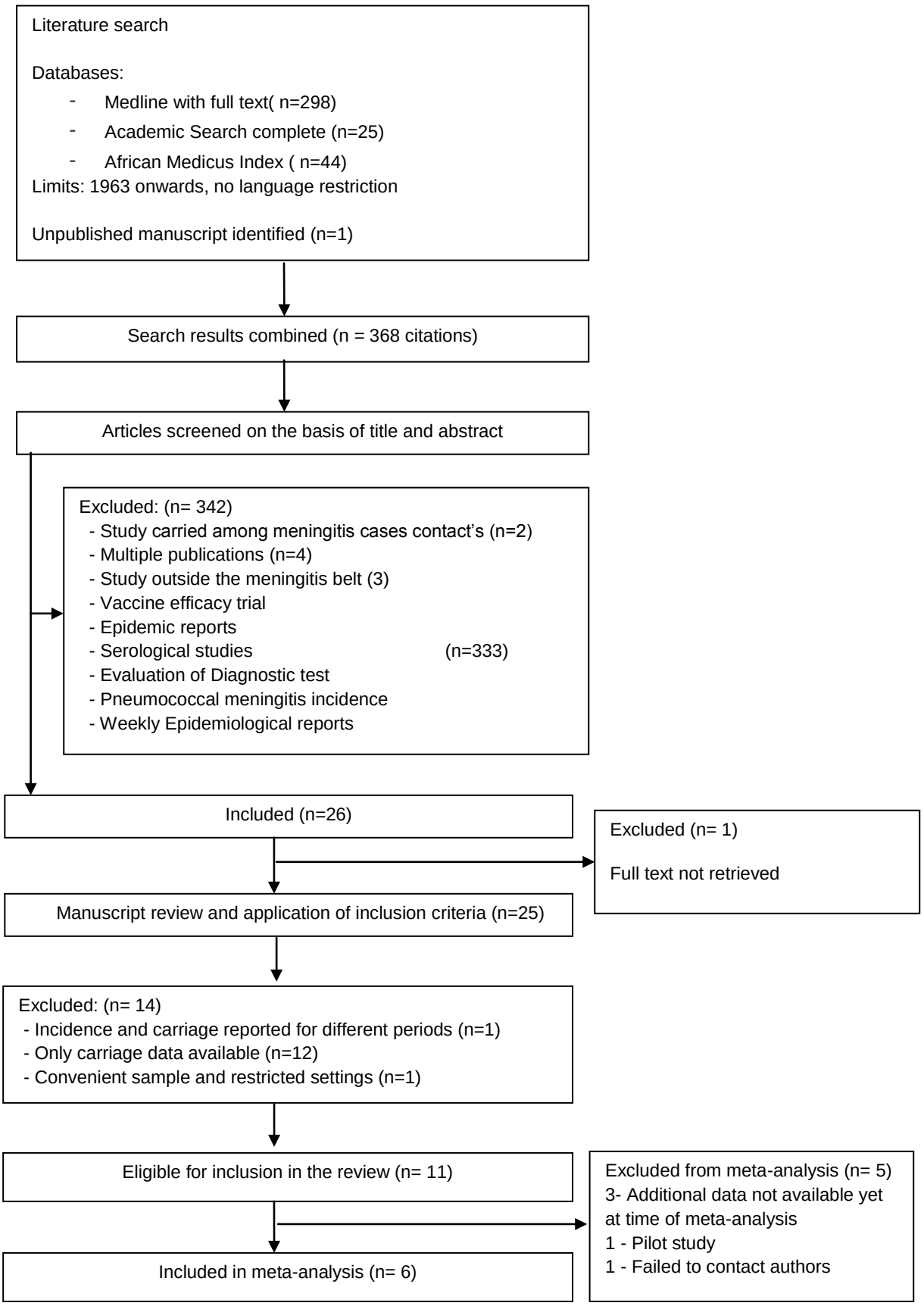


Figure 2: Flow diagram of study selection and inclusion in the review.

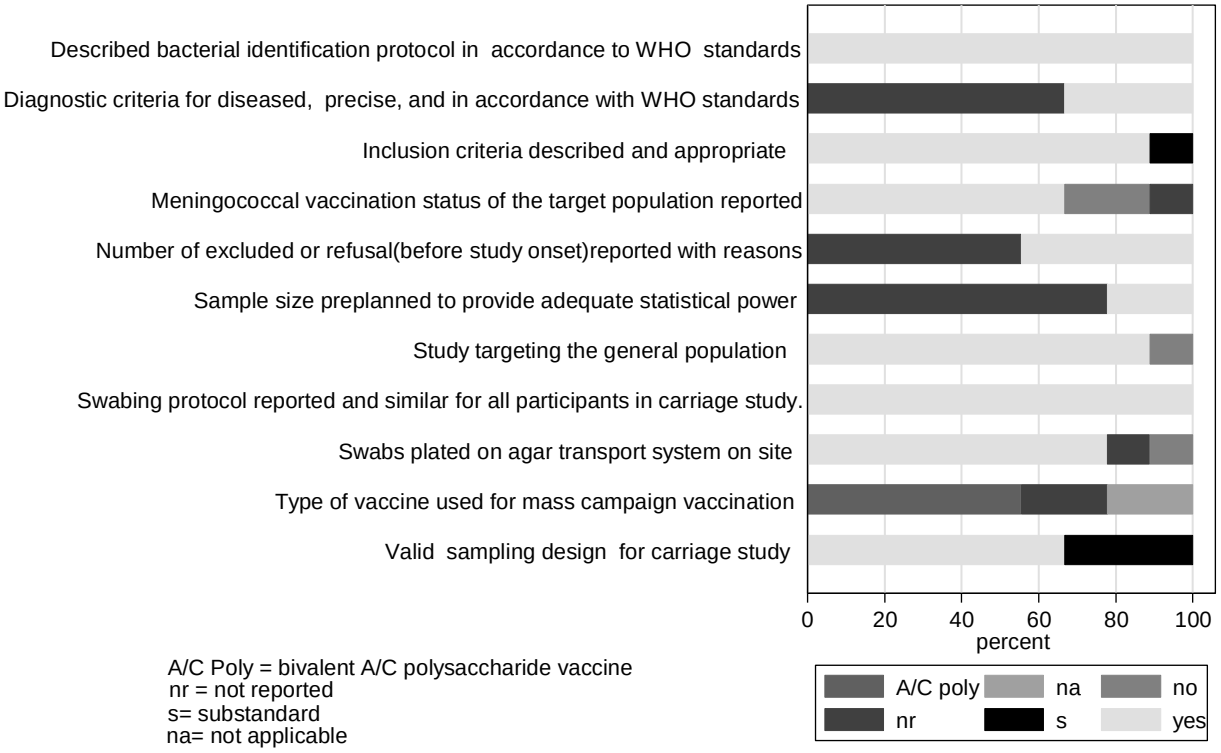


Figure 3: Assessment of methodological quality of included studies.

3.4. Results of individual studies and CCOUs included in the review.

3.4.1. N.m A carriage and meningitis incidence estimates

N.m serogroup-specific carriage prevalence and monthly cumulative incidence of Case-Carriers Observation Units from included studies are reported in table 3. Only one study[17] reported standard error of carriage prevalence. A study also reported 95% confidence intervals for prevalence[27]. We estimated case-carrier ratios and their 95% confidence interval from carriers or carriage and cases or incidence data reported or extracted from individual studies. For N.m A, the longitudinal study conducted in Northern Ghana reported three CCOUs during the wet/rainy season when meningitis is considered endemic in the meningitis belt. The carriage prevalence was 2% SE (1.2), 1.3% SE (0.8) and 0.6% SE (0.5) respectively in 2002, 2003 and 2004 rainy seasons. Meanwhile no N.m serogroup A case was recorded from surveillance during the month of the respective carriage surveys.

In the dry season (meningitis hyperendemicity context) following surveys of the rainy seasons, estimated *N.m* A carriage prevalence were 2.2% SE (1.1), 4.3% SE (1.5) and 0.9% SE (0.5) respectively. Estimated N.m A monthly cumulative incidence recorded were respectively 2.86, 4.30 and 0 per 100,000 inhabitants. Another study[27] reported three CCOUs with N.m W135 carriage prevalence ranging from 0.8% to 1.7% and monthly cumulative incidence of 1.57 to 2.76 per 100,000 inhabitants during the early dry season.

During epidemics reported N.m A carriage prevalence and monthly cumulative incidence were much higher compare to those reported when meningitis is considered hyper endemic. Two studies conducted in Ghana (2006) [26] and the Gambia (1987) [28] reported N.m A carriage prevalence of 12.2% and 16% and N.m A monthly cumulative incidence of 443 and 284.6 per 100,000 population respectively. Another study conducted in Burkina-Faso (2006) in epidemic context reported N.m A carriage prevalence of 6.4%, 18.8% and 21.9 % in three different villages of the sanitary district Secteur 15. Estimated monthly cumulative incidences reporting to the three villages were 77; 280 and 843 per 100,000 inhabitants respectively.

For a given epidemiologic context a difference was observed in *N.m* A carriage prevalence and disease incidence between geographic settings and even within the same population from year to year. Figure 4 and 5 shows respectively the distribution of *N.m A* carriage prevalence and the relation between carriage and disease incidence in different epidemiologic context. N.m A carriage prevalence did not differ in general between endemic and hyperendemic context (figure 4). Results from pooled analysis of N.m A carriage rates confirmed this observation. The pooled carriage prevalence was 0.43% (95%CI, 0.15%–0.86%) during endemicity and 0.44% (95%CI, 0.16%–0.86%) during hyperendemicity.

A marked difference was observed in *N.m* A carriage prevalence between hyperendemic and epidemic context. The pooled carriage prevalence estimate during epidemics was 14.7%; (95%CI, 9.4%–20.8%) suggesting a 33 fold increase in N.m A carriage prevalence from hyperendemic to epidemic context. During epidemics, *N.m* A carriage prevalence was above 6% in all studies (figure 5).

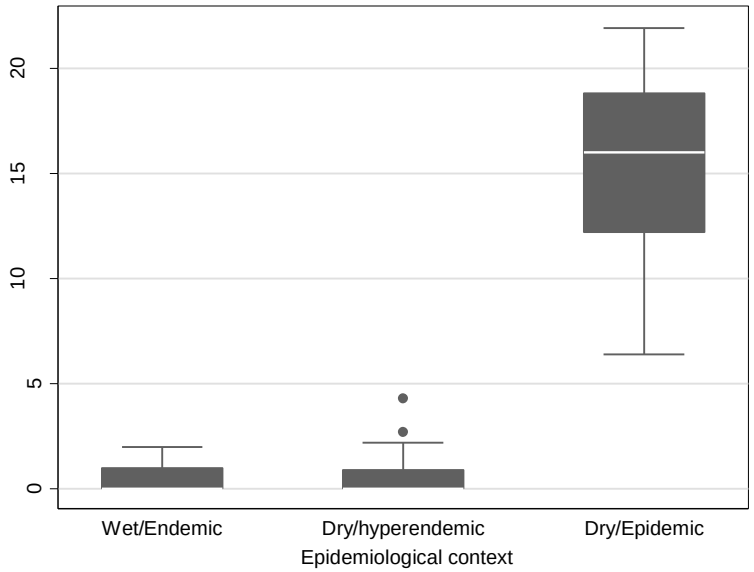


Figure 4: N.m A carriage according to season and epidemiological situation.

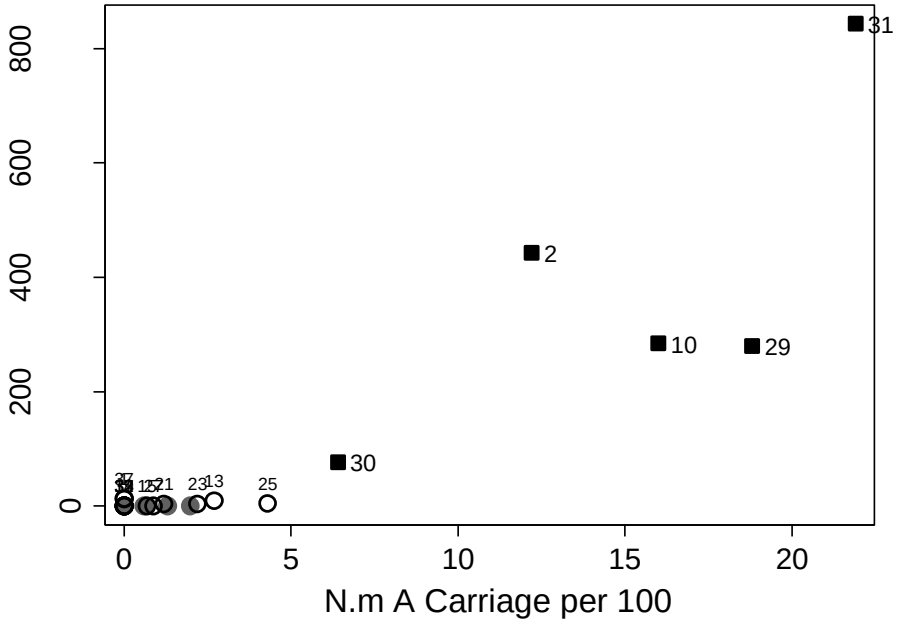


Figure 5: N.m A carriage and monthly incidence according to season and epidemiological situation. Numbers are Id of CCOU. Endemic context (full gray circles), hyperendemic context (Hallow circles), epidemic context (squares). Label numbers are case-carrier observation units ID and are displayed for hyperendemic and epidemic context.

3.4.2. Case-carrier ratio estimates:

Cases carrier ratio estimated from CCOUs are provided with 95% CI in table 3 by epidemiological situation and season.

Table 3: Cases carrier-ratio estimates for meningococcal A according to season and epidemiologic context in the African meningitis belt.

Study. Year	CCOU Id	Case-carrier Ratio x 10^{-2}	[95% Conf. Interval]	
Wet/Endemic context				
Leimkugel et al. 2007	22	0.0	0.0	0.3
Leimkugel et al. 2007	24	0.0	0.0	0.4
Leimkugel et al. 2007	26	0.0	0.0	0.9
Dry/ Hyperendemic context				
Sie et al .2008	1	7.8	0.5	134.4
Leimkugel et al. 2007	13	0.3	0.1	0.8
Leimkugel et al. 2007	15	0.0	0.0	0.9
Leimkugel et al. 2007	19	0.7	0.0	16.3
Leimkugel et al. 2007	21	0.2	0.1	1.0
Leimkugel et al. 2007	23	0.1	0.0	0.4
Leimkugel et al. 2007	25	0.1	0.0	0.3
Leimkugel et al. 2007	27	0.0	0.0	0.6
Mueller et al. 2006	33	0.6	0.0	14.0
Trotter et al. 2008 (unpublished)	37	14.3	0.9	229
Dry / Epidemic context				
Sie et al .2008	1	3.6	1.5	8.8
Hassan-king et al. 2011	10	1.8	1.0	3.1
Mueller et al. 2011	29	1.5	0.8	2.7
Mueller et al. 2011	30	1.2	0.3	5.3
Mueller et al. 2011	31	3.9	2.0	7.3

3.5. Meta-analysis of case-carrier ratios.

Both random and fixed effect models were used to estimate the combined or summary case-carrier ratio for NmA in the different epidemiologic context. Results of the random effect model were considered for the meta-analysis because significant heterogeneity was observed across CCOUs in the hyperendemic context. Both models provided the same summary point estimate in endemic and epidemic context. In endemic context, cases and carriers data were

available for 6 CCOUs reported in the eight-year longitudinal study conducted in Ghana between 1998 and 2005. Three of them were excluded from the pooled analysis because they reported no cases and no carriers in endemic context. Thus our estimate was based on three CCOUs reporting no N.m A meningitis cases but some N.m A carriers for endemic context. We found a case carrier ratio significantly lower during the rainy season or meningitis endemic context CCR=$0.0x10^{-2}$ (95%CI, $0.0x10^{-2}$–$0.1x10^{-2}$). There was no evidence of heterogeneity across included CCOUs (I^2=0%).

In hyperendemic context, the pooled analysis was based on 10 CCOUs reported in four studies[26][17][27][29].Two studies were conducted in Burkina-Faso and two were conducted in Ghana. Of the two studies conducted in Burkina-Faso one is unpublished yet and reported one CCOU[29]. Estimated N.m A case-carrier ratio for hyper endemic context was $0.3x10^{-2}$ (95%CI, $0.1x10^{-2}$–$9.0x10^{-2}$), I^2= 69.3% p=0.001).

Five CCOUs reporting to three studies[26][28][19] conducted in Ghana, the Gambia and Burkina-Faso were included in the pooled analysis for meningitis epidemic context. The estimated case-carrier ratio for meningococci in epidemic context was $2.2x10^{-2}$ (95%C, $14x10^{-2}$ –3.4 $x10^{-2}$) , (I^2 = *43.3%* p=*0.133*).

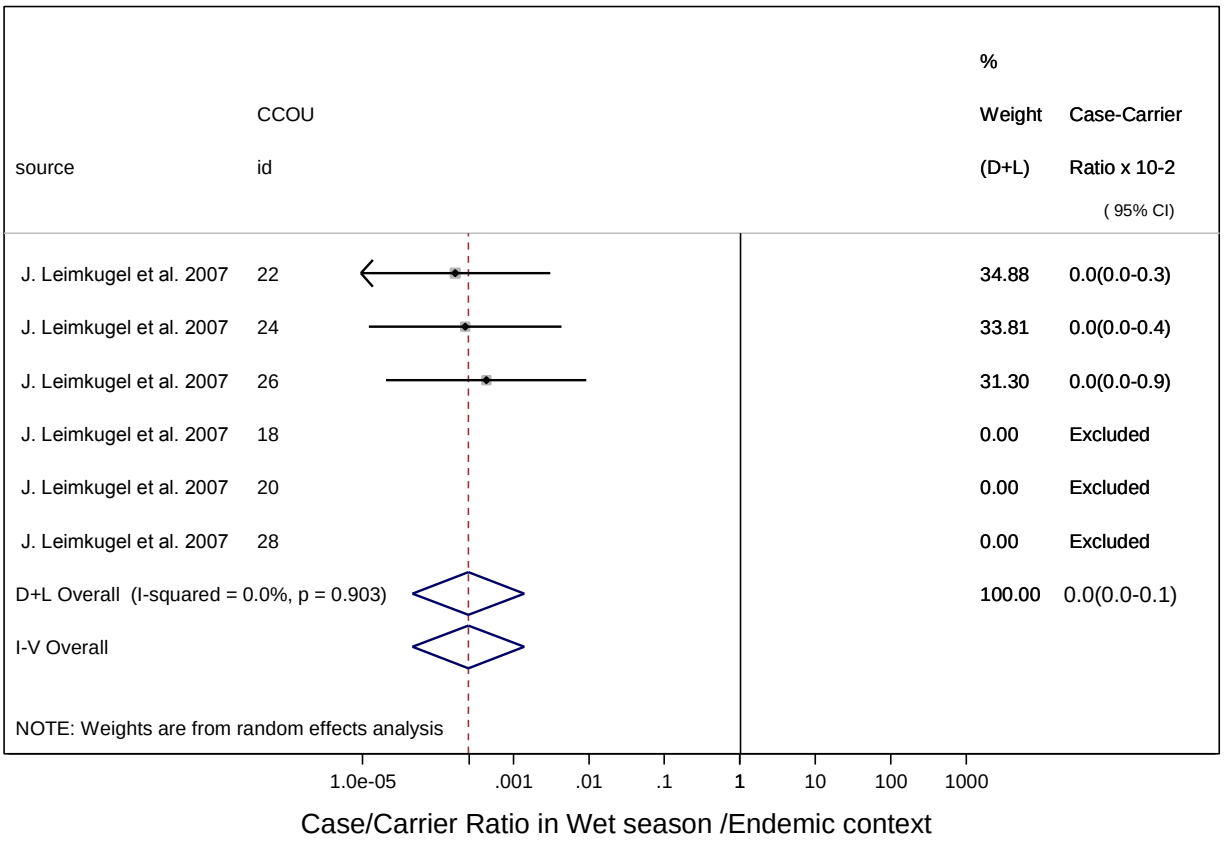
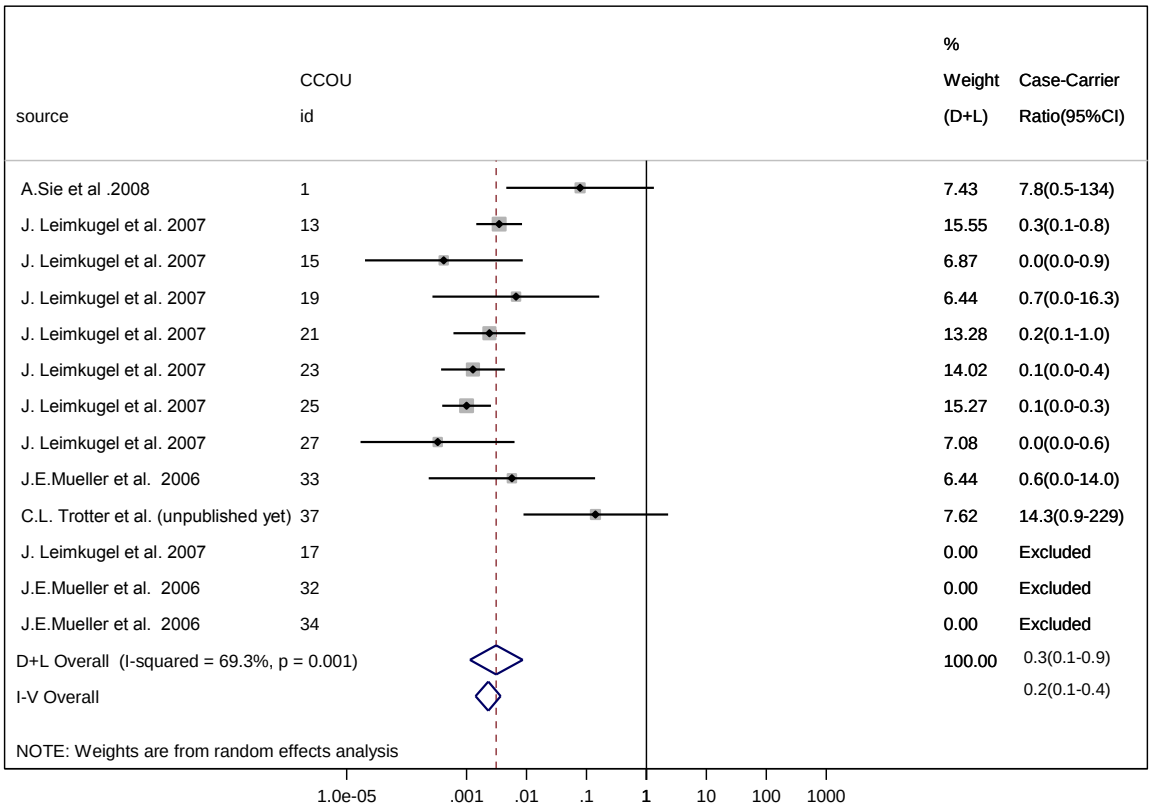
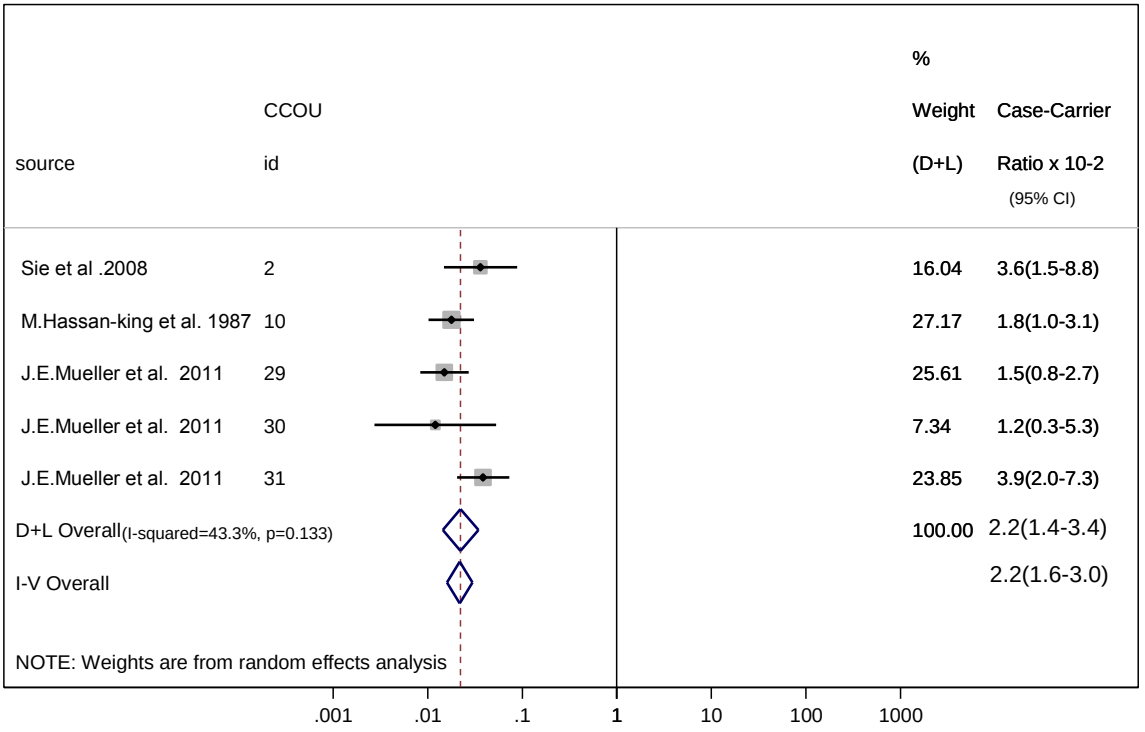


Figure 6: Forest plots of meta-analysis of N.m A case-carrier ratios in endemic situation.



Case/Carrier Ratio in Dry season / Hyperendemic context

Figure 7 : Forest plots of meta-analysis of N.m A case-carrier ratios in hyperendemic situation.



Case/Carrier Ratio in Dry season / Epidemic context

Figure 8: Forest plots of meta-analysis of N.m A case carrier ratios in epidemic situation.

4. Discussion.

This study is novel in that it combined in a systematic way data available from the literature and research groups to estimate meningococci A case-carrier ratio as a proxy for the risk of invasion given assymptomatic carriage of *Neisseria meningitidis* serogroup A according to season and meningitis epidemiologic context in the African meningitis belt. It attempts to contribute to the understanding of the occurrence of localized epidemics of meningitis in the African meningitis belt.

First, we found not increase in NmA carriage between endemicity and hyperendemicity, with relatively low carriage prevalence (<1%). This result is consistent with the finding of a systematic review of meningococcal carriage in the African meningitis belt published in 2006 and the results of a study of nasopharyngeal carriage of meningococci in Sokoto, Nigeria[22].

Second, we found a 33-fold increase (pooled results) in N.m A carriage prevalence between hyperendemic and epidemic context in the African meningitis belt. This finding is consistent with results of a review published in 2011 that described a hypothetical explanatory model for meningococcal meningitis in the African meningitis belt[18]. They suggested that the transition from hyperendemic to epidemic situation involves increased pharyngeal colonization and transmission of about 10- to 100-fold, possibly favored by epidemic cofactors like viral respiratory infection epidemics occurring during the dry season. A hypothesis that this study confirmed.

We found that the NmA case-carrier ratio was significantly higher in the epidemic compared to endemic situation, with an estimated 7-fold increase. The NmA CCR was borderline significantly higher in the hyperendemic context compared to the rainy season (endemic context). Due to absence of NmA cases during endemicity, in the included studies, the fold-increase of CCR between endemicity and hyperendemicity is infinite. Assuming that the estimated CCR for meningococci A was 0.01 (the upper limit 95% CI value for endemic context), the increase is at least 3-fold. In their hypothetical explanatory model for meningococcal meningitis in the meningitis belt, Mueller et al suggested that the transition between hyperendemic incidence and epidemic incidence may be associated with about a 4 fold increase in the risk of invasion given colonization with a virulent meningococcus. A hypothesis that this study set out to confirm. In their study the case carrier ratio was estimated from 2 studies and was computed as the ratio of weekly cases to carriers(x100). While the present study could not stipulate which of the two epidemiologic transitions has the highest fold increase in the case-carrier ratio, it does suggest that an increase in the case-carrier ratio is involved in both transitions (endemic-hyperendemic, hyperendemic-epidemic).

The present study also suggests that N.m A carriage does not vary systematically between endemic and hyper endemic context, but that it does from hyperendemic to epidemics context.

The 7-fold increase observed in our study suggests an increase of risk of meningitis given pharyngeal colonization with a virulent meningococcus from hyperendemic to epidemic situation. Such increase could be considered important and may be consider as a contributing factor to the occurrence of localized epidemics in the African meningitis belt. Therefore a surge in pharyngeal colonization and transmission observed from the hyperendemic to epidemic situation is necessary and likely the most important factor, but probably not sufficient to explain occurrence of localized epidemics in the African meningitis belt. Increased host susceptibility has been the most common explanation of meningococcal epidemics[30]. Factors leading to increased carriage acquisition and factors leading to increased risk of meningitis given colonization need therefore to be identified to explain meningococcal epidemics. Some factors have been discussed in the literature as possible cofactors of epidemics in the meningitis belt. Influenza virus infections, e.g., could have a double role in both facilitating meningococcal colonization due to respiratory secretion on the pharyngeal surface [39] and increasing the risk of invasive disease due immune depression during the weeks following flue [42]. The role of coincident respiratory viral and mycoplasmal agents in the pathogenesis of meningococcal meningitis had been investigated using matched case-control study of 62 patients with serogroup A meningococcal meningitis during an epidemic in chad. It suggested that case patient were more likely to have nasal colonization or infection with respiratory virus and mycoplasma species (matched odd ratio, 23 (95%CI, 3.1-170)[31]. Because a variety of respiratory pathogens were recovered from the meningitis patients, it have been inferred that respiratory infections probably increased susceptibility to meningitis through a non-specific mechanism such as damage of the pharyngeal mucosa[31]. Symptomatic respiratory infections that cause coughing and sneezing could also potentially enhanced transmission of meningococci during epidemics. This view have been supported by a study of localized epidemics in three villages in Burkina-Faso which conclusion was that upper respiratory tract infections and flulike disease are implicated in the epidemic process possibly by contributing to the strength of epidemics[19]. However it is still unclear whether it is co-occurrence of viral infections epidemics that favored meningitis epidemics or it is the context of meningitis epidemics that favored co-occurrence of viral infections. Also based on the assumption that co-occurrence of upper respiratory infections epidemics in the dry season contribute to increased risk of meningitis disease and epidemics, it is not clear why epidemics tend to be limited to the meningitis belt since upper respiratory tract infections are likely common in the dry season in other part of Africa and the rest of the world[31], particularly during the winter in developed

countries. Therefore particular physical and social environmental conditions or level of co-infecting respiratory agents could place the meningitis belt at higher risk of epidemic meningitis compare to other part of the continent and the world, but evidence are needed. Socioeconomic factors may also contribute to the increased risk of meningitis and the occurrence of localized epidemics. They have been poorly investigated in the meningitis belt.

Climatic factors including low air humidity, dust load and wind speed have been previously discussed as important contributing factors to the risk of meningitis given colonization [22][15] and the occurrence of epidemics in the meningitis belt [16]. However climate factors likely plays an important role in the increase of the risk of meningitis given asymptomatic carriage between endemic and hyperendemic context than they do from hyperendemic to epidemic context in the dry season[18]. Climatic factors as measured during the dry season do not vary substantially between years or communities in a given region[18]. Yet localized epidemics occur in a given year but not in the following year or in a given community not in neighborhood communities[18][22][15]. In their study of the relation between climate and year to year variability in meningitis outbreaks in Niger and Burkina-Faso, Yaka. et al. found that 25% of the disease variance from year-to-year in Niger can be explained by the winter climate but fail to represent accurately the disease dynamics in Burkina Faso[32]. Therefore climates factors are unlikely to substantially explain the occurrence of localized epidemics at the height of the dry season. Some other factors inherent to the host and the meningococcus strain and interaction between them and the social environment are likely to substantially contribute to increase risk of meningitis given asymptomatic carriage and occurrence of localized epidemics at the height of the dry season. In an experimental study using an intranasally challenged mouse disease model it has been demonstrated that N. meningitidis is able to pass directly from nasopharynx to meninges through the olfactory nerve system escaping humoral immunity[33] which have been described as the most important host factor in the prevention of meningococcal meningitis[34]

A population's susceptibility to disease might increase as antibody level decline and herd immunity is reduced by new birth cohorts or population movements[35]. Individual risk factors such as immune deficiencies, smoke exposure and population characteristics were also documented as prerequisites for meningococcal disease epidemics[36]. It was also hypothesized that lack of temporally stable and genetically diverse resident pharyngeal flora of meningococci might contribute to the susceptibility to meningococcal meningitis epidemics of residents of the meningitis belt[17]. However none of these factors alone or in combination appears to be sufficient to trigger epidemics in the meningitis belt. Further research are needed

and should explore the role of socio-economic factors in N.m meningitis epidemics risk and the interplay between, hosts genetic factors, the meningococcus, and social factors.

5. Limitations of the study:

Limitations of this study include possible underestimation of incidence and carriage prevalence. Underestimation of incident cases may come from poor surveillance of the disease in rural area where health centers are rare and far away from inhabitants and likelihood of missing meningitis cases is reasonably higher. This limitation might apply to studies conducted before the 2000s as important efforts have been made in collaboration with WHO since then to enhance surveillance of meningitis in countries of the meningitis belt. Possibility of underestimating carriage also exists if carriage survey is conducted at the early stage of an epidemic compare to after epidemic picked. In such circumstance, the case carrier ratio for epidemic context would be expected to be even higher as will do its increased fold from hyperendemic situation to epidemic pick. Although described bacterial identification protocols of studies included in this review were in accordance to WHO guidelines, variability in sensitivity and specificity of diagnostic test of N.m meningitis is likely and could explain partly variability in carriage prevalence observed within a given epidemiologic situation. Proportion of collected CSF analyzed in some studies was unknown, which could also reflect an underestimation of confirmed cases of meningitis. Three studies eligible for inclusion and conducted in Niger and Burkina-Faso where excluded from meta-analysis because additional data requested from authors were not available yet at the time we conducted the meta-analysis of available data. However the same patterns of variation of CCR are expected in those studies. Another limitation is that we were not able to conduct subgroup analysis by age groups although we planned to do so in the protocol. We obtained age specific data from three studies but were not able to use them as they didn't cover both epidemiologic transitions. Individual risk to develop meningitis given asymptomatic carriage may be modified by age; however variation of the risk of disease given carriage from an epidemiologic context to another or from a season to another is expected to be similar across age groups but this assumption need to be confirmed. We have not taken into account population vaccination status. Bivalent polysaccharide A/C Meningococcal vaccines were used in the last 3 years before most included study onset (figure3). However it has been suggested that bivalent polysaccharide A/C meningococcal vaccine has no substantial effect on meningococcal carriage but has an effect on disease incidence in a vaccinated population. It efficacy has been demonstrated only in young children and adults [40][41] and therefore the CCR is expected to be underestimate in that age group. However we believe that accounting for polysaccharide A/C vaccine status of the population will

not change in a drastic way the observe pattern of the case-carrier ratio and overall conclusion of this study.

6. Strengths of the study

We used serogroup-specific laboratory-confirmed data, and this reduced considerably outcomes assessment bias. The standard definition of suspected bacterial meningitis cases is not specific to *N. meningitidis*; therefore using case report (suspected cases) data could have overestimated the case-carrier ratio. Also the interaction between the host immune system and the meningococcus is serogroup dependant and it was important to account for that in this study.

7. Conclusion

In an attempt to explain the periodic and localized epidemics of meningococcal meningitis in the meningitis belt, several research have been conducted in this geographic area since decades and the role of season and nasopharyngeal carriage of *N. meningitidis* and population immunity as well as strain biology in the epidemiology and distribution of meningococcal disease has come under careful scrutiny by several research groups. However, there is still gap in our knowledge about mechanisms underlying occurrence of epidemics in the meningitis belt. Our study brings a new insight into the nature of factors contributing to the occurrence of localized epidemics in the meningitis belt. It appears that increased individual risk of meningitis given carriage is a contributing factor to the occurrence of epidemics in the meningitis belt. Overall, this study validates the hypothetical explanatory model for meningococcal meningitis in the meningitis belt suggested by Mueller & Gessner, and it brings a new element to the model in that it underscores the contribution of increased susceptibility for epidemic occurrence. We could not conclude on whether this increase in susceptibility is greater or lesser compared to the increase between wet to rainy season; which is most likely caused by climatic factors. Both factors causing the sudden increase in carriage acquisition and those causing an increase in the individual risk of meningococcal disease given asymptomatic carriage need to be investigated in more depth for a better insight into the occurrence of meningitis localized epidemics in the meningitis belt.

8. Recommendations

There is need to carefully investigate factors contributing to increased individual risk of invasion given carriage of a virulent meningococcus. The role of socioeconomic and hosts genetic factors in the occurrence of meningitis epidemics have been poorly investigated in the meningitis belt and there is need to develop research agenda focusing on their potential

contribution to the occurrence of meningitis epidemics. Also very few studies investigating concomitantly carriage and disease dynamics have been performed in the meningitis belt and we would recommend that carriage studies be conducted in parallel with disease surveillance in order to better understand the relation between both. A collaborative research project between research groups on meningitis in Africa aiming at conducting meta-analysis on available databases could provide strong evidence about arguments put forward by different groups in explaining meningitis epidemics in the African meningitis belt.

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9. Appendix

Table 1-a: Iterative process for search equation generation in Medline with full text via ebscohost)

Id #	Search equation	Results
S1	SH Meningitis, Meningococcal AND AB Meningitis, Meningococcal OR AB Meningococcal Meningitis OR AB Neisseria meningitis OR AB Meningitis, Cerebrospinal OR AAcute meningitis OR AB Epidemic meningitis OR AB Meningitis, Meningococcic	3565
S2	SH Meningitis, Meningococcal AND TI Meningitis, Meningococcal OR TI Meningococcal Meningitis OR TI Neisseria meningitis OR TI Meningitis, Cerebrospinal OR TA cute meningitis OR TI Epidemic meningitis OR TI Meningitis, Meningococcic	2593
S3	SH Meningitis, Meningococcal AND AB Meningitis, Meningococcal, Serogroup Y OR AB Serogroup Y, Meningococcal Meningitis OR AB Meningococcal Meningitis, Serogroup Y OR AB Meningitis, Meningococcal, Serogroup C OR AB Serogroup C Meningococcal Meningitis OR AB Meningococcal Meningitis, Serogroup C	9
S4	SH Meningitis, Meningococcal AND AB Meningitis, Meningococcal, Serogroup W-135 OR AB Serogroup W135, Meningococcal Meningitis OR AB Meningitis, Meningococcal, Serogroup W135 OR AB Meningococcal Meningitis, Serogroup W135 OR AB Meningococcal Meningitis, Serogroup W-135	0
S5	AB Meningitis, Meningococcal, Serogroup W-135 OR AB Serogroup W135Meningococcal Meningitis OR AB Meningitis, Meningococcal, Serogroup W135	0
S6	AB Meningococcal Meningitis, Serogroup W135 OR AB Meningococcal Meningitis, Serogroup W-135	0
S7	SH Meningitis, Meningococcal AND AB Meningococcal Meningitis, Serogroup W 135 OR AB Serogroup W-135 Meningococcal Meningitis OR AB Serogroup W 135	203
S8	SH Meningitis, Meningococcal AND AB Meningitis, Meningococcal, Serogroup A OR AB Serogroup A Meningococcal Meningitis OR AB Meningococcal Meningitis, Serogroup A	29
S9	SH Meningitis, Meningococcal AND AB Meningitis, Meningococcal, Serogroup B OR AB Serogroup B Meningococcal Meningitis OR AB Meningococcal Meningitis,	3

	Serogroup B	
S10	S1 or S2 or S3 or S7 or S8 or S9	5556
S11	SH Meningitis, Meningococcal AND TI Meningitis, Meningococcal, Serogroup Y OR TI Serogroup Y, Meningococcal Meningitis OR TI Meningococcal Meningitis, Serogroup Y OR TI Meningitis, Meningococcal, Serogroup C OR TI Serogroup C Meningococcal Meningitis OR TI Meningococcal Meningitis, Serogroup C	3
S12	SH Meningitis, Meningococcal AND TI Meningitis, Meningococcal, Serogroup B OR TI Serogroup B Meningococcal Meningitis OR TI Meningococcal Meningitis, Serogroup B	2
S13	SH Meningitis, Meningococcal AND TI Meningitis, Meningococcal, Serogroup A OR TI Serogroup A Meningococcal Meningitis OR TI Meningococcal Meningitis, Serogroup A	12
S14	SH Meningitis, Meningococcal AND TI Meningococcal Meningitis, Serogroup W 135 OR TI Serogroup W-135, Meningococcal Meningitis OR TI Serogroup W 135	78
S15	SH Meningitis, Meningococcal AND TI Meningitis, Meningococcal, Serogroup X OR TI Serogroup X Meningococcal Meningitis OR TI Meningococcal Meningitis, Serogroup X	5
S16	SH Meningitis, Meningococcal AND AB Meningitis, Meningococcal, Serogroup X OR AB Serogroup X Meningococcal Meningitis OR AB Meningococcal Meningitis, Serogroup X	3
S17	S11 or S12 or S13 or S14 or S15 or S16	98
S18	S11 or S12 or S13 or S14 or S15 or S16 or S1 or S2 or S3 or S7 or S8 or S9	5581
S19	AB Carriage OR AB asymptomatic carri$ OR AB incidence OR AB Disease OR AB Carriage prevalence, OR AB coloni?ation OR AB Coloni?ation prevalence , OR AB clonal waves OR AB Meningococcal carri$ OR AB meningococci carrier$ OR AB Neisseria coloni? ation, OR AB carriage waves OR AB pharyngeal coloni? ation OR AB meningitis Incidence OR AB meningitis incident cases, OR AB meningitis cases	1794528
S20	S17 and S19	46
S21	MH Africa/ OR MH African meningitis belt/ OR MH meningitis belt/ OR MH Africa south of the Sahara/ OR MH sub-Saharan Africa / OR MH Burkina Faso/ OR MH Niger/ OR Niamey/ OR MH Mali/ OR MH Togo/ OR MH Ghana/ OR MH Côte d'Ivoire/	66661

	OR MH Ivory Coast/ OR MH Senegal/ OR MH Chad/ OR MH Ethiopia/ OR MH Sudan/ OR MH Benin/ OR MH Nigeria/ OR MH Cameroun/ OR MH The Gambia/ OR MH Gambia/	
S22	S18 and S21	298
S23	S18 and S19 and S21	154

Table 2: Assessment of methodological quality of studies included in the review.

Criteria	Sié et al. (2008)	Boisier et al.(2006)	Hamidou et al.(2006)	Raghunathan et al (2006)	Hassan-King et al. (1998)	Leimkugel et al. (2007)	Muller et al.(2011)	Muller et al.(2006)	Trotter et al. (unpublished)
Study targeting the general population	yes	yes	no	yes	yes	yes	yes	yes	yes
Valid sampling design for carriage study	yes	s	s	yes	s	yes	yes	Yes	yes
Inclusion criteria described and appropriate	yes	s	yes	yes	yes	yes	yes	Yes	yes
Number of excluded or refusal (before study onset) reported with reasons	nr	nr	nr	yes	nr	yes	nr	yes	yes
Sample size preplanned to provide adequate statistical power	nr	nr	nr	yes	nr	yes	nr	nr	nr
Meningococcal vaccination status of the target population in the 3 preceding years of study onset reported.	yes	no	yes	yes	nr	yes	yes	yes	no
Type of vaccine used for mass campaign vaccination in the 3 preceding year of study onset reported.	A/C poly	na	nr	A/C poly	Nr	A/C poly	A/C poly	A/C poly	na
Swabing protocol reported and similar for all participants in carriage study.	yes	yes	yes	yes	yes	yes	yes	yes	yes
Swabs plated on agar transport system on site	yes	yes	yes	yes	Yes	nr	yes	yes	no
Diagnostic criteria for diseased, precise, and in accordance with WHO standards	yes	nr	nr	nr	nr	yes	yes	nr	nr
Described bacterial identification protocol in accordance to WHO standards	yes	yes	yes	yes	yes	yes	yes	yes	yes

Table 4: Summary characteristics of studies and CCOUs eligible for inclusion in the systematic review of case carrier ratio for meningococci the African meningitis belt.

Source	ID of CCOU	setting(Country)	Local season	Epidemiologic context	carriage survey sample	age range	Sampling time point/ follow up
A.Sie et al .2008	1	Nouna DSS[1](Burkina-faso)	dry	Hyperendemic	316	unreported	April 2006
Sie et al .2008	2	Village covered by ira health centre (Burkina-faso)	dry	Epidemic	180	unreported	May 2006
P. Boisier et al. 2006	3	Djinguinis, Azao, Fardak and Dallé villages(Niger)	dry	hyperendemic	80	2–65	May 2003
P. Boisier et al. 2006	4	Djinguinis, Azao, Fardak and Dallé villages(Niger)	wet	Endemic	70	2–65	February 2004
A. Hamidou et al. 2006	5	Primary schools in Niamey(Niger)	wet	Endemic	287	7–16	February 2003
A. Hamidou et al. 2006	6	Primary schools in Niamey(Niger)	dry	Hyperendemic	277	7–16	March 2003
A. Hamidou et al. 2006	7	Primary schools in Niamey(Niger)	dry	Hyperendemic	272	7–16	May 2003
L. Raghunathan et al. 2006	8	Yako district (Burkina-faso)	dry	Postepidemic[2]	460	5–25	17-26 May 2002
L. Raghunathan et al. 2006	9	Dedougou district (Burkina-faso)	dry	Hyperendemic	439	5–25	17-26 May 2002
M.Hassan-king et al. 1987	10	Farafenni.(The Gambia)	dry	Epidemic	100	2–20	January –April 1983
M.Hassan-king et al. 1987	11	Farafenni(the Gambia)	dry	Hyperendemic	250	2–20	June 1984
M.Hassan-king et al. 1987	12	Villages at border in Senegal of the Gambia	dry	Hyperendemic	500	2–20	June 1985
J. Leimkugel et al. 2007	13	KND(Ghana)	dry	Hyperendemic	301	< 5 – 50+	April 1998
J. Leimkugel et al. 2007	14	KND(Ghana)	wet	Endemic	299	< 5 – 50+	November 1998
J. Leimkugel et al. 2007	15	KND(Ghana)	dry	Hyperendemic	292	< 5 – 50+	April 1999
J. Leimkugel et al. 2007	16	KND(Ghana)	wet	Endemic	308	< 5 – 50+	November 1999
J. Leimkugel et al. 2007	17	KND(Ghana)	dry	Hyperendemic	298	< 5 – 50+	April 2000
J. Leimkugel et al. 2007	18	KND(Ghana)	wet	Endemic	301	< 5 – 50+	November 2000
J. Leimkugel et al. 2007	19	KND(Ghana)	dry	Hyperendemic	310	< 5 – 50+	April 2001
J. Leimkugel et al. 2007	20	KND(Ghana)	wet	Endemic	306	< 5 – 50+	November 2001
J. Leimkugel et al. 2007	21	KND(Ghana)	dry	Hyperendemic	339	< 5 – 50+	April 2002
J. Leimkugel et al. 2007	22	KND(Ghana)	wet	Endemic	319	< 5 – 50+	November 2002
J. Leimkugel et al. 2007	23	KND(Ghana)	dry	Hyperendemic	312	< 5 – 50+	April 2003
J. Leimkugel et al. 2007	24	KND(Ghana)	wet	Endemic	297	< 5 – 50+	November 2003
J. Leimkugel et al. 2007	25	KND(Ghana)	dry	Hyperendemic	350	< 5 – 50+	April 2004
J. Leimkugel et al. 2007	26	KND(Ghana)	wet	Endemic	313	< 5 – 50+	November 2004
J. Leimkugel et al. 2007	27	KND(Ghana)	dry	Hyperendemic	321	< 5 – 50+	April 2005

J. Leimkugel et al. 2007	28	KND(Ghana)	wet	Endemic	334	< 5 – 50+	nov-05
J.E.Mueller et al. 2011	29	Lena village(Burkina-Faso)	dry	Epidemic	316	1 -39	March 2006
J.E.Mueller et al. 2011	30	Kofila village(Burkina-Faso)	dry	Epidemic	203	1 -39	March 2006
J.E.Mueller et al. 2011	31	Konkourouna village(Burkina-Faso)	dry	Epidemic	105	1 -39	March 2006
J.E.Mueller et al. 2006	32	Urban Bobo-Dioulasso(Burkina-Faso)	dry	Hyperendemic	448	4–29	Feb 2003
J.E.Mueller et al. 2006	33	Urban Bobo-Dioulasso(Burkina-Faso)	dry	Hyperendemic	482	4–29	March2003
J.E.Mueller et al. 2006	34	Urban Bobo-Dioulasso(Burkina-Faso)	dry	Hyperendemic	469	4–29	April2003
J.E.Mueller et al. 2006	35	Urban Bobo-Dioulasso(Burkina-Faso)	dry	Hyperendemic	478	4–29	mai-03
J.E.Mueller et al. 2006	36	Urban Bobo-Dioulasso(Burkina-Faso)	wet	Endemic	474	4–29	June2003
C.L. Trotter et al. (unpublished yet)	37	Urban Bobo-Dioulasso(Burkina-Faso)	dry	Hyperendemic	538	0–59	Feb 28-March 7th 2008

ID of CCOU	participants	Inclusion criteria
1	GP	Resident of the Nouna DSS Area
2	GP	Residents of an outbreak village close to Ira health center.
3	GP	Residents of villages having registered at least one N.m W135 cases in March and April 2003 in the district of Illela.
4	GP	Residents of villages having registered at least one N.m W135 cases in March and April 2003 in the district of illela.
5	SC	Children attending primary schools not far from the CERMES Niamey, Laboratory.
6	SC	Children attending primary schools not far from the CERMES Niamey, Laboratory.
7	SC	Children attending primary schools not far from the CERMES Niamey Laboratory.
8	GP	Residents of Yako district in May 2002.
9	GP	Residents of Dedougou district in May 2002.
10	GP	Children and young adults living in the in the Farafenni Study area during the course of a trial of chemoprophylaxis with rifampicin and erythromycin.
11	GP	Persons living in two villages in the centre of the Farafenni study area where nationwide vaccination (Nov-1983) with A/C polysaccharide, has taken place and Persons living in two villages in two villages across the border in Senegal where nationwide vaccination (Nov-1983) with A/C polysaccharide, has not taken place.
12	GP	Persons living in two villages in the centre of the Farafenni study area where nationwide vaccination (Nov-1983) with A/C polysaccharide, has taken place.
13	GP	Inhabitant of KND

14	GP	Inhabitant of KND
15	GP	Inhabitant of KND
16	GP	Inhabitant of KND
17	GP	Inhabitant of KND
18	GP	Inhabitant of KND
19	GP	Inhabitant of KND
20	GP	Inhabitant of KND
21	GP	Inhabitant of KND
22	GP	Inhabitant of KND
23	GP	Inhabitant of KND
24	GP	Inhabitant of KND
25	GP	Inhabitant of KND
26	GP	Inhabitant of KND
27	GP	Inhabitant of KND
28	GP	Inhabitant of KND
29	GP	Healthy residents of Lena village as of march 2006
30	GP	Healthy residents of Kofila village as of march 2006
31	GP	Healthy residents of Konkourouna village as of march 2006
32	GP	Residents of the urban area of sanitary districts Secteur 15 and Secteur 22 as of Feb-june 2003 (Urban Bobo-Dioulasso.)
33	GP	Residents of the urban area of sanitary districts Secteur 15 and Secteur 22 as of Feb-june 2003 (Urban Bobo-Dioulasso.)
34	GP	Residents of the urban area of sanitary districts Secteur 15 and Secteur 22 as of Feb-june 2003 (Urban Bobo-Dioulasso.)
35	GP	Residents of the urban area of sanitary districts Secteur 15 and Secteur 22 as of Feb-june 2003 (Urban Bobo-Dioulasso.)
36	GP	Residents of the urban area of sanitary districts Secteur 15 and Secteur 22 as of Feb-june 2003 (Urban Bobo-Dioulasso.)
37	GP	Residents of the urban area of Bobo-Dioulasso, aged 1 month -59 years

GP= General population
SC= Schoolchildren
[1] DSS= Demographic Surveillance System
[2] 2 week after epidemic peak has drop down
KND= Kessena Nankana District

Table 5: N.m serogroup-specific carriage prevalence and monthly cumulative incidence of Case-Carriers Observation Units from included studies.

Authors .year	CCOU Id	Epidemiologic Context	N.m Serogroup	Monthly incidence		Prevalence	
				cases/N	/100,000 pop	carriers/n	(%)
J. Leimkugel et al. 2007	22	Endemic/Wet	A	0/140000	0	6/319	2
J. Leimkugel et al. 2007	24	Endemic/Wet	A	0/140000	0	4/297	1.3
J. Leimkugel et al. 2007	26	Endemic/Wet	A	0/140000	0	2/313	0.6
J. Leimkugel et al. 2007	13	Hyperendemic/Dry	A	13/140000	9.3	8/301	2.7
J. Leimkugel et al. 2007	15	Hyperendemic/Dry	A	0/140000	0	2/292	0.7
J. Leimkugel et al. 2007	21	Hyperendemic/Dry	A	4/140000	2.9	4/339	1.2
J. Leimkugel et al. 2007	23	Hyperendemic/Dry	A	4/140000	2.9	7/312	2.2
J. Leimkugel et al. 2007	25	Hyperendemic/Dry	A	6/140000	4.3	15/350	4.3
J. Leimkugel et al. 2007	27	Hyperendemic/Dry	A	0/140000	0	3/321	0.9
A.Sie et al .2008	2	Epidemic/Dry	A	6 [μ]/1354	443	22/180	12.2
M.Hassan-king et al. 1987	10	Epidemic/Dry	A	37[£]/13000	284.6	16/100	16
J.E.Mueller et al. 2011	29	Epidemic/Dry	A	13/4640	280.1	59/316	18.8
J.E.Mueller et al. 2011	30	Epidemic/Dry	A	2/2600	76.92	13/203	6.4
J.E.Mueller et al. 2011	31	Epidemic/Dry	A	14/1660	843.3	23/105	21.9
A.Sie et al .2008	1	Hyperendemic/Dry	Y	2/76847	2.6	36/316	11.4
A.Sie et al .2008	2	Hyperendemic/Dry	Y	0/1354	0	1/180	0.6
J. Leimkugel et al. 2007	13	Hyperendemic/Dry	Y	0/140000	0	4/301	1.3
J. Leimkugel et al. 2007	15	Hyperendemic/Dry	Y	0/140000	0	2/292	0.7
J. Leimkugel et al. 2007	17	Hyperendemic/Dry	Y	0/140000	0	4/298	1.3
J. Leimkugel et al. 2007	21	Hyperendemic/Dry	Y	0/140000	0	3/339	0.9
J. Leimkugel et al. 2007	22	Endemic/Wet	Y	0/140000	0	1/319	0.3
J. Leimkugel et al. 2007	23	Hyperendemic/Dry	Y	0/140000	0	1/312	0.3
J. Leimkugel et al. 2007	24	Endemic/Wet	Y	0/140000	0	1/297	1.3
J. Leimkugel et al. 2007	25	Hyperendemic/Dry	Y	0/140000	0	1/350	1.3
J.E.Mueller et al. 2011	29	Hyperendemic/Dry	Y	0/4640	0	17/321	5.5
J.E.Mueller et	30	Hyperendemic/Dry	Y	0/2600	0	16/203	7.9

al. 2011							
J.E.Mueller et al. 2011	31	Hyperendemic/Dry	Y	0/1660	0	4/105	3.8
C.L. Trotter et al. (unpublished yet)	37	Hyperendemic/Dry	Y	0/253605[$]	0	3/538	0.6
J.E.Mueller et al. 2006	34	Hyperendemic/Dry	w135	5/253605	1.97	6/469	1.3
J.E.Mueller et al. 2006	33	Hyperendemic/Dry	w135	7/253605	2.8	4/482	0.8
J.E.Mueller et al. 2006	32	Hyperendemic/Dry	w135	4/253605	1.6	8/448	1.7
J. Leimkugel et al. 2007	26	Endemic/Wet	w135	0/140000	0	2/313	0.6
J. Leimkugel et al. 2007	25	Hyperendemic/Dry	w135	0/140000	0	3/350	0.9
J. Leimkugel et al. 2007	13	Hyperendemic/Dry	w135	0/140000	0	1/301	0.3
J. Leimkugel et al. 2007	13	Hyperendemic/Dry	X	0/140000	0	0/301	0
J. Leimkugel et al. 2007	15	Hyperendemic/Dry	X	1/140000	0.7	10/292	3.4
J. Leimkugel et al. 2007	17	Hyperendemic/Dry	X	2/140000	1.4	52/298	17.4
J. Leimkugel et al. 2007	18	Endemic/Wet	X	0/140000	0	33/301	11
J. Leimkugel et al. 2007	19	Hyperendemic/Dry	X	0/140001	0	49/310	15.8
J. Leimkugel et al. 2007	20	Endemic/Wet	X	0/140000	0	4/306	1.3
J. Leimkugel et al. 2007	21	Hyperendemic/Dry	X	0/140001	0	2/339	0.6
J. Leimkugel et al. 2007	22	Endemic/Wet	X	0/140001	0	2/319	0.6
J. Leimkugel et al. 2007	24	Endemic/Wet	X	0/140001	0	3/297	1
J.E.Mueller et al. 2006	33	Hyperendemic/Dry	X	0/253605	0	1/482	0.2
J.E.Mueller et al. 2006	34	Hyperendemic/Dry	X	0/253605	0	2/469	0.4
C.L. Trotter et al. (unpublished yet)	37	Hyperendemic/Dry	X	0/253605	0	1/538	0.2

[$] Urban population aged 4-29 was estimated (253605) by applying age strata proportions of urban Bobo-Dioulasso (2006) to the total urban population of sanitary district 15 and 22 of Bobo-Dioulasso). It assumes that age distribution of Secteur 15 and 22 is the same as the whole urban part of bobo-dioulasso sanitary district.

[£] Monthly incident cases calculated as incident cases over the 4 month period (148) divided by the number of months (4) covered.

[µ] Monthly incident cases calculated as incident cases over the 4 month period (27) divided by the number of months (4) convered.

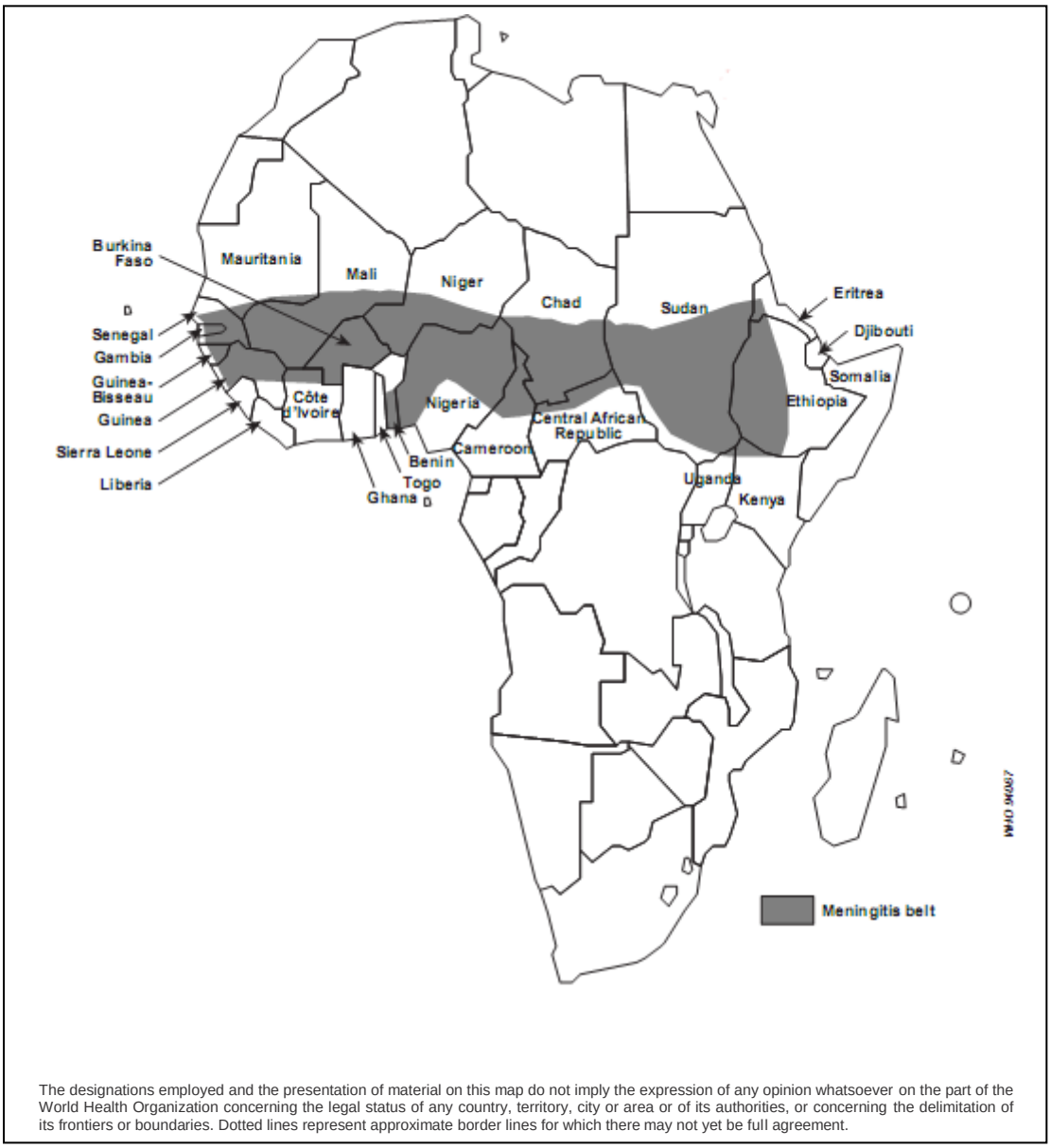
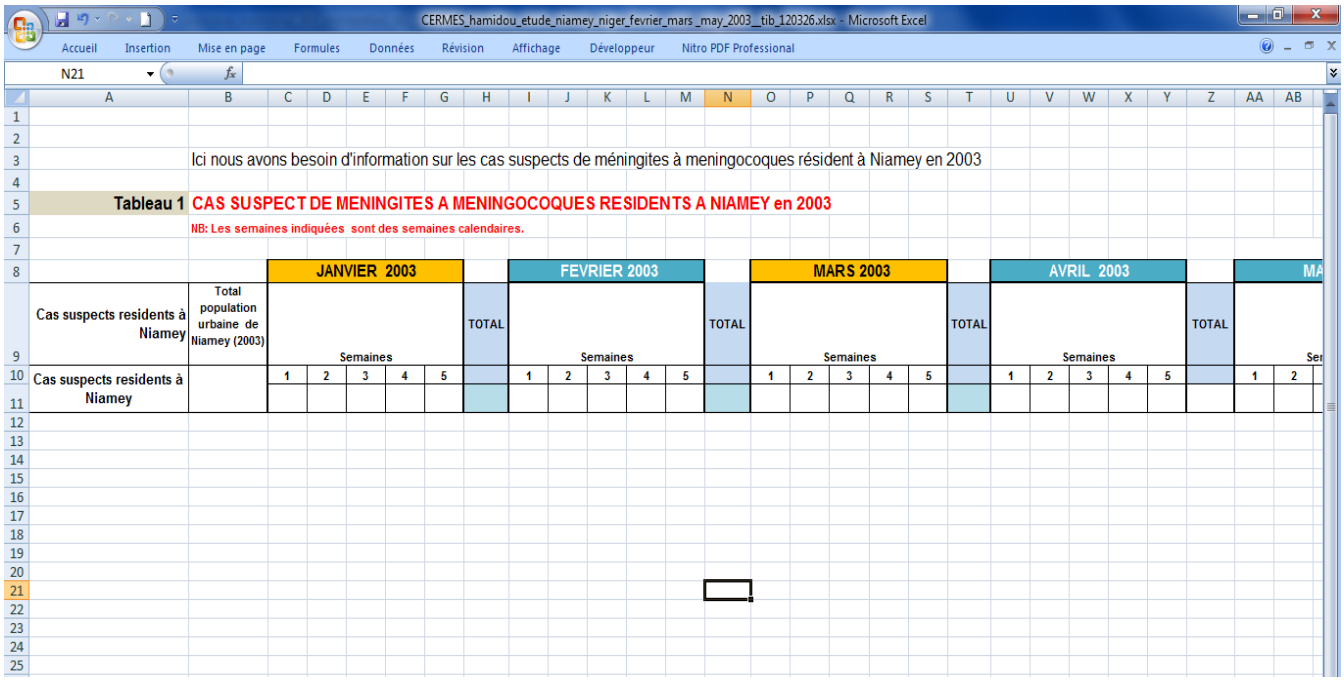


Figure 1: African meningitis belt. Source: CDC website, NCID, Travelers' health (available at http://wwwnc.cdc.gov/travel/).



Ici nous avons besoin d'information sur les cas suspects de méningites à meningocoques résident à Niamey en 2003

Tableau 1 CAS SUSPECT DE MENINGITES A MENINGOCOQUES RESIDENTS A NIAMEY en 2003

NB: Les semaines indiquées sont des semaines calendaires.

Cas suspects residents à Niamey	Total population urbaine de Niamey (2003)	JANVIER 2003 Semaines 1 2 3 4 5	TOTAL	FEVRIER 2003 Semaines 1 2 3 4 5	TOTAL	MARS 2003 Semaines 1 2 3 4 5	TOTAL	AVRIL 2003 Semaines 1 2 3 4 5	TOTAL	MA Se 1 2
Cas suspects residents à Niamey										

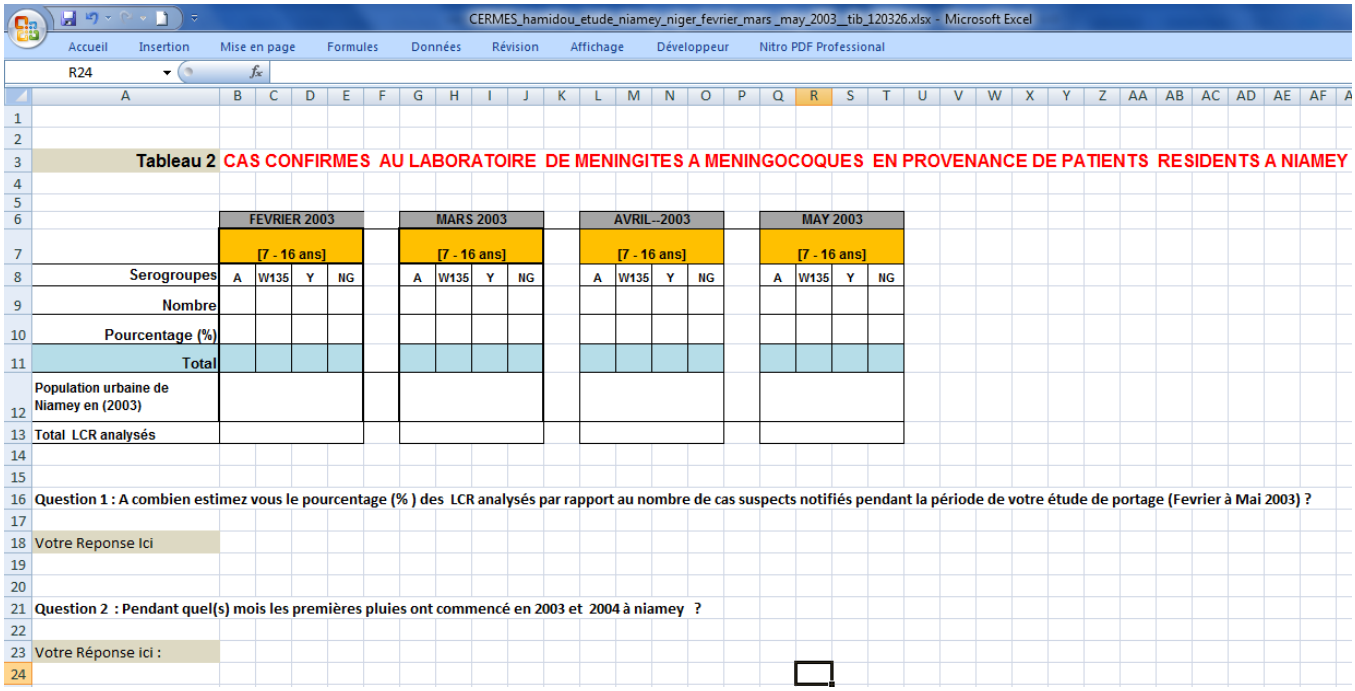


Tableau 2 CAS CONFIRMES AU LABORATOIRE DE MENINGITES A MENINGOCOQUES EN PROVENANCE DE PATIENTS RESIDENTS A NIAMEY

	FEVRIER 2003 [7 - 16 ans]				MARS 2003 [7 - 16 ans]				AVRIL--2003 [7 - 16 ans]				MAY 2003 [7 - 16 ans]			
Serogroupes	A	W135	Y	NG	A	W135	Y	NG	A	W135	Y	NG	A	W135	Y	NG
Nombre																
Pourcentage (%)																
Total																
Population urbaine de Niamey en (2003)																
Total LCR analysés																

Question 1 : A combien estimez vous le pourcentage (%) des LCR analysés par rapport au nombre de cas suspects notifiés pendant la période de votre étude de portage (Fevrier à Mai 2003) ?

Votre Reponse Ici

Question 2 : Pendant quel(s) mois les premières pluies ont commencé en 2003 et 2004 à niamey ?

Votre Réponse ici :

Figure 9: Sample data collection sheets.

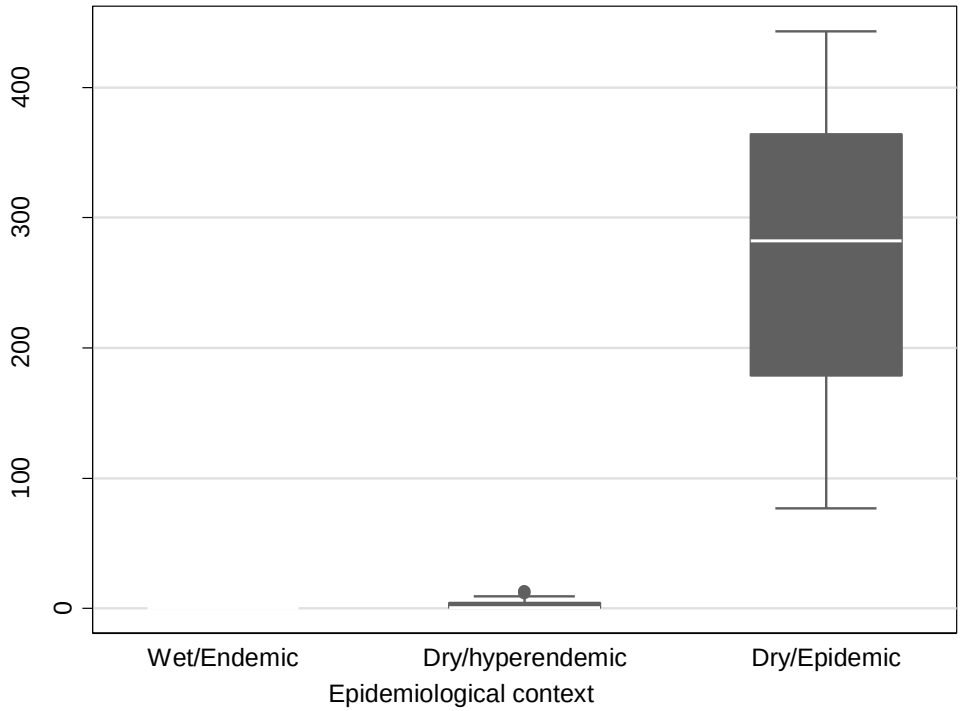


Figure 10: N.m A monthly incidence per 100,000 populations according to epidemiological situations

Assessing methodological quality of study to be included in the review
Critical appraisal form

Section 1: Reference of Article

Author(s) and Affiliation(s):

Title of Article:

Journal:

Volume and Page Numbers:

Year of Publication:

Review ID code:

Section 2: General Methodological Issues

For each criterion, the appropriate box is checked according to how we think it is addressed:

(Y= Yes, S= substandard, N= No, NC= Not Clear, NR= Not Reported, NA= Not Applicable, NQ= Not Qualified to Assess)

Criteria	Y	S	N	NC	NR	NA	NQ	Comments
Study targeting the general population	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	
Source population identified	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	
Valid sampling design for carriage study	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	
Inclusion criteria described and appropriate	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	
Exclusion criteria described and appropriate	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	
Number of excluded or refusal (before study onset) reported with reasons	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	
Sample size preplanned to provide adequate statistical power	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	
Number considered for enrollment reported	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	
Characteristics of survey participants at enrollment reported	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	
Meningococcal vaccination status of the target population in the 3 preceding years of study onset reported.	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	
Type of vaccine used for mass campaign vaccination in the 3 preceding year of study onset reported.	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	

Section 3: Specific methodological issues

(Y= Yes, S= substandard, N= No, NC= Not Clear, NR= Not Reported, NA= Not Applicable, NQ= Not Qualified to Assess); cite page number for key comments.

Criteria	Y	S	N	NC	NR	NA	NQ	Comments
Swabing protocol reported and similar for all participants in carriage study.	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	
Swabs plated on agar transport system on site	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	
Diagnostic criteria for diseased, precise, and in accordance with WHO standards	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	
Described bacterial identification protocol in accordance to WHO standards	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	

Section 4: Author's key results and conclusions

(Including quantitative estimates, confidence intervals, and p values if reported)

Section 5: Conclusions and assessment of the article

I. Strengths of the paper

II. Weaknesses of the paper

III. Our own conclusions: Reviewer's conclusions (if different from author's conclusion)

IV. Overall quality of study

Very good [ ]
Good [ ]
Admissible [ ]
Poor [ ]

For question: Carriage study participants sampled appropriately? Answer: Yes, No, Not clear enough to be assessed.
Note: Appropriate sampling method must include at least the following items described in the method section of the article.

- Sample size pre-planned to provide adequate statistical power.
- Simple random sampling or systematic sampling or multi stage cluster sampling
- Must be free of coverage bias (Sampling frame not restricted to a subset of the target population)