Published in final edited form as:

Expert Rev Vaccines. 2009 July ; 8(7): 851–861. doi:10.1586/erv.09.48.

Meningococcal vaccines and herd immunity: lessons learned from serogroup C conjugate vaccination programmes

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Summary

Effective vaccines provide direct protection to immunised individuals, but may also provide benefits to unvaccinated individuals by reducing transmission and hence lowering the risk of infection. Such herd immunity effects have been demonstrated following the introduction of meningococcal serogroup C conjugate (MCC) vaccines, with reductions in disease attack rates in unimmunised individuals and significantly lower serogroup C carriage attributable to the vaccine introduction. In the UK targeting teenagers for immunisation was crucial in maximising indirect effects, as most meningococcal transmission occurs in this age group. Questions remain regarding the duration of herd protection and the most appropriate long-term immunisation strategies. The magnitude of the herd effects following MCC vaccination was largely unanticipated, and has important consequences for the design and evaluation of new meningococcal vaccines.

Keywords

Neisseria meningitidis; immunisation; epidemiology; herd immunity; meningococcal vaccines; conjugate vaccine; meningococcal carriage

Introduction

Neisseria meningitidis is an important cause of meningitis and septicaemia in most parts of the world. The epidemiology of meningococcal disease varies globally, but nearly all disease is caused by six (A, B, C, W-135, X and Y) of the thirteen recognised serogroups, which are defined on the basis of different immunochemical variants of the polysaccharide capsule that the bacteria can elaborate. Devastating epidemics of meningococcal disease continue to occur in the meningitis belt of sub-Saharan Africa, and elsewhere meningococcal disease is endemic, with an incidence typically less than 10 per 100,000 population^{1,2}. Despite the public health importance of the meningococcus as a pathogen, it is a commensal of the respiratory tract and is most commonly found colonising the mucosal

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Financial and competing interests disclosure: Caroline Trotter is supported by a Personal Award Scheme Post-Doctoral Award from the National Institute of Health Research (Department of Health, UK). Martin Maiden is a Wellcome Trust Senior Research Fellow in Basic Biomedical Sciences. We have no competing interests to declare.

surfaces of the human nasopharynx. Transmission from person to person occurs via aerosol droplets, and disease is a rare consequence of acquisition.

Recent progress in the prevention and control of meningococcal disease has included the development and introduction of meningococcal serogroup C conjugate (MCC) vaccines. The UK was the first country to implement a national MCC immunisation programme in 1999, followed by several other European countries, Australia, and Canada, all of which have subsequently observed substantial declines in serogroup C disease³. A large part of the success of MCC vaccines - in common with the glycoconjugate vaccines against *Haemophilus influenzae* type b (Hib) and major serotypes of *Streptococcus pneumoniae* - has been attributed to the ability of the vaccines, not only to provide direct protection against disease, but also to reduce carriage and transmission of vaccine-type bacteria in the population, thus indirectly reducing disease even in the unvaccinated⁴. This review summarises the current evidence on herd immunity resulting from immunisation with meningococcal vaccines, and provide perspectives on future challenges.

Herd immunity

In its simplest meaning, *herd immunity* refers to the prevalence of immune individuals in a population, but the term is commonly used in a broader sense to relate to the concept that the presence of immune individuals in a population can indirectly protect those who are not immune against infection^{5,6}. The rate of transmission of an infection depends upon the characteristics of the infectious agent, the frequency and patterns of contact between hosts, and the proportion of individuals who are susceptible to infection in the host population. Transmission will be highest in a fully susceptible population. The basic reproduction number (R_0) describes the number of secondary infections resulting from a single infection introduced into a fully susceptible population, and is an intrinsic measure of transmissibility. If immunological experience, as a consequence of vaccination or natural exposure, induces some degree of immunity against infection, then ongoing chains of transmission of the infection can be interrupted. The net reproduction number (R_n) describes the actual number of transmissions per infection, and is equivalent to the basic reproduction number R_0 multiplied by the proportion susceptible in the population. In order for the infection to persist in the population, each infected individual must in turn infect at least one other person (i.e. R_n must be ≥ 1). If the proportion of the population who are immune is sufficiently high (i.e. $> 1 - 1/R_0$) then R_n will fall below 1 and the infection incidence will decline; this is known as the herd immunity threshold. A substantial body of mathematical theory underpins and extends these ideas (e.g. to cover more credible scenarios where populations are not homogeneous and do not mix at random), as reviewed in detail elsewhere⁵⁻⁷.

Epidemiology of meningococcal disease and carriage

The epidemiology of meningococcal disease varies markedly by region^{1,2}. The most striking contrast is between the 'meningitis belt' of sub-Saharan Africa, which is characterised by large, periodic, epidemics of meningitis that occur during the dry season⁸, with the rest of the world, where most regions experience only endemic levels of disease. In major African

epidemics, incidence ranges from 100 to 800 per 100,000 population⁹, but attack rates in individual communities may be much higher⁸. Outside of epidemics, disease still occurs seasonally, with reported endemic incidence of around 25 per 100,000¹⁰. In Europe, the Americas and other developed countries disease incidence is typically in the range between 1 and 10 per 100,000, with occasional 'hyper-endemic' periods with persistent disease due to particular strains, such as that experienced in Norway¹¹ and Cuba in the 1980s¹² and more recently in New Zealand¹³, where incidence reached 18 per 100,000¹⁴. Meningococci are characterised into serogroups on the basis of the capsular polysaccharide that surrounds the bacteria and the distribution of serogroups causing disease varies globally. Most epidemics in Africa have been caused by serogroup A meningococci, although serogroup C – and more recently serogroup W-135 and X – outbreaks have been described¹⁵. In Europe, serogroup B and C meningococci are responsible for most disease¹⁶, whereas in the USA serogroup Y is also important¹⁷. The incidence of meningococcal disease varies by age: in developed countries incidence is typically highest in infants, and declines through childhood, with a smaller secondary peak in disease incidence in teenagers and young adults. In the African meningitis belt the burden of disease is also concentrated in 0-19 year olds, in both endemic and epidemic situations, with lower incidence generally observed in older adults (particularly those aged over 30 years)^{10,18}. Mortality from meningococcal disease remains high; for example, in Niger the case fatality of meningococcal disease (all ages) was around 12% in endemic and epidemic settings¹⁰. In European countries case fatality persists at around 7%¹⁹ despite reported improvements in survival following intensive therapy in specialist units^{20,21}.

The relationship between carriage and disease is not straightforward and carriage and disease rates are not proportional^{22,23}. For example, in industrialised countries the incidence of disease is highest in young children, whereas carriage rates peak in older teenagers. Meningococci identified in carriers are also typically genetically and antigenically more diverse than those isolated from patients with meningococcal disease²⁴. Since most transmission occurs among carriers, it is necessary to consider the carrier state as the key stage in the natural history of infection in order to understand fully the epidemiology of meningococcal disease and the impact of control measures such as vaccination (figure 1). The population prevalence of meningococcal carriage (detected by nasopharyngeal swabbing) is often quoted as 10%, but this masks the heterogeneity observed by age and by setting²⁵⁻²⁷. In general, in developed countries, carriage prevalence is low in young children, then rises to a peak in teenagers and young adults, declining again in older adults^{25,26}. In the African meningitis belt, reported overall prevalence varied from 3% to over 30% and, while meningococcal carriage was more evenly distributed by age than elsewhere, studies were not large enough to determine robust profiles of carriage by age²⁷. Although meningococcal disease is seasonal, carriage rates do not appear to vary by season.

Meningococcal vaccines

Efforts to produce meningococcal vaccines date back to the early 20th century, but the first efficacious vaccines, based on purified capsular polysaccharide, were developed in the 1960s at the Walter Reed Army Institute²⁸. Bivalent (serogroups A and C) and tetravalent (A, C, W-135, Y) polysaccharide vaccines have been available since the 1970s. Although

effective (at least in the short-term in older children and adults), their use has mainly been to disrupt outbreaks and epidemics of meningococcal disease. They have not been used in routine vaccination campaigns (despite some advocates²⁹), because, in general, polysaccharide-only vaccines are essentially T-cell independent antigens, which are poorly immunogenic in young children and only confer short-term protection.

Polysaccharide-conjugate vaccines, in which the capsular polysaccharide is attached to an immunogenic carrier protein, induce a T-cell dependent immune response, and are thus immunogenic in infants and prime for memory³⁰. This approach was first used with Hib vaccines, which were successfully introduced in many infant immunisation programmes in the early 1990s³¹. Meningococcal conjugate vaccine trials were accelerated to respond to increasing rates of serogroup C disease in the UK, leading to the licensure of three monovalent meningococcal serogroup C conjugate (MCC) vaccines (two conjugated to CRM₁₉₇ and one to tetanus toxoid) in 1999/2000³². The UK was the first country to implement a national MCC vaccine programme³², followed by The Netherlands, Spain, Canada, Australia and several other European countries³. Quadrivalent (A, C, W-135 and Y) conjugate and combination (Hib-MenC) vaccines have subsequently been developed, licensed and implemented in national programmes in the US³³ and UK³⁴ respectively. Of the other meningococcal conjugate products still under development, most prominent is the Meningitis Vaccine Project's monovalent serogroup A conjugate vaccine manufactured by the Serum Institute of India for use in the African meningitis belt. This vaccine is being evaluated in immunogenicity and safety studies (a phase III efficacy trial will not be performed) and is expected to be licensed and introduced in 2009/2010³⁵.

The third category of meningococcal vaccines is the protein-based vaccines, which are designed to offer protection against disease caused by serogroup B *N. meningitidis*; however, since the antigens are sub-capsular, these vaccines should offer protection across serogroups, depending on the prevalence and distribution of vaccine antigens, and are better termed serogroup B substitute vaccines. The capsular polysaccharide for serogroup B is particularly poorly immunogenic and, although various methods are available to improve the immunogenicity of the serogroup B capsule, including conjugation, the similarity of the B polysaccharide to a neural cell adhesion molecule raises the possibility of an autoimmune response in vaccine recipients³⁶. Alternative antigens are thus targeted for vaccine development³⁷. Strain-specific outer membrane vesicle (OMV) vaccines were developed and used in Norway³⁸, Chile³⁹, Cuba¹², Brazil⁴⁰ and New Zealand¹⁴. The Cuban vaccine (VA-Meningoc-BC) also includes serogroup C polysaccharide component. These vaccines are suitable when one particular strain is dominant, but in most endemic situations serogroup B strains causing disease are diverse. For broader protection against multiple strains, vaccines containing up to nine OMVs are under development⁴¹. More recently, 'reverse vaccinology' has been used to identify novel vaccine candidates based on genomic sequences, including factor-H binding protein⁴².

Meningococcal vaccines and herd immunity

Vaccine trials and post-licensure surveillance of meningococcal vaccines have evaluated their safety, immunogenicity, and effectiveness. The primary outcomes relate to individual

protection of immunised individuals, measured directly through assessment of disease risk, or indirectly through assessment of immunologic correlates of protection⁴³. This focus on individual protection may underestimate the population impact of a vaccination programme⁴. In relation to herd immunity, the critical property of meningococcal vaccines, and indeed other vaccines against colonising bacteria, is whether they are able to offer protection against carriage acquisition and onward transmission (figure 1). A recent systematic review addressed this question⁴⁴. Although many studies were not optimally designed to detect these effects, there was some evidence that meningococcal polysaccharide vaccines could reduce carriage incidence in some settings (e.g. military establishments), but were unlikely to interrupt population transmission of an epidemic strain⁴⁴. Three randomised controlled trials of OMV vaccines targeted against serogroup B strains failed to demonstrate an effect against carriage⁴⁵⁻⁴⁷. Much more convincing evidence of a vaccine effect on colonisation exists in the case of meningococcal serogroup C conjugate vaccines, which is reviewed in detail below.

The mechanisms by which meningococcal vaccines exert herd immunity are poorly understood⁴⁸. By measuring carriage prevalence before and after immunisation, it is possible to confirm whether carriage rates are reduced, but this could be due to either lower rates of carriage acquisition in vaccinees, more rapid clearance of infection, or both. Detailed longitudinal carriage studies are required to establish the relative contribution of these effects. Correlates of protection are well defined for meningococcal disease (at least for serogroup C)^{49,50}, but there are no equivalent immunological correlates of protection against meningococcal carriage, so carriage must be measured directly through pharyngeal swab sampling. Since meningococci colonise the mucosal surface of the nasopharynx, immune responses at the local mucosal level may be important⁵¹, but are more difficult to measure than serological markers of immunity. The importance of these local antibodies relative to serum antibodies that leak into the mucosa remains to be determined.

Experience with meningococcal serogroup C conjugate vaccines

United Kingdom

From 1995, the UK experienced an increase in morbidity and mortality due to serogroup C meningococcal disease, predominantly because of the introduction and spread of a hyperinvasive clone associated with the sequence type (ST) 11 clonal complex. In response, at the end of 1999 the UK implemented a national MCC vaccination programme. MCC vaccines were incorporated into the routine infant immunisation schedule at 2,3,4 months of age and a catch-up campaign targeting all those aged up to 18 years was launched. The vaccine was well accepted and routine coverage remains consistently above 90%. Uptake in the catch-up campaign varied by age group, with over 75% of pre-school children and over 85% of school children aged 5-16 immunised. Coverage was lower in 17-18 year olds in school (~65%) and for those out of education (~40%)⁵². The catch-up campaign was rolled out over 12 months, with older teenagers and young children, i.e. those assessed to be at highest risk of disease, targeted first. The winter of 2000/2001 was therefore the first opportunity to observe the full effect of the vaccine campaign. Cases of serogroup C disease declined rapidly: by 2007/08, fewer than 30 cases occurred, a decrease of over 97%

compared to 1998/99 (figure 2). This success was attributed to both high vaccine effectiveness (direct protection), and to herd immunity (indirect protection).

A formal randomised efficacy trial had not been performed prior to the introduction of MCC vaccines into the UK, and high quality post-licensure surveillance was essential for assessment of the performance of the vaccine programme³². In parallel with enhanced disease surveillance activities, a major research study was undertaken to investigate the impact of MCC vaccines on the prevalence of meningococcal carriage and the effect on meningococcal population biology^{53,54}. Evidence from both of these sources was necessary to understand the importance of herd immunity.

Direct protection in England was measured by estimating vaccine effectiveness using the screening method⁵⁵. In the first year following immunisation, effectiveness was high (above 87%) in all age groups. Over a longer time period (1-4 years post-immunisation), vaccine effectiveness waned slightly but remained high in children targeted in the catch-up campaign⁵⁶; however, in children immunised with a 2, 3, 4 month schedule, direct protection did not persist more than 1 year after immunisation⁵⁶. The fact that serogroup C disease remained low in routinely vaccinated cohorts, despite the lack of direct protection, was attributable to herd immunity. Indirect protection was measured using surveillance data by estimating the percentage reduction in the attack rate in vaccinated compared with unvaccinated children in the same birth cohorts⁵⁷. The attack rate in unimmunised individuals was significantly lower in 2001/02 (post-MCC introduction) compared to 1998/99 (pre-MCC introduction)⁵⁷. Overall, in the age groups targeted for catch-up immunisation, a reduction of 67% (95% confidence interval 52% to 77%) in the attack rate was observed, with a range of 48% to 80% across the age groups. For older adults not eligible for vaccination (>25 years), the incidence was 35% lower (95% CI 20% to 29%). This decline in attack rates could possibly be explained by a natural decline in the incidence of serogroup C disease, rather than as a consequence of vaccination. This alternative explanation seems unlikely because the incidence in 19-24 year olds, who were not initially targeted for vaccination, continued to increase in 1999/00 and 2000/01. In addition, further evidence supporting substantial herd immunity effects was obtained by measuring the effect of mass immunisation on carriage prevalence itself.

A large multi-centre study in the UK was designed to measure the prevalence of meningococcal carriage, particularly serogroup C, in teenagers at the time of vaccine introduction in 1999, and again 1 and 2 years after vaccination in 2000 and 2001^{53,54}. The study focused on teenagers, because serogroup C carriage was known to be rare and, since older teenagers are the most prevalent carriers, such a study would have maximum power to detect a difference in prevalence before and after vaccination. Over 14,000 teenagers were recruited to each round of the study. The overall meningococcal carriage rate was 16.7%, 17.7% and 18.7% in 1999, 2000, and 2001 respectively; the increase over time possibly reflects improved sampling efficiency. Serogroup C carriage declined significantly from 0.45% in 1999 to 0.15% in 2000 ($p=0.0013$)⁵³. This reduction was sustained in 2001 (rate ratio 2001:1999, 0.19, $p<0.001$)⁵⁴.

While these prevalence measures were extremely useful in interpreting the changes to meningococcal disease epidemiology, in combination with disease surveillance data, the evidence collected was also pertinent for addressing broader questions about the effect of MCC vaccines on meningococcal biology. The meningococcal capsule is synthesised by enzymes encoded by genes at the *cps* region of the chromosome (figure 3). Some meningococci are acapsulate due to the lack of genes at this region (capsule null, *cnl*); whilst in other acapsulate meningococci the expression of synthesis genes is down-regulated by various mechanisms^{58,59} Genetic exchange at this region can result in changes in the capsule expressed either by exchanges of the whole region or, in the case of the sialic acid containing capsules (corresponding to serogroups B, C, Y, and W-135), of the *siaD* gene⁶⁰

Genotyping of the *siaD* locus of carried meningococci collected before and after the introduction of MCC vaccines in the UK demonstrated that the reduction in serogroup C carriage prevalence was due to both a decrease in the number of organisms containing the serogroup-C specific allele (*siaD_C*) and lower rates of expression of this gene⁵⁴. These data were consistent with the MCC vaccine having a greater effect on ST-11 complex meningococci carrying the *siaD_C* allele, probably because of the high degree of capsule expression within this clonal complex, although the reasons for this are not fully understood. The implications of this finding however are very important: the large herd immunity effects observed against ST-11/*siaD_C* strains may not be seen in situations where other meningococci are dominant. This cautions against extrapolating the UK experience with MCC vaccines to vaccines against other serogroups, or indeed the use of MCC vaccines in different epidemiological situations⁴⁸. Another important finding from the carriage studies was that there was no major increase in carriage of other serogroups, and no evidence of capsule replacement among carrier isolates⁵⁴. Analysis of disease trends also provided no evidence for widespread capsular switching or capsule replacement⁶¹.

Mathematical modelling studies have enhanced our understanding of herd immunity following MCC vaccination⁶². Although these models are simplifications, they provide a number of advantages including the opportunities of assessing a much broader range of vaccine strategies than could be tested experimentally, and investigating the sensitivity of effects to changes in different parameters. In order to capture herd immunity effects, it is appropriate to employ age-structured transmission dynamic models⁶³ and, since most transmission of meningococci occurs among carriers, these models must incorporate both carriage and disease dynamics. The other key features of the models are that: vaccinated individuals are protected to some degree (66% in the base case) against carriage acquisition; individuals are assumed to be colonised by only one serogroup; contact patterns are assumed to be highly assortative by age (i.e. individuals are much more likely to contact other individuals of a similar age than those who are older or younger); the risk of disease given infection is age-specific and is highest in the youngest children^{23,62}. Comparisons of the observed number of cases of serogroup C disease with the predicted number of cases for models that do and do not include a parameter that reduces the risk of serogroup C acquisition in vaccinated individuals show that the model that does not include this herd immunity mechanism greatly overestimates the number of cases of disease (figure 4). This comparison also emphasises the scale of herd immunity experienced in England & Wales.

The transmission models underline the importance of targeting teenagers, in whom meningococcal carriage is most common, in order to maximise these indirect effects.

Other countries

MCC vaccines were introduced into routine publicly funded immunisation programmes in Ireland and Spain in 2000, Canada in 2001, The Netherlands, Iceland and Belgium in 2002, Australia in 2003 and later in 2006 in Portugal, Germany, Switzerland, and Greece, which had offered MCC privately since 2001 ³⁶⁴ (www.euvac.net). Catch-up campaigns were conducted in Ireland (up to 23 years), Spain (variable by regions, but minimum of up to 6 years initially, extended to 18 years subsequently), Canada (variable by region⁶⁵) The Netherlands (1 to 19 years), Iceland (up to 20 years), and Portugal (up to 18 years). In the case of the early implementers, all experienced substantial declines in serogroup C disease following MCC vaccine introduction ³⁶⁴. Vaccine effectiveness was formally evaluated in Spain⁶⁶ and Quebec⁶⁷, Canada. In both countries short-term (within 1 year) vaccine effectiveness was high in all age-groups, with Spanish data also showing a decline in effectiveness in the longer term in children immunised in infancy with a 2, 4, 6 month schedule⁶⁶.

A number of observations were made with respect to herd immunity during MCC introductions in these countries. In The Netherlands, a single dose of MCC vaccine at 14 months of age was implemented in the routine programme with a one-off catch-up campaign, a decision largely influenced by cost-effectiveness studies ⁶⁸. Despite the lack of direct protection in infants, the number of cases in children under 14 months old fell from 20 in 2001 to just 1 in 2004 and the number of cases in adults too old to be targeted for immunisation also declined ⁶⁹. These reductions were most likely a consequence of decreased population transmission following widespread MCC immunisation, although alternative explanations cannot be excluded. In Spain, herd immunity effects following MCC introduction were much less marked than in England or the Netherlands, with no discernible effect in unvaccinated infants ⁶⁶. This may be because the Spanish catch-up campaign only initially targeted children up to the age of six years, and did not immunise teenagers, in whom carriage prevalence is highest ⁶⁶. The most important reservoir of carriers thus remained unimmunised, and population transmission is unlikely to have been reduced. The results from mathematical models are consistent with these observations^{16,62}. In Canada, two papers have reported on attack rates in unvaccinated groups following the introduction of MCC vaccines. In Quebec, the incidence of serogroup C disease decreased among unvaccinated individuals in the target population (<20 years), but it was unchanged in those over 20 years of age who were not immunised ⁶⁴. In contrast, temporal trend analysis of disease incidence data by age and serogroup in Ontario showed a decline in serogroup C disease in both those aged <20 years and adults ≥20 years⁷⁰.

Remaining questions regarding MCC immunisation

The indirect protection arising from MCC vaccination to date has been striking, but it is not clear how long herd immunity will persist and whether changes to the current immunisation programmes will be required to maintain these effects in the longer term. In the UK, cases of serogroup C disease remain rare (figure 2), despite observed waning of direct protection in

children immunised at 2,3,4 months of age⁵⁶, and modest seroprotection in younger children^{71,72}. Assuming that circulating antibody is the best correlate of protection, even in the presence of immune memory, there is a cohort of children in the UK who may be susceptible to serogroup C disease as they enter teenage. Such reduced levels of individual protection will only be relevant if transmission of serogroup C disease increases⁷³. Mathematical models predict that: (i) indirect effects will persist for several more years; and (ii) when transmission increases, it will do so slowly, because the estimated R_0 for serogroup C meningococci is low at around 1.3, i.e. they are not highly transmissible²³. The models, however, do not take into account possible introductions of novel, more-transmissible serogroup C strains from other countries. This is an important limitation as such introductions do occur; the spread of the ST-11 clonal complex in many European countries in the 1990s, which led to the MCC vaccine introduction, providing an example. These events cannot be predicted and, for this reason, emphasis remains on ensuring continued high-quality disease surveillance.

Reducing transmission of vaccine-type meningococci in the population is largely seen as a positive outcome of vaccination. However, there was concern at the time of MCC introduction that selective vaccination could drive capsule switching and/or capsule replacement, thus eroding the benefits of MCC immunisation⁷⁴. In Spain^{75,76} and Canada⁷⁷, clinical isolates with characteristics suggestive of capsule switching have been reported following mass MCC immunisation, although case numbers remain low. There is no evidence to date that widespread capsular replacement has occurred following MCC introduction⁶¹, however since this remains a theoretical possibility (which has been observed following pneumococcal conjugate vaccination⁷⁸) continued surveillance remains essential. It may also be important to consider the potential negative consequences of preventing natural exposure. For example, if carriage is reduced natural boosting will also be decreased, potentially leading to lower levels of natural immunity⁴⁸. This lack of natural boosting was thought to be an important factor in the re-emergence of Hib disease in adults in the UK, in whom antibody levels had fallen following Hib vaccine introduction⁷⁹. This may be less important for MCC vaccines than for other meningococcal vaccines, because serogroup C colonisation was rare and exposure to serogroup C probably did not contribute a great deal to the development of natural immunity.

Implications of the MCC experience for other meningococcal vaccines

While the MCC experience highlights the potential indirect effects that can be achieved with meningococcal vaccines, it is not advisable to extrapolate the effects of this vaccine to others and careful evaluations are required in each case. For herd immunity to be convincingly demonstrated studies of disease rates in the unvaccinated, and carriage studies showing a reduction in the targeted strain will be necessary in either observational studies or, more robustly, using community or cluster randomised controlled trials. Observational studies are likely to be more feasible, given the precedent for meningococcal vaccine licensure on the basis of immunogenicity and safety studies, but with observational rather than experimental studies, it will not be possible to rule out alternative explanations for observed results (e.g. 'natural' fluctuations in incidence).

In the US, a quadrivalent (A, C, W-135, Y) meningococcal conjugate vaccine has been licensed since 2005, and is currently recommended for routine adolescent immunisation. Vaccine coverage in 2007 was modest (32%)⁸⁰ and disease incidence is low, so it is unlikely that indirect effects on disease will be observable. A carriage study performed among US high school students, with the aim of investigating changes in carriage pre- and post immunisation, reported very low overall carriage prevalence, with too few carriers of serogroups included in the vaccine to measure any vaccine effect⁸¹.

The Meningitis Vaccine Project's serogroup A conjugate vaccine will first be introduced into Burkina Faso in 2009/10 in a demonstration project, before being rolled out across other countries of the meningitis belt³⁵. The vaccine strategy is to target 1-29 year olds in a mass immunisation campaign. This age range was chosen because the burden of disease is concentrated in those under the age of 30 years and because one dose of vaccine is sufficiently immunogenic in those aged 1 year or above (clinical trials are ongoing in infants, who would likely require more than one dose for sustained protection). It is also hoped that significant herd immunity will result from immunising such a large proportion of the population, as observed with MCC vaccines in the UK and in The Netherlands (the latter example being particularly relevant as Dutch infants were not immunised with MCC). There is certainly room for optimism that this strategy will be successful, but careful studies of the vaccine's effect on disease and carriage are essential. Meningitis surveillance in Africa typically relies on a simple case definition that can be applied in any health care setting, with the aim of rapidly detecting emerging epidemics⁹. Relatively few cases are laboratory confirmed but in many countries surveillance systems have been strengthened by the use of PCR testing to confirm diagnoses and identify serogroups⁸². Given the limited resources available in these settings, establishing comprehensive surveillance that is sufficiently robust enough to determine the relative contributions of direct and indirect vaccine effects will be challenging, although data on disease incidence before and after vaccine introduction should be available. The importance of confirming the vaccine's effect on carriage has also been recognised and carriage studies in across the meningitis belt are being performed. The change in prevalence of serogroup A carriage before and after vaccine introduction will be evaluated in at least 4 countries; having multiple sites is important because several recent studies have detected no or very low serogroup A carriage in non-epidemic situations. Large cross-sectional studies will also be conducted in a larger range of countries to better define the epidemiology of carriage across the belt, leading to a greater understanding of the patterns of meningococcal transmission and the prevalence of carriage by age. This will inform vaccine strategy, e.g. which population groups drive transmission and should therefore be targeted for vaccination in order to maximise herd immunity, and contribute to the parameterisation of mathematical models.

There is no evidence that OMV vaccines used to date have had any impact on the prevalence of carriage of the targeted strain⁴⁴. The new generation of serogroup B substitute vaccines contain previously unused proteins, such as factor-H binding protein³⁷ and it is difficult to make predictions about the likely effect of these vaccines on carriage, particularly since the immune mechanisms by which MCC vaccines are able to prevent carriage are poorly defined. However, this is clearly an important question to address, because whether the vaccine has the ability to prevent carriage will influence both the vaccine strategy, for

example whether to target the age-group with the highest incidence of disease or the highest incidence of carriage, and the cost-effectiveness of vaccine implementation. In addition, if the vaccine antigens are commonly expressed in a large proportion of meningococci, these vaccines could potentially have much greater effects on meningococcal population biology.

Expert opinion

The UK was the first country to adopt MCC vaccines, and the data collected following MCC introduction have been crucial in informing our understanding of the way these vaccines work. The experience of other countries, where different schedules have been used, has added to the body of evidence confirming the contribution of herd immunity to the success of MCC immunisation programmes. To understand the impact of any vaccination programme, continuing high-quality disease surveillance is essential. The value of carriage studies in providing additional information in relation to vaccine effects on meningococcal population biology has also been demonstrated. The MCC experience cannot be extrapolated to other meningococcal vaccines and careful studies are needed in each case. Further research is also required to improve our understanding of the mechanisms underlying herd immunity (e.g. to investigate the role of mucosal immunity, to define correlates of protection against carriage).

Five year view

Surveillance of serogroup C disease will continue, and the long-term effects of MCC vaccination will be evaluated, addressing issues such as the duration of herd immunity. The Meningitis Project's serogroup A conjugate vaccine is expected to be introduced for 1-29 year olds in Burkina Faso in 2009/2010 and studies are underway in countries in the African meningitis belt to evaluate the impact of this vaccine on both disease and carriage. New protein-based vaccines aiming to prevent serogroup B meningococcal disease are also likely to become available in industrialised countries, and will also require rigorous evaluation.

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Key issues

- Meningococcal serogroup C conjugate vaccines are safe and effective.
- In England and Wales MCC vaccine programmes resulted in substantial herd immunity, as shown by reductions in serogroup C carriage prevalence and serogroup C disease in unvaccinated individuals.
- Immunising teenagers, the most prevalent carriers of meningococci, was important in generating herd immunity.
- MCC vaccination had important consequences for meningococcal population biology and carriage studies were essential in measuring these effects.
- The potential for herd immunity should be taken into consideration by policy makers deciding vaccine strategy.
- Similar herd effects are yet to be demonstrated for other meningococcal vaccines.

Figure 1. Transmission of meningococci in the population

Figure 2. Cases of laboratory-confirmed serogroup C disease in England & Wales by age-group and year (July to June), July 1993 to June 2007.

Source: Health Protection Agency Centre for Infections and Meningococcal Reference Unit.

Figure 3. Diagrammatic representation of the *cps* region in meningococci that express sialic acid containing capsules.

Genes are represented by arrows, which point in the direction of transcription. The genetic organisation of capsule null (*cnl*) meningococci, which cannot express a capsule, is shown for comparison. Exchanges of the *siaD* gene result in capsule switching among the different serogroups. After Claus H, et al 2002⁸³ and Dolan-Livengood JM et al, 2003⁵⁸.

Figure 4. Observed reduction in serogroup C disease in England & Wales, compared to model predictions with and without herd immunity.