The impact of meningitis vaccines and their future role

MARK GREENER

The success of the meningococcal group A (MenA) vaccination in the African meningitis belt, public support for the extension of the MenB vaccination in the UK and the importance of vaccination in the fight against antimicrobial resistance all endorse the need for additional meningitis vaccines in the future.

Public perception can make or break a vaccine programme. Vaccine coverage plummeted in the wake of the now discredited link between autism and the MMR vaccine, although rates have since recovered. According to the Health and Social Care Information Centre (HSCIC), 92.3 per cent of children in England had received the MMR jab by the age of 24 months during 2014–15 compared with 79.9 per cent in 2003–4 at the height of the misplaced concerns.

Yet the public’s attitude to vaccines seems, to put it mildly, incongruous. MPs are now obliged to debate extending the meningococcal group B (MenB) vaccination from one year up to 11 years of age after the most-signed petition in UK parliamentary history. The petition reflects the vaccine programme’s remarkable success in the fight against meningitis.

But there is no room for complacency. There is a pressing need for additional meningitis vaccines to extend protection against this deadly disease and to reduce antibiotic use. Indeed, as the Review on Antimicrobial Resistance (AMR) noted recently, vaccines could help avert the ‘antibiotic apocalypse’. Yet, the report identified major gaps in vaccine coverage and uncovered little evidence that they will be bridged any time soon.

“An amazing success”

Few healthcare professionals need convincing that vaccines are one of the most effective public health measures. Gavi, an organisation that improves access to vaccines in the world’s poorest countries, estimates that immunisations save between two and three million lives a year globally.

The UK’s national routine vaccination programme provides more than 20 vaccines to infants, children, the elderly and vulnerable groups. As a result, many diseases – including smallpox, measles, polio, diphtheria and tetanus – are medical curiosities rather than the widely feared causes of death and disability that they were for much of the last century. The introduction of the rotavirus vaccines seems to have cut the number of infections by 77 per cent and hospitalisations
MenAfriVac has almost eliminated serogroup A meningococcal disease from the African meningitis belt in just five years. Cases fell from more than 250,000 during a 1996 outbreak to 80 confirmed cases in 2015, delegates heard at the Meningitis Vaccine Project Closure Conference held in Addis Ababa, Ethiopia in February. The cases occurred in countries without mass immunisation and among unvaccinated people.

Since MenAfriVac’s introduction in Burkina Faso in late 2010, 16 of the 26 countries in the meningitis belt, which runs from Senegal to Ethiopia, have conducted mass vaccination campaigns, immunising more than 235 million people aged between one and 29 years of age. Five countries will conduct campaigns this year either nationwide or in high-risk areas. The remaining five countries are expected to target high-risk areas in 2016/17. Many countries in the meningitis belt plan to include MenAfriVac in their national childhood vaccination programmes.

“MenA vaccination in the African meningitis belt has been an amazing success,” says Claire Wright, medical information manager at the Meningitis Research Foundation (MRF). “The number of cases and the case-mortality rate in this part of Africa is much higher than in the UK. But the dramatic reductions as the programme was rolled out across the meningitis belt underscores the efficacy of vaccines.” On the other hand, the relatively small number of meningitis cases each year in the UK sometimes breeds a degree of complacency. “A minority of parents would rather rely on herd immunity than expose their child to a perceived risk of vaccine-related harm,” she told Prescriber.

Indeed, vaccines are victims of their own success. I suffered German measles and mumps as a child. Almost 50 years later, I can still recall how dreadful I felt, especially with mumps. Today’s parents do not generally appreciate how unpleasant and dangerous measles, mumps or diphtheria are. They are more familiar with, for instance, autism spectrum diseases. As Miton and Mercier noted recently: “The very efficacy of vaccination has rendered the threat from vaccine-preventable diseases much less salient.”

Nevertheless, meningitis carries a “fear factor” that is not shared by some other childhood diseases prevented by vaccination. “The recent pictures in the media of Faye Burdett and others who tragically died of this disease have been harrowing. The disease can rapidly become fatal, yet the symptoms of meningitis overlap with other milder illnesses making it particularly difficult to spot in the early stages. So, parents are often more worried about meningitis than some other infections,” Ms Wright comments.

In addition to MenB, children receive the Haemophilus influenzae type b (Hib), pneumococcal and MenC vaccines in the first few months of life, followed by a booster just after their first birthday (see Table 1). This timing might increase engagement with health services and protect against negative views perpetuated through lay networks that could contribute to the lower coverage with later boosters, such as MMR.

Nevertheless, few regions meet the WHO target of “at least 95 per cent” coverage. In 2014–15, according to the HSCIC report, 92.1 per cent of children in England had received the combined Hib/MenC booster by two years of age. Coverage varied from 95.6 per cent in the North East to 86.8 per cent in London. At five years of age, only the North East (95.7 per cent) and Yorkshire and Humber (95.2 per cent) met or exceeded the WHO target in 2014–15. Nevertheless, Ms Wright notes: “The introduction of the Hib/MenC vaccine virtually wiped out the cases of meningitis caused by these pathogens. There is now only a handful of cases each year.”

**MenB and MenW vaccination**

From September 2015, babies born on or after 1 July 2015 have been routinely immunised with the conjugate Haemophilus influenzae type b (Hib), pneumococcal and MenC vaccines at 6 weeks, with a second dose at 12 months. The wastewater monitoring programme for rotavirus infections has shown a 40% reduction in the number of rotavirus-related acute gastroenteritis cases in both England and Wales. This reduction has continued into the second year of the rotavirus immunisation programme. A single dose of the conjugate Hib/MenC booster is now given at 12 months, with a second dose at 24 months.

**Rotarix reduces rotavirus infections by 77 per cent**

From 1 July 2013, the childhood immunisation programme has routinely offered all babies a rotavirus vaccine (Rotarix) at two months and at least four weeks later. Public Health England’s (PHE’s) sentinel programme suggested that between February 2014 and March 2015, routine rotavirus vaccine coverage averaged 93.3 and 88.3 per cent for one and two doses respectively. “In children younger than five years in the UK, this infection has been responsible for around 140,000 GP visits and 14,000 hospitalisations every year and the immunisation programme is preventing a significant number of young infants from developing this infection,” says Shamez Ladhani, consultant in the Immunisation, Hepatitis and Blood Safety team at PHE.

Most rotavirus infections occur between January and March. The number of rotavirus laboratory reports in England was 67 and 69 per cent lower in the 2013/14 and 2014/15 seasons respectively compared with the 10-season average between 2003/2004 and 2012/13. In addition, a Freedom of Information request posted on the PHE website revealed that between July 2012 and June 2013, there were 1214 rotavirus-coded hospitalisations among children under one year of age. Between July 2013 and June 2014, hospitalisations fell to 424.

“The rotavirus vaccine has resulted in a rapid reduction in the burden of the virus. Latest figures for July to September 2015 show that uptake of the vaccine remains high at 89.3 per cent, resulting in around 70 per cent fewer laboratory reports of cases than prior to the introduction of the programme,” says Dr Ladhani. “We have seen a 77 per cent decline in rotavirus infections and 26 per cent fewer hospitalisations for vomiting and diarrhoea in infants within 12 months of starting the programme. Older children and adults are also benefiting from the infant rotavirus immunisation programme through herd protection. These reductions have continued into the second year of the rotavirus immunisation programme.”

**Box. Rotavirus vaccine success**
offered the MenB vaccine (Bexsero). Ms Wright believes that the programme could cut the number of cases of meningitis in babies caused by MenB by up to 90 per cent. However, in its response to the petition, which – at the time of writing – still needs to be debated by MPs, the Department of Health claimed that offering the vaccine outside of the recommendations made by the Joint Committee on Vaccination and Immunisation (JCVI) “would not be cost-effective”.

The MRF would like to see all age groups protected from MenB. But further research is needed to target MenB vaccine most effectively. The charity accepts that extending vaccination to, for example, 11 years of age would not prove cost effective. Instead, Ms Wright suggests that targeting teenagers might be the key to protecting people of all ages.

According to Ms Wright, about one in four teenagers carries meningococcal bacteria in their nose or throat, compared with about one in 10 of the rest of the population. “If the vaccine is found to prevent acquisition and carriage of bacteria then vaccinating teenagers might be a cost-effective approach, which will prevent transmission and ensure herd protection across the whole population,” she says. “The JCVI suggested assessing the effectiveness of targeting teenagers in 2014, but nothing’s been done. The study needs backing from central government as many teenagers in the UK would need to be offered the vaccine. I hope that the current political momentum for increased coverage will persuade the government to begin the study. We don’t want to lose the groundswell of support, but it needs to be channelled properly, so that we can demonstrate a compelling cost-effective argument to protect the wider population by immunising teenagers.”

In response to the outbreak, Public Health England (PHE) called for emergency vaccination of all 14 to 18-year-olds, who will be offered the MenACWY vaccine, which protects against meningitis A, C, W and Y, by late summer 2017.

Two months old
- 5-in-1 (DTaP/IPV/Hib) vaccine (for diphtheria, tetanus, whooping cough (pertussis), polio and Haemophilus influenzae type b)
- Pneumococcal conjugate (PCV) vaccine
- Rotavirus vaccine
- Meningococcal group B (MenB) vaccine (introduced September 2015)

Three months old
- 5-in-1 (DTaP/IPV/Hib) vaccine, second dose
- MenC vaccine
- Rotavirus vaccine, second dose

Four months old
- 5-in-1 (DTaP/IPV/Hib) vaccine, third dose
- PCV vaccine, second dose
- MenB vaccine second dose (introduced September 2015)

12–13 months old
- Hib/MenC booster, given as a single jab containing MenC (second dose) and Hib (fourth dose)
- Measles, mumps and rubella (MMR) vaccine, given as a single jab
- PCV vaccine, third dose
- MenB vaccine third dose (introduced September 2015)

Two, three and four years old plus school years one and two
- Children’s flu vaccine (annual)

From three years and four months old (up to starting school)
- MMR vaccine, second dose
- 4-in-1 (DTaP/IPV) preschool booster (for diphtheria, tetanus, whooping cough (pertussis) and polio)

12–13 years old (girls only)
- Human papilloma virus (HPV) vaccine (for cervical cancer – two injections given between six months and two years apart)

13–18 years old
- 3-in-1 (Td/IPV) teenage booster (for diphtheria, tetanus and polio)
- MenACWY vaccine

19–25 years old (first-time students only)
- MenACWY vaccine

65 years old and over
- Flu (every year)
- Pneumococcal polysaccharide (PPV) vaccine

70 years old (and 78 and 79-year-olds as a catch-up)
- Shingles vaccine

Table 1. Current NHS vaccination schedule (routinely offered to everyone in the UK on the NHS)“ST-11 is a particularly virulent and deadly strain,” Ms Wright explains. “This is the same strain that has been causing epidemic disease in Argentina, Brazil and Chile, where it is associated with a death rate of 28 per cent compared to 10 per cent for other strains in the country.”
“We expect to see a reduction in carriage and a protective effect in the wider population arising from the vaccination of teenagers against ST-11,” Ms Wright remarks. “It’s relatively easy to vaccinate 14 to 16-year-olds at school. It’s much harder to reach older teenagers as they are about to go to college or start work. Vaccination is often the last thing on their mind. That might be why the take-up of MenW doesn’t seem to have been as great as we had hoped.” PHE has not yet published uptake figures for the MenACWY vaccination programme.

From carriage to infection
While carriage of the pathogens responsible for meningitis is common, thankfully relatively few people develop meningitis. The risk that carriage will develop into infections seems to depend on the interplay of genetic and environmental factors. Ms Wright notes that teenage behaviour – such as smoking, living in close proximity, kissing and so on – dramatically increases the chance of acquiring the bacteria. But what triggers an infection is less clear. The answer may reside in the MRF Meningococcus Genome Library, a unique database of meningococcal meningitis in the UK. The library, which includes genomes of meningococcal strains responsible for clinical cases of meningitis, helped identify the virulent strain of meningococcal W as ST-11. Currently, researchers are also using the library to match genomes of patients who developed clinical meningitis with the genomes of the strains responsible. “In the future, understanding the interaction between the host and the pathogen should help us understand why some people are susceptible to the infection and why some people are not,” Ms Wright comments. “This should help us develop new approaches to treatment and prevention as well as – as we saw with ST-11 – helping inform policy.”

The need for a group B Streptococcus vaccine
Despite the successes of meningitis immunisation worldwide, the MRF stresses that there is still a pressing need for novel vaccines. “There is, for example, currently no vaccine for mothers against group B Streptococcus, which can cause meningitis in neonates within the first few weeks of life,” Ms Wright says.

Between 20 and 30 per cent of adults in the UK carry group B Streptococcus (also called β-haemolytic streptococci and Streptococcus agalactiae), according to Group B Strep Support (GBSS), which is the UK’s most common cause of life-threatening infection in newborn babies and of meningitis in babies up to three months. Between 2003 and 2005, Group B Streptococcus was indicated in 32 per cent of neonatal death certificates that specified a bacterial infection. Indeed, Group B Streptococcus contributed to 11 per cent of all infection-related neonatal deaths and causes preterm delivery, maternal infections, stillbirths and late miscarriages.

“The rate of early-onset group B streptococcal infections in babies in the UK has risen since the UK’s risk-based prevention strategy was introduced in 2003, despite predictions that it would fall by as much as 50 per cent. At least 500 UK babies a year are now infected with group B Streptococcus. Of these, one in 10 dies,” Jane Plumb MBE, GBSS chief executive told Prescriber. “Half of the survivors of meningitis caused by group B Streptococcus suffer long-term mental and physical problems.

“A maternal vaccine has the potential to prevent more cases of group B streptococcal infection than any other strategy, including most early-onset infections, preterm labour and stillbirths, postdelivery infection in the mother and late-onset infection in the baby caused by group B Streptococcus, for which no prevention strategies currently exist,” Ms Plumb remarks. “Such vaccines may also reduce the smaller but still important burden of group B streptococcal disease in the elderly.

“Significant investment into developing a vaccine against group B Streptococcus is urgently needed and should be prioritised,” Ms Plumb adds. “Unfortunately, a safe and effective maternal Streptococcus vaccine is probably at least 10 to 15 years away from being widely available. But given the length of the negotiations between the developer and the UK government on the MenB vaccine, this may be an underestimate, and we must do more to protect babies until it is available.”

For example, GBSS wants every pregnant woman to routinely receive information on group B Streptococcus during antenatal care. In addition, low-risk pregnant women should be offered testing for group B Streptococcus colonisation at 35–37 weeks of pregnancy using Enriched Culture Medium (ECM), which PHE’s UK Standard suggests is gold-standard method. If ECM tests are not freely available, the charity wants the NHS to inform pregnant women that the tests are available privately. “At the moment, most pregnant women never hear about group B Streptococcus, so how can they make an informed decision about what’s right for them and their babies?” Ms Plumb asks.

Babies are at higher risk when their mothers carry the bacterium during pregnancy or have previously had a baby with group B streptococcal disease. UK guidelines recommend that women whose newborn babies are at higher risk of developing group B streptococcal infection should be offered intravenous antibiotics from the start of labour and at intervals until delivery. So, a vaccine would help limit antibiotic use. “Vaccination against group B streptococcal infection would avoid the small but real risks of allergic reactions to the recommended antibiotics and concern about the emergence of antibiotic-resistant bacteria,” Ms Plumb adds.

Boosting antimicrobial stewardship
Vaccination’s role as part of antimicrobial stewardship is attracting increasing interest. In its report Vaccines and Alternative Approaches: Reducing Our Dependence on Antimicrobials, the independent Review on AMR notes that “there has been international recognition of the importance of vaccines and other interventions as part of the package of measures to combat antimicrobial resistance”.

“Universal coverage with a pneumococcal conjugate vaccine, something that is already used in many parts of the world, could largely prevent the 800,000 yearly
deaths of children under five years caused by Streptococcus pneumoniae,” Lord Jim O’Neill, chairman of the Review on AMR commented at the report’s launch. “It could also prevent over 11 million days of antibiotic use in these children, reducing the chance of resistance developing.” Indeed, universal coverage with the Str. pneumoniae vaccine could cut antibiotic use for this infection by 47 per cent.

Unfortunately, the report identified some yawning chasms in vaccine coverage and little evidence that pharmaceutical companies will bridge these gaps. Escherichia coli, Clostridium difficile, Klebsiella and drug-resistant gonorrhoea are probably the most pressing AMR threats. The report notes that a vaccine against certain E. coli strains – notably those causing diarrhoea, urinary tract infections (UTIs) and bacteraemia – “would be of enormous global benefit”. Several programmes found only two candidate vaccines, both in early clinical development, and both focusing on E. coli UTIs. However, as many bloodstream infections caused by E. coli arise from a UTI, the vaccine could prevent bacteraemia. Vaccines are being developed for C. difficile, but not, the review found, for Klebsiella or drug-resistant gonorrhoea.

On the other hand, in 2013, more than 70 vaccines were in development for viral infections other than HIV, with many targeting respiratory diseases, such as influenza. How many will reach the market remains a moot point, however. As the Review on AMR noted: “Extensive basic research before 2007 had resulted in at least seven candidates for Ebola vaccines that had been tested in animals with promising results. However, due to lack of investment and the lack of a market during nonepidemic periods, most of these vaccines were languishing in the pipeline when the crisis hit.”

Adverse public perception is one reason why some vaccines never reach the market. The Review on AMR noted that the MMR vaccine scare in the UK and a Lyme disease vaccine withdrawn in the USA showed that “public perceptions can make or break vaccine uptake”.

Certainly, you do not need long on the internet to find emotive, powerful and intuitive antivaccine sites, including tragic stories of side-effects, genuine concerns over excipients, accusations of big pharma profiteering and disease mongering, or claims of governmental eugenics. Advocacy and public health sites base their arguments around reason, balance and science. Often parents do not know which way to turn. As a recent US study reported: “Parents who sought out vaccine information were often overwhelmed by the quantity and ambiguity... and, consequently, had to rely on their own instinct or judgment.” For instance, parents knew the link between autism and MMR is discredited scientifically. Yet the “media hype... generated doubts and fears in the back of their minds that were difficult to silence”.

Nevertheless, at least for the time being, the success in the meningitis belt, the grounds swell of support for MenB immunisation and Lord O’Neill’s highlighting of the importance of vaccines in the ongoing struggle against AMR mean vaccines are attracting headlines for all the right reasons. How long the public’s goodwill lasts remains to be seen.

References

Declaration of interests
Mark Greener is a full-time medical writer and, as such, regularly provides editorial and consultancy services to numerous pharmaceutical, biotechnology and device companies and their agencies. However, he has not worked directly or indirectly with any company relevant to this feature in the last two years. Mark worked with the GBSS on a CPD module for healthcare professionals as a clinical editor funded by mumandbabyacademy.com

Mark Greener is a freelance medical writer