Meningococcal carriage by age: a systematic review and meta-analysis

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Summary

Background ***Neisseria meningitidis*** **is an important cause of meningitis and septicaemia, but most infected individuals experience a period of asymptomatic carriage rather than disease. Previous studies have shown that carriage rates vary by age and setting; however, few have assessed carriage across all ages. We aimed to estimate the age-specific prevalence of meningococcal carriage.**

Methods **We searched Embase, Medline, Web of Science, the Cochrane Library, and grey literature for papers reporting carriage of** ***N meningitidis*** **in defined age groups in European countries or in countries with a similar epidemiological pattern (where disease caused by serogroups B and C predominates). We used mixed-effects logistic regression with a natural cubic spline to model carriage prevalence as a function of age for studies that were cross-sectional or serial cross-sectional. The model assessed population type, type of swab used, when swabs were plated, use of preheated plates, and time period (decade of study) as fixed effects, with country and study as nested random effects (random intercept).**

Findings **Carriage prevalence increased through childhood from 4·5% in infants to a peak of 23·7% in 19-year olds and subsequently decreased in adulthood to 7·8% in 50-year olds. The odds of testing positive for carriage decreased if swabs were not plated immediately after being taken compared with if swabs were plated immediately (odds ratio 0·46, 95% CI 0·31–0·68; p=0·0001).**

Interpretation **This study provides estimates of carriage prevalence across all ages, which is important for understanding the epidemiology and transmission dynamics of meningococcal infection.**

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Introduction

Meningococcal disease remains an important public health problem, despite improvements in the management of patients and the availability of vaccines against some serogroups. Meningococcal disease can result in substantial morbidity, including deafness, skin scarring, and amputation, and was responsible for a quarter of all deaths attributable to infectious disease in children less than 5 years old in England and Wales in 2007.[1] However, invasive disease is a relatively rare outcome of meningococcal infection. In most individuals, infection leads to a period of asymptomatic carriage, during which meningococci colonise the pharynx and after which the organism is naturally cleared. Investigations into meningococcal carriage are crucial to the understanding of transmission dynamics and epidemiology.

Meningococcal carriage is assumed to be common, with a population prevalence of 10% often quoted. However, carriage varies with age and setting. Higher carriage rates have been reported in teenagers compared with other age groups.[2] High rates of carriage have also been found in household contacts of people with the disease[3] and in military and naval personnel.[4,5] The relation between disease incidence and carriage prevalence is unclear. Olsen and colleagues[6] reported increasing carriage with increasing disease incidence in the Faroe Islands, whereas Fernández and colleagues[7] noted no difference in carriage prevalence between an area in Galicia, Spain, that had a high incidence of disease and another that had a low incidence. Methodological factors such as the site of sampling,[8] type of swab used,[5] and subsequent handling of swabs[9,10] can also affect the yield of isolates obtained.

Because of logistic and financial reasons, few carriage studies have been undertaken across all age groups. Instead, most focus on narrow age bands or select groups in which carriage is expected to be high, and as a result robust estimates of carriage prevalence across all ages are not available at present. Estimates of carriage prevalence by age are important for studying the dynamics of carriage and disease and for understanding the potential effect of control programmes, such as vaccination, on the transmission of meningococci. For example, the serogroup C conjugate vaccination programme in the UK was successful because the vaccines not only protected against disease but also reduced carriage prevalence, thus leading to herd immunity.[11] These herd effects were particularly marked in countries (including the UK and the Netherlands) that targeted teenagers in a catch-up campaign.[12]

We did a systematic review and meta-analysis of meningococcal carriage studies to estimate carriage prevalence by year of age and to explore the reasons for heterogeneity in carriage prevalence between studies.

Methods

Search strategy and study selection

This paper was prepared in accordance with the meta-analysis of observational studies in epidemiology guidelines.[13] The search was done by one author (HC) in October, 2007, and updated in June, 2009, and March, 2010. Embase (1980–2010), Medline (1950–2010), Web of Science (no date restriction), and the Cochrane Library (no date restriction) were searched for papers reporting carriage of *Neisseria meningitidis* in defined age groups by the following combination of medical subject headings (MeSH) terms and text words (((meningitis, Meningococcal or exp *Neisseria meningitidis* or Meningococcal infections or meningitis) and carrier state) or ((meningococ* or neisseria meningitid* or meningitis) and (carrier* or carriage))) not (pneumococ* or Africa* or staphylococ* or haemophilus), where exp is an exploded term and * is a wildcard. Papers were limited to human studies in Medline and Embase searches. Grey literature was searched in the following databases: System for Information on Grey Literature in Europe (SIGLE), BIOSIS Previews, ISI proceedings, and ZETOC. References of relevant papers, including reviews, were also checked for additional studies.

Studies were eligible for inclusion if they reported pharyngeal carriage of all meningococcal serogroups in defined age groups (that is, ages of those from whom samples were taken were specified or studies took place in population groups of a known age, for example, high-school children) and if they were published after 1969 (because the distinction between *N meningitidis* and *Neisseria lactamica* was not made until 1969,[14] and *N lactamica* has a different pattern of carriage by age compared with *N meningitidis*).[2,15] Studies were excluded if they were in groups defined as adults or children without specific age ranges. Studies from Africa, Asia, or Russia, where a substantial proportion of disease is caused by serogroup A were excluded, because the epidemiology of disease is not comparable to the UK, which is dominated by serogroups B and C.[16] Studies were also excluded if they could not be generalised to the broader population; for example, studies among close contacts of a case (studies that included household and family contacts were excluded but those that included school contacts were included), military personnel (with the exception of those sampled on day of entry into the military), and isolated communities. No language restrictions were applied.

Data extraction and classification

We attempted to contact authors for additional information if retrieved studies were only available as abstracts, the reported age band of study participants was wider than 10 years (for groups of people under 60 years of age) and a mean age was not reported in the text (mean age requested from author), carriage prevalence was only presented as a graphic in the text (numbers used to create the graphic requested), or if carriage prevalence was presented without numerator and denominator figures (numerator and denominators requested). Several publications reported results from the same study; in these instances, the publication with the most information for each section of the study was included. For papers that included results from several populations, some of which did not meet the inclusion criteria, data were extracted only for the relevant populations. Extracted data included the language, study location and country, time period of study, study design, study setting including background disease levels and population studied, use of random sampling, type of swab used, site of swabbing, culture methods, age or age range of individuals, number of people swabbed to assess carriage status, number of people positive for carriage, and the percentage of positive carriers for each age or age band.

For papers in English, data were extracted by two authors (HC and LB) independently, with disagreements resolved via consultation with a third author (CLT). For papers in a foreign language, papers were translated via verbal consultation with a translator and data extracted by one author (HC). Studies were then separated into categories by one author (HC).

Studies were assigned to a decade by use of, in order, the reported study date, the decade in which most of the study took place if the study spanned more than one decade or the later decade if this was unknown, or the year of publication if study dates were unknown. Because of variability in the details about background disease that was provided, we did not attempt to classify and include background disease in our models. The population type was categorised into the following groups: civilians; military personnel; hospital patients, staff, or both; or mixed. Hospital patients or staff included hospital inpatients, people who worked at a hospital, and doctors and pharmacists if the place of work was unknown; preclinical students and people attending medical (including outpatient) or dental clinics were classified as civilians.

We did not attempt to classify study quality because no gold standard exists for undertaking meningococcal carriage studies; instead, we included several methodological factors within our models. Studies were classified as having used random sampling if this was specifically stated; otherwise "no" was recorded. Studies were classified as having used preheated plates if their use was stated; otherwise "no" was recorded (plates are usually used at room temperature). Studies were classified as having directly plated swabs if the methods stated so, for example, with the use of the words "immediate(ly)", "direct(ly)", "straight away", or "instantly"; if transport medium was used, methods were unclear, or if no information was available the study was classified as "other". We did not attempt to classify the site of the swab taken because often we were unsure whether the information provided was about the route taken to obtain the swab or the area in the pharynx

from which the swab was taken. If a study compared carriage from different sample locations in the same individuals, the location with the highest carriage prevalence was included.[8]

Where carriage prevalence was reported in age groups with an age band of 10 years or less, we used the midpoint age for analysis. Where age bands were of more than 10 years, we attempted to obtain the mean age for the group, either from the text or from the author. For open-ended older age bands, for example 65 years or older, we calculated a midpoint with an upper age limit of 75 years, with the exception of studies that reported carriage in university students, for which an upper limit of 35 years was used.[17–19]

Data analysis

All statistical analyses were done with Stata (version 10).[20] We expected carriage by age to be non-linear; therefore, we used mixed-effects logistic regression with a natural cubic spline to model carriage prevalence as a function of age for studies that were cross-sectional or serial cross-sectional. We used the RC_SPLINE function[21] in Stata to generate variables for the restricted cubic spline function of age. The model assessed population type, type of swab used, when swabs were plated, use of preheated plates, and time period (decade of study) as fixed effects, with country and paper as nested random effects (random intercept). We used fixed effects for factors that were assumed to have a constant effect across all studies in the meta-analysis (eg, when swabs were plated). Random effects are judged to be representative of the total population and are assumed to be normally distributed with sampled individual levels varying randomly around the population mean. We modelled country as a random effect because we view each country as a random sample of all of the countries that could have been included.

The model allows variation in carriage prevalence between studies, but constrains the general shape of the curve to be consistent across studies—ie, the peak is always at the same age. We chose this structure a priori because we believe it is a reasonable assumption that carriage prevalence by age is consistent across countries, but might be higher (or lower) at all ages than the average for particular countries. This structure also allows inclusion of data from countries for which only a few studies are available.

We investigated several models and used Akaike's information criterion (AIC) to select the best fitting model (a lower value suggests a better model fit). Bias corrected 95% CIs for the predictions of carriage by age were obtained with 10 000 bootstrap samples. Bootstrap estimates can produce biased results when used with small sample sizes.[22] However, our samples sizes were large and we used a bias-corrected method.[23]

For the meta-analysis, we excluded data from age bands that were over 20 years because we felt that changes in carriage by age might be masked by such wide bands. We did not include data from most longitudinal studies; however, we did include estimates of carriage prevalence from longitudinal studies of military recruits when they were sampled on the day of entry to the military because they should represent the wider population from which the recruits came.

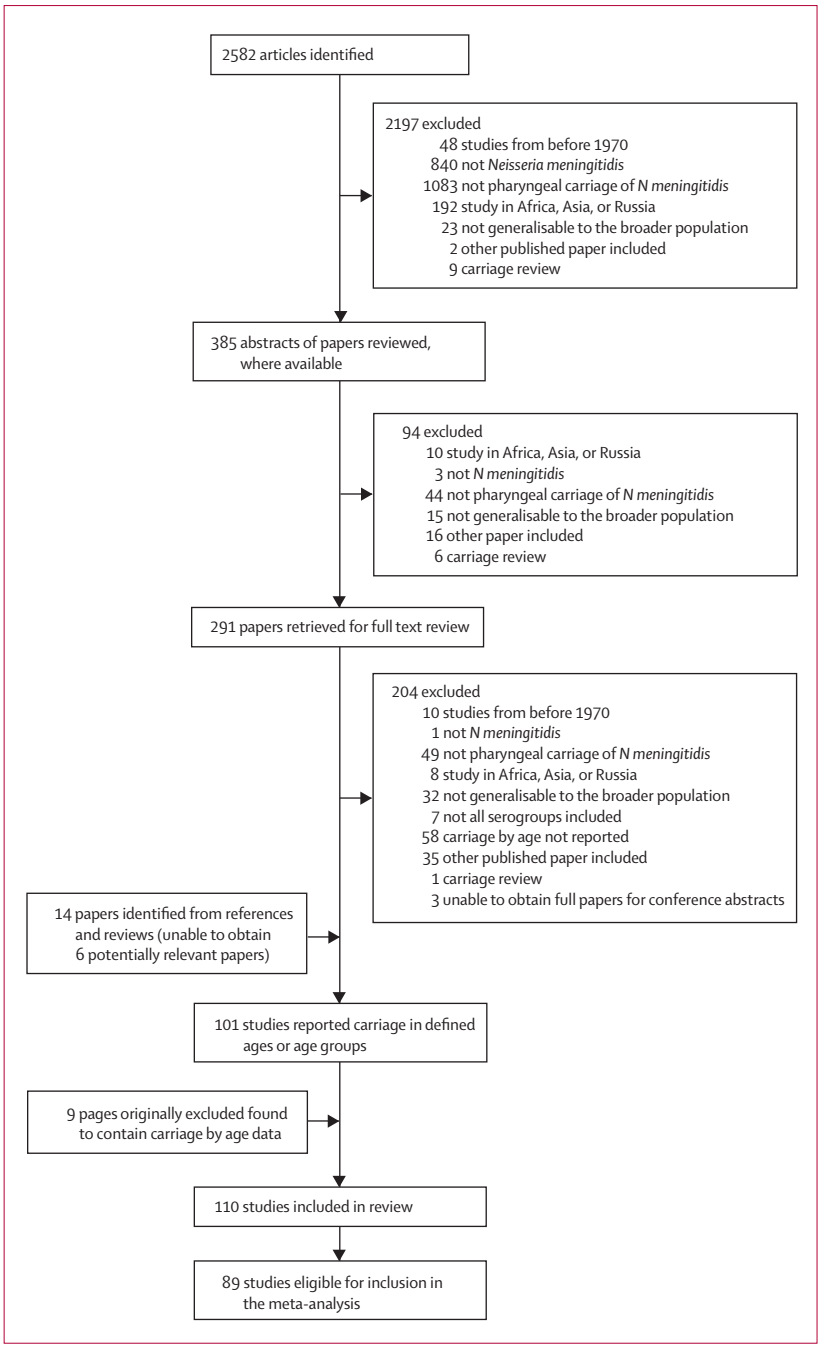

Figure 1: **Study selection**
For details of all the papers that were reviewed, including reasons for exclusion, please contact the corresponding author.

In a sensitivity analysis, we excluded non-European countries (as defined by the UN) because some of these countries have seen a recent increase in non-serogroup B or C carriage and disease (eg, an increase in serogroup Y in America).[24]

See Online for webappendix

	Value
Fixed effect parameter estimates: when plated	
Plated immediately*	OR 1·00
Other	OR 0·46 (95% CI 0·31–0·68; p=0·0001)
Random effect parameter estimates	
Country	Variance 0·10 (95% CI 0·003–3·05)
Study	Variance 0·77 (95% CI 0·48–1·23)

OR=odds ratio. *Baseline category.

Table 1: **Fixed and random effect estimates from the main analysis**

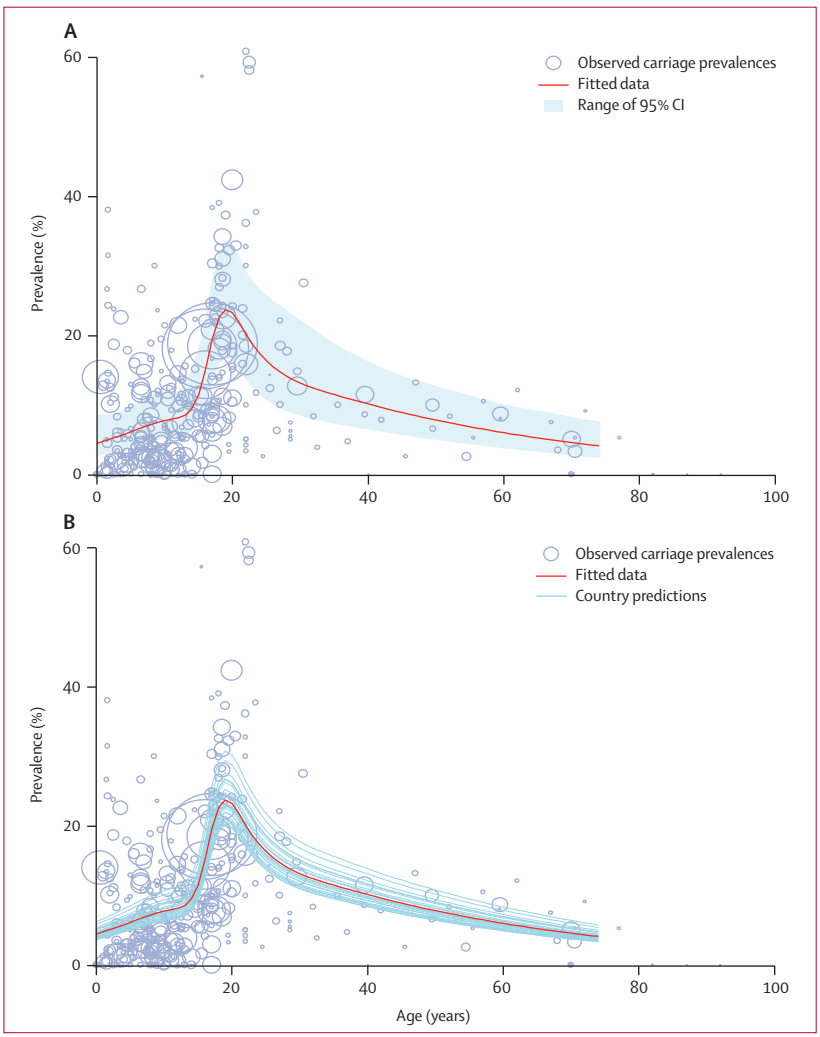

Figure 2: **Estimates of meningococcal carriage by age when swabs were plated immediately after collection**
Circles are the datapoints included, with the larger circles representing a larger sample size. The largest circles represent the results of the serial cross-sectional studies in teenagers aged 15–19 years old in the UK, before and after the introduction of the meningococcal serogroup C vaccine.[105,110,113] (A) 95% bias-corrected CIs. (B) With individual country predictions.

Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 110 relevant articles (figure 1); 37 were in languages other than English. Nine publications that were initially excluded because of their titles[17,25–32] were found to contain age-specific carriage data when reviewed for another purpose, and were subsequently included. Three articles were available as abstracts only.[33–35] The selected publications[2–4,7,8,15,17–19,25–125] reported carriage studies from 28 countries (webappendix pp 1–33). 18 studies were longitudinal (three in military recruits), five combined longitudinal, 69 cross sectional, ten serial cross sectional, seven a combination of cross sectional and longitudinal, and for one paper the study type was unclear.

Longitudinal studies that reported carriage by age in non-military populations have been undertaken in 15 countries. The number of repeated measures of carriage prevalence within a given population ranged from two to 13 and the frequency ranged from monthly to annual swabs (webappendix pp 10–33). Repeated measures on the same population showed small differences over time in some studies but large differences in others. For example, Rønne and colleagues[62] reported a carriage prevalence of 20·4% in people aged 16–20 years old in a school in Denmark in November 1983 and 19·8% in the following March, whereas Fraser and colleagues[36] reported a carriage prevalence of 25·7% in a cohort of boys aged 15–16 years old attending a naval school in April 1972 and 75·8% 9 months later. However, most of the other longitudinal studies reported a difference of 10% or less over the course of the study.

89 studies reported age-specific carriage data from cross-sectional studies, serial cross-sectional studies, or first swab results from a longitudinal study in military recruits, 16 of which reported the use of random sampling. Few papers reported carriage in older age groups; only 48 estimates of carriage prevalence were reported for individuals 25 years old and over compared with 341 in those under 25 years old (webappendix pp 10–33). The number of age groups investigated in each study varied greatly from a single age or age group (reported in 28 papers) to 19 different ages within the same population: Bogaert and colleagues[116] reported carriage by single year of age in people aged 1–19 years old and Caugant and colleagues[74] reported carriage in 5-year age bands from 0 years to 94 years, although there were small numbers of people in the upper age groups. Carriage estimates vary greatly even within age bands. The greatest variation was seen for 20–29-year olds, with reported prevalence ranging from 2·6% to 60·7%.

Data from 82 papers, comprising 143 114 individual swabs, were available for the quantitative data synthesis.

	Value
Fixed effect parameter estimates: time period of study	
1970–79*	OR 1·00
1980–89	OR 1·51 (95% CI 0·83–2·74; p=0·17)
1990–99	OR 0·82 (95% CI 0·50–1·35; p=0·44)
2000–09	OR 0·54 (95% CI 0·30–0·99; p=0·048)
Random effect parameter estimates	
Country	Variance 0·15 (95% CI 0·02–1·31)
Study	Variance 0·42 (95% CI 0·26–0·67)

Table 2: **Fixed and random effect estimates from European studies only**

Our initial regression models used knots (points marking the start and end of different curve sections which make up the spline) placed at locations on the basis of percentiles, as recommended by Harrell.[126] Our best fitting model was that with six knots (at 1·5, 11, 15, 17, 22, and 34 years), with several knots concentrated around the carriage peak in late teenage years (AIC 3402·3). In addition to the variables for the spline of age (likelihood-ratio test p<0·0001), the plating method was independently associated with carriage by age, after accounting for the nested random-effects structure of country and study (likelihood-ratio test p<0·0001). For a given age, the odds of testing positive for carriage decreased if swabs were not plated immediately after being taken (p=0·0001; table 1).

Predicted carriage prevalence estimates by single year of age for swabs that were plated immediately after collection are shown in figure 2 and in the webappendix p 34. Carriage by age was non-linear, increasing through childhood from 4·5% in infants to 7·7% in 10-year olds and peaking at 23·7% in 19-year olds before decreasing into older adulthood (13·1% in 30-year olds and 7·8% in 50-year olds). The point estimate of the variance for the country random-effects parameter was lower than that for the study random-effects parameter (table 1). The highest prevalence estimates were obtained for Serbia and the lowest for Australia.

In the sensitivity analysis of European studies only (n=63) the plating method was not important (data not shown), but there was some evidence that decade of the study was independently associated with carriage by age after accounting for the nested random effects structure of country and study (likelihood-ratio test p=0·049; table 2). The predicted peak in carriage remained at 19 years of age. Again, greater variation in carriage prevalence was noted between studies within a given country compared with between countries in the European analysis.

Discussion

In this systematic review of meningococcal carriage, age was the most important factor in establishing carriage prevalence. Our model estimated low carriage in young children, increasing through childhood to a peak in 19-year olds, and subsequently declining in older adulthood. Only one of the other variables that we assessed—immediate plating of swabs—influenced carriage prevalence in the model with data from all countries. Although carriage was previously known to be high in teenagers, our finding of a peak in carriage in 19-year olds is important to help understand the transmission of *N meningitidis* and develop potential vaccination strategies. The high carriage rate in teenagers might be attributable to a number of factors, including contact patterns and social behaviour. Results from recent surveys of children and young adults have shown that contact rates are highest among people of the same age,[127] and an increased number of pub and club visits and kissing partners are associated with increased meningococcal carriage.[105] Mathematical models have shown that much of the success of the sero-group C conjugate vaccination programme in the UK was because of herd immunity effects,[11] and the largest serial cross-sectional study of carriage confirmed a decrease in serogroup C carriage in teenagers.[113] If new meningococcal vaccines targeted against the predominant serogroup B strains are able to disrupt carriage, the results from this analysis could be used to help decide whether, and to whom, to offer catch-up vaccination to generate herd immunity.

We chose not to stratify the analysis by meningococcal serogroup or strain. Our main aim was to identify age-specific patterns in overall carriage because the new meningococcal vaccines in development are based on protein antigens and are not serogroup specific, and the predominant strains circulating in a population do change over time. We aimed to minimise bias by searching several published paper and grey literature sources, not restricting our search to English language papers, and attempting to obtain additional data for analyses. In our data synthesis, we tried to use as much of the available data as possible. A third of the papers included in the meta-analysis reported carriage prevalence for a single age or age group and most studies reported carriage in people age less than 25 years old. This focus on younger people is probably because of the disease epidemiology (meningococcal disease is rare in older adults), the ease of taking samples from people in nurseries or full-time education compared with older adults, and the expectation that carriage in teenagers is probably high. The model structure that we used constrains the curve for each country to have the same general shape, with the peak in carriage occurring at the same place in each curve. However, the model does allow some variation by country because the curve can be higher or lower than the average for any given country. Although assessment of whether the distribution of carriage by age varies by country in relation to peak age of carriage would be interesting, only limited data are available for some of the countries we included; thus, an individual curve cannot be generated for each country.

The analysis of cross-sectional studies revealed greater between-study compared with between-country variation. This result is reassuring because studies were only included if they were undertaken in countries with comparable epidemiology of meningococcal disease to the UK. Few papers reported the use of random sampling; thus, for many studies, recruitment bias might have resulted in estimated prevalence rates that are not representative of the population from which they were drawn. The populations under investigation in each study might have differed in socioeconomic position; the proportion of smokers and number of people living in the same home (both of which are associated with socioeconomic position) have been reported to influence carriage prevalence in some studies.[86,95,128] Studies also varied in their inclusion and exclusion criteria; some studies excluded individuals if they had received antibiotics before the carriage study[57,77,85,112] but others did not report such restrictions. Additionally, the sensitivity of one swab for detecting carriage might be low, and isolation of meningococci can vary according to the person who took the swab,[5] although the concordance of results between people taking swabs is high in some studies.[2] However, despite these limitations and differences between studies, the mixed-effects model we used allows average estimates of carriage to be produced across studies and countries.

The results from our main model support the conclusions of Roberts and colleagues;[129] that direct plating of swabs results in a higher yield of meningococci compared with other methods. In the European subanalysis, direct plating of swabs was not independently associated with carriage. However, unlike the findings of Roberts and colleagues,[129] we did not identify an association between carriage prevalence and the type of swab used or whether plates were preheated, although few studies reported the latter. Direct comparisons of techniques used to take samples within the same populations would probably be required to fully assess the differences in yield. The papers we reviewed also varied in the amount of detail provided about sampling methods (and other factors, such as background disease incidence), which restricted the analysis. Our results for some factors might be a product of reporting insufficiency rather than an absence of real association. Our finding of a possible association in the European subanalysis between decade of study and carriage by age might be an artifact; the association was driven by the estimate for the last decade assessed, 2000–09, in which there were fewer datapoints than in earlier decades; a situation not seen in the analysis of all countries. Subsequent meta-analyses of carriage by age would be improved if future carriage studies reported the actual incidence of disease in the population swabbed (not simply high or low incidence), the regions of the throat swabbed and the route of swabbing, and presented the number of individuals swabbed and numbers positive for carriage in 5-year age bands.

Our results confirm the importance of age as a key determinant of meningococcal carriage prevalence. Our systematic approach and use of meta-analytic techniques to estimate carriage prevalence by single year of age provide greater quantitative detail than traditional narrative reviews and improve our understanding of the epidemiology of meningococcal infection.

Contributors

HC, MH, and CLT conceived and designed the study. HC ran the searches; HC and LB extracted data and CLT resolved discrepancies. HC and MM analysed the data. HC, MM, MH, and CLT interpreted the data. All authors wrote the paper and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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