

Carriage and transmission of *Neisseria meningitidis*

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Introduction

Despite the fact that the meningococcus is a pathogen of global significance, causing the severe syndromes of meningitis and septicemia, it is a member of the normal microbiota of the nasopharynx of healthy humans. Indeed, this is the natural habitat of *Neisseria meningitidis*, and no other reservoir is known to exist for this bacterium. As the process of causing disease does not contribute to person-to-person transmission of meningococci, it is most usefully characterized as an ‘accidental pathogen’ of humans; host invasion is a dysfunctional event for both the microbe and its host, from which neither gains any benefit [1] (Figure 2.1). Although the significance of the carrier state has been long recognized, it has become increasingly apparent that an understanding of carriage is crucial to an understanding of meningococcal disease and its prevention. Here we shall outline the important features of meningococcal carriage and its study, and their implications for understanding disease.

Detecting the carrier state

The presence of meningococci in asymptomatic carriage has been appreciated from the early 20th century, when early carriage and transmission studies were conducted in UK military populations [2]. In most of

the studies conducted since that time, carriage has been detected by conventional microbiological techniques, which remains the predominant method. Typically, a cotton-wool tipped (or similar) swab is used to sample the back of the throat and the material is transferred directly or indirectly on to a selective culture plate. There are various approaches to this type of sampling and culture, with success depending on choosing the appropriate location (uvula and/or tonsils), route of access (per-oral preferred to per-nasal) and ensuring that the meningococci remain viable until they are incubated for growth.

The density of growth in the nasopharynx can vary appreciably and after incubation culture plates can exhibit anything from very few colonies to confluent growth of putative *Neisseria*, which are identified as Gram-negative, oxidase-positive diplococci. *N. meningitidis* has to be

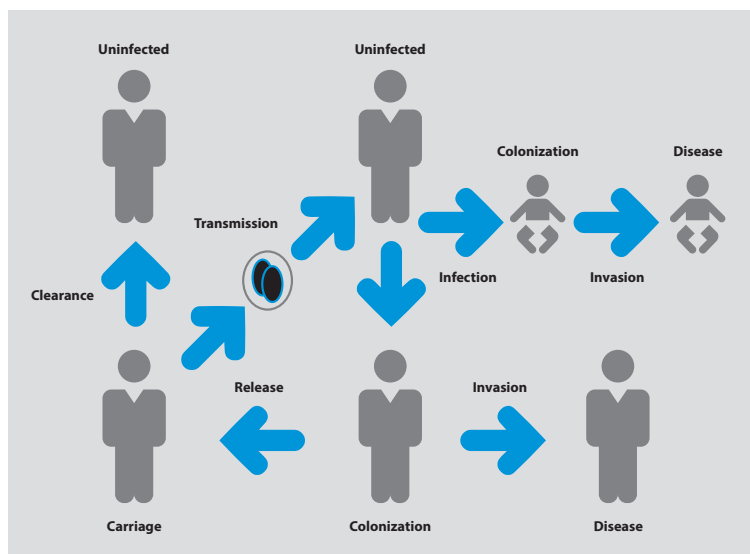


Figure 2.1 The natural history of infection with *Neisseria meningitidis* in high-income countries. Meningococcal carriage is common, at around 10% of the population, and capsulated meningococci are released from colonized individuals in aerosols. These bacteria infect human hosts and the great majority of these infections result in asymptomatic colonization. In adults carriage is common and the development of disease is very rare, whilst in small children carriage is rare but disease relatively more common. There is no onward transmission from invasive disease. In most individuals carriage is cleared, presumably as a consequence of host immune responses. Adapted from Trotter and Maiden [3].

distinguished from related organisms, especially members of the genus *Moraxella* and other *Neisseria* (studies prior to 1960 are of limited value as they did not differentiate adequately between species). Biochemical techniques have been used to do this for many years, and they can be effective, although they are time-consuming and can lack resolution. In particular, the detection and differentiation of *Neisseria* species relies on a few biochemical characteristics that are not always reliable. Molecular methods are increasingly used, although it has been necessary to develop high-resolution methods for speciation: the small subunit 16S rRNA can distinguish *Neisseria* from other genera, particularly *Moraxella*, but will not discriminate species within the genus [4]. Other sequence-based techniques such as multilocus sequence analysis (MLSA) and ribosomal multilocus sequence typing (rMLST) are effective for speciation within the genus, and the latter has been developed into a high-resolution rapid single–single locus approach, the *rplF* assay [5–7]. Developments in very high throughput ‘next generation’ sequencing (NGS) present the prospect of the use of metagenomic techniques to monitor the frequency and density of colonization of meningococci in the context of other organisms, but at the time of writing the potential of these approaches has not been realized.

Most carriage studies are cross-sectional, designed to measure the prevalence of carriage and provide a snapshot of the population. The prevalence of carriage is determined by the acquisition rate and the duration of carriage, which can only be determined empirically through longitudinal studies that follow-up individuals over time. Although less well described, the acquisition rate is important because disease is thought to occur soon after acquisition.

The natural history of meningococcal carriage

Exposure to meningococci through respiratory droplets can result in acquisition of carriage. For colonization to occur the bacteria must adhere to the mucosal surface, exploit locally available nutrients (including iron), and evade the human immune system. There are several important structures and molecules that facilitate colonization; pili facilitate initial attachment to the epithelial cell surfaces and opacity-associated proteins allow a more intimate engagement [8]. Phase and antigenic

variation of a number of surface components permits immune evasion during infection [8].

A period of carriage may be transient or last for many months. The duration of carriage is not well established as few longitudinal studies of carriage have been performed. Studies in Europe have suggested periods of nine or more months, whereas a study in Africa estimated a much shorter duration of three months [9].

Antibiotic chemoprophylaxis may be used to eliminate carriage from an individual and is an appropriate public health response for close contacts of a case or during an outbreak (Chapter 6). Asymptomatic carriage will otherwise resolve naturally. It is likely that carriage is an immunizing event, although the immune responses elicited by carriage, particularly in the mucosa, are not well characterized [10].

Given the extent of horizontal gene transfer observed in meningococci, it is likely that carriage of multiple meningococcal strains is relatively frequent. However, most culture-based studies have not been designed to be able to measure this, as they tend to pick a single colony, or at most very few, for characterization. As culturing many isolates from single throat swabs by conventional microbiology is very time-consuming, appropriately designed carriage studies using molecular techniques, especially metagenomic approaches, provide novel means of addressing this issue.

Epidemiology of carriage

Meningococcal carriage appears to be universal among human populations with carriage prevalence varying from a few percent to a substantial proportion of the population under study, according to time, place, host, and bacterial factors [11]. Unfortunately, there is no reliable relationship between carriage prevalence and disease incidence, and carriage studies remain uninformative in predicting disease risk.

The meningococcus is a highly diverse organism. This diversity includes surface antigens, which is perhaps to be expected in an organism that lives in close association with the human immune system, but diversity is also evident genome wide, including in ‘housekeeping’ genes, which are apparently not exposed to host immune responses [12]. Studies of meningococci isolated from asymptomatic carriage and disease have

demonstrated that not all variants are equally likely to cause invasive disease [13]. Typically the meningococci isolated from carriage are more diverse than collections obtained from disease. Disease isolates are likely to belong to one of a few particular genetic types referred to as 'hyper-invasive lineages'. It is important to emphasize that the spread of even the hyper-invasive meningococci is by asymptomatic carriage: while all meningococci have to be efficient at asymptomatic carriage and transmission, only a small subset of meningococci exhibit a propensity to cause disease [1].

Meningococcal carriage is highly age dependent. The great majority of studies have been conducted in industrialized societies, and in such settings meningococcal carriage is usually very rare in infancy and increases with age, carriage prevalence reaching a peak during the teenage years (Figure 2.2) [14]. This has been shown to be largely due to social behavior with carriage rates, and by extension transmission, increased by factors such as smoking, pub and club attendance, and kissing [15]. Studies in Africa have shown a less consistent age distribution, carriage prevalence being generally highest in younger children aged 5 to 14 years [16].

Seminal studies suggest that the peak in meningococcal disease incidence in infants, where carriage is rare, is due to poor immunity following the waning of maternal antibodies [17], whilst the second peak in disease incidence in young adults, which is characteristic of the meningococcus, is probably attributable to increased exposure of individuals to virulent meningococci that they have not experienced earlier in life. The conundrum that individuals acquire immunity whilst apparently not carrying meningococcus is yet to be resolved, but the carriage of closely related members of the genus *Neisseria* may be involved.

Meningococcal carriage prevalence is generally higher in males than females and particularly high rates of carriage have been observed in closed or partially closed communities, such as military training establishments and university halls of residence. This is most likely due to intense mixing of people from different geographical locations carrying a diversity of strains [18,19]. The annual Hajj pilgrimage has provided opportunities for the regional and global spread of meningococci [20].

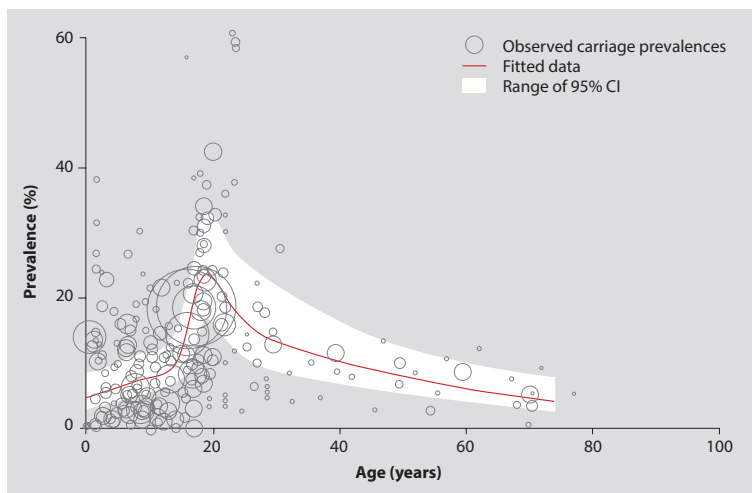


Figure 2.2 Estimates of meningococcal carriage by age in high-income countries. Swabs were plated immediately after collection, from a systematic review and meta-analysis [14]. Circles are the data-points included, with the larger circles representing a larger sample size. The largest circles represent the results of the serial cross-sectional studies in teenagers aged 15 to 19 years in the UK, before and after the introduction of the meningococcal capsular group C vaccine. Shaded area represents 95% bias-corrected confidence intervals. Reproduced with permission from © Elsevier.

Other *Neisseria* species

With the exception of *Neisseria gonorrhoeae*, other members of the genus have not been studied as extensively as the meningococcus, as they do not cause disease frequently. *Neisseria lactamica* has attracted most interest as it is closely related to the meningococcus and shares the same ecological niche. The age distribution of *N. lactamica* is very different from that of the meningococcus, with carriage in children more common than carriage in adults. Following birth, children commonly acquire *N. lactamica* and carriage persists for months and perhaps years [21]. It has been proposed that carriage of this organism leads to immunity to the meningococcus, but this has not been definitively established [22]. However, recent genomic studies have shown that at least two other *Neisseria* species, *N. polysaccharea* and *N. bergeri* [23], are more closely related to the meningococcus than *N. lactamica* and these species may be important in the development of immunity. The study of these organisms remains limited at the time of writing, but their interactions with

the human host may also be important in childhood when neither the meningococcus nor *N. lactamica* are routinely isolated from carriage or in settings other than high-income countries.

Effect of vaccination on carriage

Carriage studies have assumed more importance with the realization that herd immunity (or ‘herd protection’) acting on carriage is an important element in the success of meningococcal protein-polysaccharide conjugate vaccines (Chapter 7). Large-scale studies of meningococcal carriage following the introduction of capsular group C conjugate vaccines in the UK showed a marked drop in the prevalence of carriage of group C meningococci within a year, a trend that continued over subsequent years [24]. Incidence of disease declined in the unimmunized, also an indication of herd protection. As protective responses declined in those immunized under 1 year of age, herd protection was a major reason for the success of these vaccines, with the outbreak strain (the hyper-invasive ST-11 complex group C meningococcus) particularly affected by the vaccination program [10].

These observations have been highly influential in the implementation of these vaccines in other countries, the modification of the immunization schedule in the UK, and the implementation of the group A protein-polysaccharide conjugate vaccine (PsA-TT) in the African meningitis belt. Evidence gathered following mass vaccination campaigns suggests that PsA-TT can also successfully protect against carriage and generate herd protection [25]. Most evidence suggests that plain polysaccharide vaccines do not affect carriage and interrupt transmission [26]. The effect of outer membrane vesicle (OMV) and other noncapsular vaccines on carriage is less clear but they are certainly not as effective as conjugate vaccines [27].

Summary points

- An understanding of carriage is central to understanding the population and transmission dynamics of meningococci.
- It is now appreciated that the spectacular effects of the bacterial conjugate vaccines are due to the herd protection that they

confer through their effect against asymptomatic carriage, which reduces transmission.

- Carriage studies have been very important in understanding the virulence of the hyper-invasive lineages and will play a central role if we are to understand the reasons for the high levels of variability in invasiveness of these organisms and design effective interventions against them.

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