Epidemiol. Infect. (2005), **133** (Suppl. 1), S37–S39. © 2005 Cambridge University Press
doi:10.1017/S0950268805004310

11. The Stonehouse survey

Cartwright KAV, Stuart JM, Jones DM, Noah ND. Epidemiol Infect 1987; **99**: 591–601

AN APPRECIATION BY KEITH CARTWRIGHT

Health Protection Agency South West, Stonehouse, Glos., UK
(Keith.Cartwright@HPA.org.uk)

The Stonehouse meningitis survey took place in 1986 [1]. The context was a substantial and highly focal outbreak of meningococcal disease affecting the population of southern Gloucestershire and particularly the town of Stroud and its adjacent communities – a population of some 90 000 individuals in the west of England. Almost all cases of meningococcal disease were due to a serogroup B, type 15, subtype P1.7,16 sulphonamide-resistant strain that had not been documented in Gloucestershire (and only rarely in the United Kingdom) prior to 1982, the first year of the outbreak. As is often the case at the start of an outbreak of meningococcal disease in a temperate country, the attack rate rose particularly in older children. For the population of Stroud as a whole the meningococcal disease attack rate rose from approximately 1·0 cases per 10^5 to approximately 8 per 10^5 population.

Studies of meningococcal carriage are not new. Following Weichselbaum's first isolation of meningococci from spinal fluid of patients with meningitis in 1887, it was in 1896 that meningococci were first isolated from the nasopharynx by Kiefer, elucidating a key step in the pathogenesis of the disease, namely colonization of the nasopharynx as a precursor to invasive disease. (We now know that this is by far the most common mechanism of invasive infection and that if invasion is to occur, it usually (though not always) follows within a day or two of initial nasopharyngeal colonization. Those carrying meningococci for weeks or months, even virulent strains, do not, in general suffer from invasive disease.)

Glover's classical and detailed epidemiological studies carried out at the Guards Depot, Caterham, in South London during the First World War (1914–1918), revealed an association between high rates of meningococcal carriage in platoons of recruits, and the development of cases of invasive disease. These studies were carried out in the pre-antibiotic era, when measures to reduce or eliminate meningococcal nasopharyngeal carriage were of a more archaic nature, involving the use of inhalation of zinc sulphate spray.

Later studies cast doubt on Glover's findings, suggesting that there was no clear relationship between meningococcal nasopharyngeal carriage and disease. A major step forward was taken by Geoffrey Rake and his colleagues in the 1930s. Rake and his co-workers showed that carriage of meningococci in healthy young office workers could be prolonged for well over a year, and that carriage could be intermittent. This was the first detailed study of meningococcal carriage in a healthy population (as opposed to one experiencing a high rate of meningococcal disease). The next major step forward in attempting to understand the complex relationship between meningococcal carriage and disease resulted from the identification of the closely related commensal bacterium *Neisseria lactamica* in 1965. Following the discovery of *N. lactamica* it became apparent that the interpretation of the results of all previous studies of meningococcal carriage that had sampled infants and young children would need to be qualified, since carriage of *N. meningitidis* in infants and young children was extremely infrequent whereas carriage of the non-pathogenic *N. lactamica* was relatively common. In 1971, Greenfield's careful longitudinal study of carriage of meningococci in families demonstrated clearly the age distribution of carriage of meningococci.

The primary purpose of the Stonehouse survey of meningococcal carriage was to attempt to tease out any differences in carriage rates between pathogenic and non-pathogenic meningococcal strains. This opportunity arose because of the highly clonal nature of the outbreak, with almost all disease-causing strains being of the same phenotype (and therefore putatively of the same genotype), and because the incidence of meningococcal disease was extremely focal even within the confines of such a small village community. Because of the low predicted carriage rate of the outbreak strain (based on results of prior swabbing studies in local schools during clusters and outbreaks), a large survey was planned to test the hypothesis that carriage of the outbreak strain might be higher in those parts of Stonehouse where disease attack rates had been high. As well as collecting throat swabs for meningococcal culture from as many as possible of the 6000+ inhabitants of the village of Stonehouse (residents and children attending schools in Stonehouse), blood samples were also collected to assess meningococcal immunity. An additional study of human secretor status was added to the study protocol at a late stage.

Swabbing was done carefully. Nurses employed to swab the Stonehouse residents were all trained to a common standard. When the reproducibility of nasopharyngeal swabbing was tested by re-sampling 202 individuals using a second swabber, concordance was 98%.

The key findings of the carriage study can be summarized briefly. The overall meningococcal carriage rate was 10·9% but carriage rates were very low in infants and in the elderly whereas peak carriage rates of 24·5% were documented in teenagers aged 15–19 years. Most meningococci that were isolated were of low pathogenic potential, with little expression of capsular polysaccharide.

The carriage rate of the outbreak strain was very low – only 1·4%. Furthermore, there was no correlation at the population level between those parts of Stonehouse that had experienced high rates of invasive meningococcal disease with the areas in the village that had the higher rates of carriage of the outbreak strain.

The low carriage rate of the outbreak strain suggested, therefore, that it was either of unusually high virulence, or alternatively, that it was being passaged through the population very quickly, but with a very low duration of carriage. In a follow-up study, duration of carriage of the outbreak strain was compared with duration of carriage of other meningococci; no differences were found, making the hypothesis of a high virulence, low transmissibility strain more likely. (A follow-up to this duration of carriage study demonstrated for the first time the association between cigarette smoking and meningococcal carriage.)

What did the Stonehouse survey add to the body of knowledge about meningococcal carriage and disease? First, the sample size was large enough to permit generation of accurate and reliable data on age-stratified rates of carriage. Because all 'picks' from selective agar culture plates were identified, similar accurate data on age-stratified carriage rates of *N. lactamica* were also produced. Second, the low carriage rate of the outbreak strain was found to be most likely attributable to its intrinsic characteristics of high virulence and low transmissibility. The implication of this latter finding was that many young children would not have encountered the strain and that, therefore, there was every likelihood that the outbreak would continue, as subsequently proved to be the case.

(Careful consideration was given at the time to the potential risks and benefits of using mass population chemoprophylaxis in an attempt to reduce circulation of the outbreak strain. Eventually, it was decided that the unproven advantages were outweighed by the known disadvantages.)

The isolation of a substantial proportion of meningococcal strains expressing little or no capsular polysaccharide, allied to the (subsequently confirmed) long duration of carriage, suggested that down-regulation of capsule expression could be an adaptation to the nasopharyngeal carriage state. This speculation was consistent with the small body of evidence available at the time (mainly from recruit studies and from laboratory-acquired infections) suggesting that when invasive meningococcal infection occurs, it does so normally only a day or two after acquisition of a virulent meningococcus and its colonization of the throat.

Would the Stonehouse survey be appropriate now? It seems unlikely that a strong scientific case could now be argued. Two advances in our understanding of meningococci have combined to make this type of study now appear dated. The first is an appreciation of the difference between carriage and acquisition. It is the latter that is crucially important in determining the risk of invasive meningococcal disease. The second is the rapid advance in techniques for genotyping meningococci and in particular, the ability to

assign strains to particular meningococcal clones. We now know that strains of, for example, groups B, C and W-135 may be very closely related at the genetic level, and may even belong to the same clone. An additional problem with the Stonehouse survey is that it provided information about meningococcal carriage in a community experiencing a high rate of meningococcal infection. Meningococcal carriage and transmission may be quite different in communities not experiencing high rates of disease.

It seems likely then, that future studies will need to employ genetic, rather than phenotypic methods of strain characterization (or both), despite the importance of capsule type for vaccine development. Studies of acquisition, although difficult and expensive to undertake, may give a better understanding of the fascinating and still-complex relationship between man and the meningococcus. Will we understand the epidemiology and pathogenesis of meningococcal disease before it is eliminated by the development and deployment of effective vaccines? Only time will tell.

Reference

1. **Cartwright KAV, Stuart JM, Jones DM, Noah ND.** The Stonehouse survey – nasopharyngeal carriage of meningococci and *Neisseria lactamica*. Epidemiol Infect 1987; **99**: 591–601.

https://doi.org/10.1017/S0950268805004310 Published online by Cambridge University Press