The Immunological Basis for Immunization Series

Module 15: Meningococcal disease
Updated 2020

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Contents

Abbreviations and acronyms

4CMenB	Bexsero
ACIP	Advisory Committee on Immunization Practices (US)
aHUS	atypical haemolytic uraemic syndrome
ALL	acute lymphoblastic leukaemia
AML	acute myeloid leukaemia
aP	acellular pertussis
CDC	Centers for Disease Control and Prevention (US)
CEACAM	human carcinoembryonic antigen-related cell adhesion molecule
CI	confidence interval
CRM197	non toxigenic natural variant of diphtheria toxin
DT	diphtheria-tetanus
DTaP	diphtheria-tetanus-acellular pertussis
DTwP	diphtheria-tetanus-whole cell pertussis
ECDC	European Centre for Disease Prevention and Control.
ELISA	enzyme-linked immunosorbent assay
EPI	Expanded Programme on Immunization
FDA	Food and Drug Administration (USA)
GBS	Guillain-Barré syndrome
GMT	geometric mean titre
GSK	GlaxoSmithKline Biologicals
Hib	*Haemophilus influenzae* type b
HBV	hepatitis B virus
HPV	human papillomavirus
hSBA	serum bactericidal antibody measured with exogenous human complement
HSCT	hematopoietic stem cell transplant
Ig	immunoglobulin
IOM	Institute of Medicine (US)
IPV	inactivated polio vaccine
JE	Japanese encephalitis

LCCD	late complement component deficiency
LOS	lipooligosaccharide
LP	lipoprotein
MATS	Meningococcal Antigen Typing System
MCC	meningococcal serogroup C conjugate
MCV4	meningococcal quadrivalent ACWY conjugate vaccine
MCV4-CRM	Menveo
MCV4-DT	Menactra
MCV4fi-TT	MenQuadfi
MCV4rix-TT	Nimenrix
ME	myalgic encephalomyelitis
MHRA	Medicines and Healthcare Products Regulatory Agency
MLST	multilocus sequence type
MMR	measles, mumps and rubella vaccine
MVP	Meningitis Vaccine Project
NACI	National Advisory Committee on Immunization Canada
NHBA	Neisseria Heparin Binding Antigen
OPA	opsonophagocytosis
OMP	outer membrane protein
OMV	outer membrane vesicle
PCR	polymerase chain reaction
PCV7	pneumococcal 7-valent conjugate vaccine
PNH	paroxysmal nocturnal haemoglobinuria
PsA-TT	MenAfriVac
rLP2086	Trumenba
rSBA	serum bactericidal antibody measured with exogenous rabbit complement
SAE	serious adverse event
SBA	serum bactericidal antibody
ST	sequence type
TT	tetanus-toxoid
Td	tetanus diphtheria-toxoid
VAERS	Vaccine Adverse Event Reporting System-USA
VE	vaccine efficacy
WHO	World Health Organization
wP	whole-cell pertussis
YF	yellow fever

Preface

This module is part of the WHO series *The immunological basis for immunization*, which was initially developed in 1993 as a set of eight modules comprising one module on general immunology and seven modules each devoted to one of the vaccines recommended for the Expanded Programme on Immunization – i.e. vaccines against diphtheria, measles, pertussis, polio, tetanus, tuberculosis and yellow fever. Since then, this series has been updated and extended to include other vaccines of international importance. The main purpose of the modules is to provide national immunization managers and vaccination professionals with an overview of the scientific basis for vaccination against a range of important infectious diseases. The modules developed since 1993 continue to be vaccine-specific, reflecting the biological differences in immune responses to the individual pathogens and the differing strategies employed to create the best possible level of protection that can be provided by vaccination. The modules also serve as a record of the immunological basis for the WHO recommendations on vaccine use, published in the WHO vaccine position papers.[1]

Acknowledgements

Conflict of interest

All authors declared their interests in advance of updating the module. Two authors reported relevant interests that were assessed not to constitute a conflict of interest in relation to the authorship of the module. All the reported relevant interests are summarized below.

Ray Borrow's research unit[2] currently receives research support from GSK, Sanofi and Pfizer for studies on meningococcal vaccines. This interest was assessed as non-personal, specific and financially significant.[3]

Caroline Trotter served as a consultant for GSK in 2018, giving input on their models for meningococcal disease and vaccination. This interest was assessed to be personal, specific and financially insignificant.[3]

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[3] According to the WHO Guidelines for Declaration of Interests (WHO expert), an interest is considered "personal" if it generates financial or nonfinancial gain to the expert, such as consulting income or a patent. "Specificity" indicates whether the declared interest is a subject matter of the meeting or work to be undertaken. An interest has "financial significance" if the honoraria, consultancy fees or other received funding, including those received by the expert's organization, from any single vaccine manufacturer or other vaccine-related company, exceeds US$ 5000 in a calendar year. Likewise, a shareholding in any one vaccine manufacturer or other vaccine-related company, in excess of US$ 1000, would also constitute a "significant shareholding".

1. Meningococcal disease

1.1 Introduction

Meningococcal disease is caused by the Gram-negative bacterium *Neisseria meningitidis*, also known as the meningococcus. Meningococcal disease remains a significant public-health issue globally, with infections occurring endemically and epidemically in countries spanning the income spectrum (Rosenstein et al., 2001; Harrison et al., 2009). Humans are the only host for the meningococcus. Typically, the bacteria colonize the mucus membranes of the nasopharynx without causing illness, but invasion of the bacteria into normally sterile sites can cause life-threatening disease. Why a particular individual colonized by the meningococcus develops systemic infection, while others who are also colonized develop immunity without progression to disease, is due to complex interactions involving characteristics of the host, the environment and the bacterium (Stephens, 1999) that are not fully understood.

1.2 Neisseria meningitidis

Meningococci are aerobic, Gram-negative, oxidase-positive, encapsulated diplococci (Vedros & Genus, 1984). Serogroups are defined based on the structure of the capsular polysaccharide, a known virulence factor and host immune system target (Branham, 1953; Vedros, 1987). Serogroups A, B, C, W, X and Y are responsible for the majority of cases of invasive meningococcal disease. Increasingly, classification of *N. meningitidis* based on molecular methods is used to characterize isolates, including sequencing the porA and fetA genes (plus the porB gene, if warranted) and the seven housekeeping genes (abcZ, adk, aroE, fumC, gdh, pdhC and pgm) that define the multilocus sequence type (MLST) (Jolley et al., 2007). The *N. meningitidis* nomenclature recommended by European reference laboratories follows the convention: serogroup; porA type; fetA type; sequence type (clonal complex) (Maiden et al., 1998; Jolley et al., 2004; Fox et al., 2007). Whole genome sequencing is increasingly the most efficient method of molecular characterization.

1.3 Epidemiology

Meningococcal disease occurs worldwide, though the epidemiology varies by age, geographically and, over time in terms of incidence of the disease and in terms of the observed serogroup distribution responsible for the burden of disease in each region. The distribution of dominant serogroups of meningococcal disease, in multiple regions of the world, is shown in Figure 1. The following sections highlight several key considerations necessary for understanding the epidemiology of meningococcal disease caused by serogroups A, B, C, W, X and Y.

Further information about the epidemiology of meningococcal disease, the distribution of disease-causing and carrier serogroups and the risk of outbreaks, can be found in recently published reviews that have provided comprehensive assessments of the distribution and spread of meningococcal disease in multiple regions of the world, including Latin America, the Middle East and Africa, the Asia-Pacific region, India and China (John et al., 2013; Safadi et al., 2015; Borrow et al., 2016; Borrow et al., 2017; Li et al., 2018).

Figure 1: Serogroup and clonal complex distribution of cases of invasive meningococcal disease worldwide
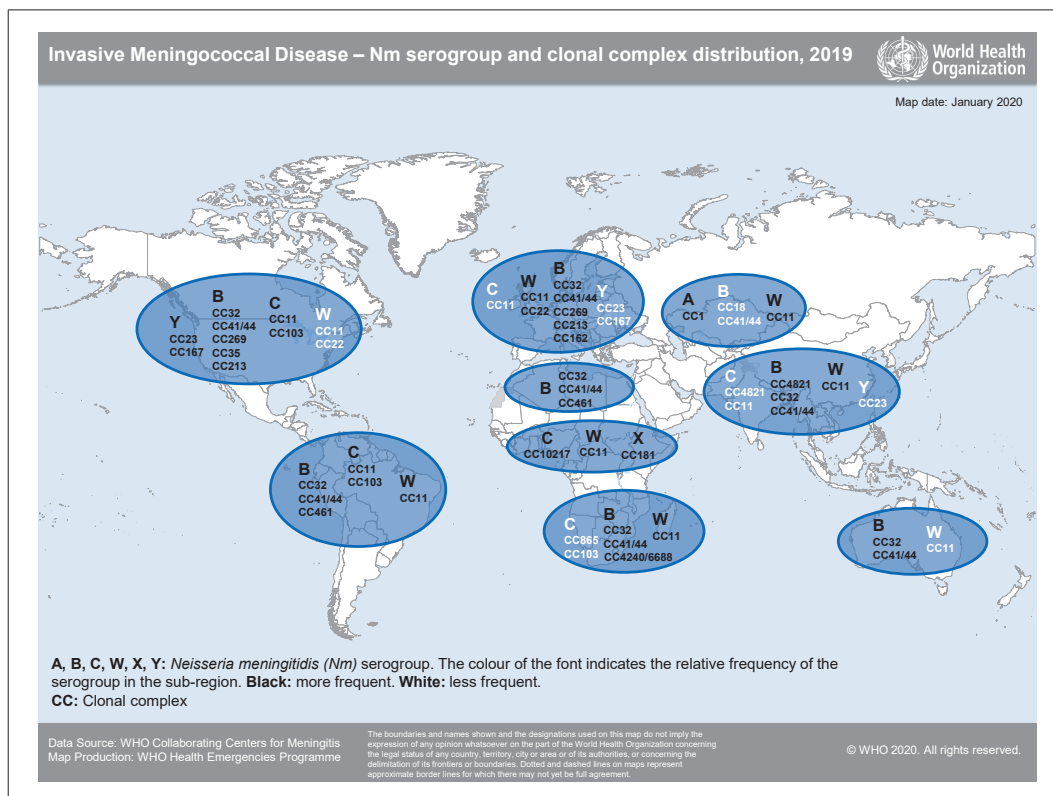
1.3.1 Disease caused by N. meningitidis serogroup A

The African meningitis belt is an area of increased risk of invasive meningococcal disease that stretches across Africa from Senegal and The Gambia on the western coast to Ethiopia and neighbouring countries in the east (Figure 2). The meningitis belt is characterized by: 1) a very high burden of disease; 2) distinct seasonal patterns; 3) pluri-annual cycles of outbreaks; 4) local geographic variation in incidence. Outbreaks in the meningitis belt typically begin during the dry season, rapidly building up to a peak and subsiding abruptly with the start of the rainy season (Greenwood, 2006). Serogroup A was responsible for causing the majority of cases in the meningitis belt during annual epidemics of meningococcal disease from early in the twentieth century until recently, leading to tens of thousands of cases and thousands of deaths. The largest recorded epidemic was in 1996, with an estimated 250 000 cases and 25 000 deaths. More recently in 2007, an epidemic in Burkina Faso led to approximately 25 000 cases of invasive MenA disease and 1700 deaths reported to the Ministry

of Health by May of that year (WHO, 2007b). The WHO Regional Office for Africa publishes the *Meningitis Weekly Bulletin* reporting on the frequency and distribution of cases identified through surveillance systems established in the region (WHO weekly reports) in addition to reports detailing outbreaks (WHO preparedness). Prior to the introduction of meningococcal A conjugate vaccine in preventative mass-vaccination campaigns across the meningitis belt, which began in 2010, most epidemics in sub-Saharan Africa were caused by serogroup A; more recently, outbreaks of serogroup C and also W and X have become more common (Greenwood, 2007; WHO, 2015a; Aku et al., 2017; Borrow et al., 2017; Nnadi et al., 2017). WHO has issued updated guidance for responding to outbreaks in the African meningitis belt, accounting for the changing epidemiology of the disease (WHO, 2014; WHO, 2015a). Epidemics of serogroup A disease have also been a significant source of disease in Asia (Hu et al., 1991; WHO, 1995; Hu, 2001; Sachdeva et al., 2005; John et al., 2013; Borrow et al., 2016).

**Figure 2: Countries of the African meningitis belt
with areas at high epidemic risk**
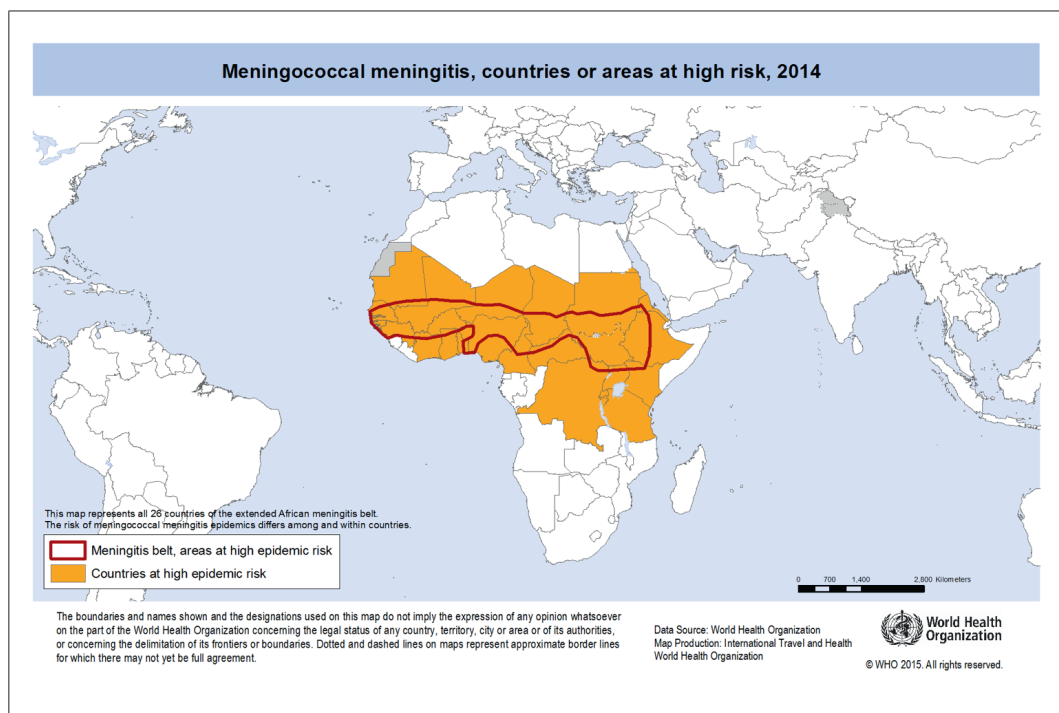
Source: World Health Organization (http://www.who.int/emergencies/diseases/meningitis/risk-of-meningitis.png.

1.3.2 Disease caused by N. meningitidis serogroup B

A number of regions have experienced prolonged hyper-endemic periods of serogroup B disease, including Norway (Bjune et al., 1991) where disease was due to ST32 clonal complex, phenotype B:15:P1.7,16 and Cuba (Sierra et al., 1991) where the clonal complex responsible for the outbreak was also ST32 but phenotype B:4:P1.19,15. This Cuban strain spread to the São Paulo region of Brazil in the late 1980s (Cruz et al., 1990; de Moraes et al., 1992). From 1991 to 2006, New Zealand experienced a high burden of disease caused by a strain identified as the B:4:P1.7–2,4, ST-41/44 clonal complex (Martin et al., 1998). In the United States of America, where meningococcal disease incidence is historically low, multiple outbreaks of serogroup B disease have occurred on college campuses in recent years (National Meningitis Association, 2017). In the United Kingdom, serogroup B disease is of significant public-health concern, especially among infants, though recent declines have been observed following the introduction of routine infant vaccination with vaccines designed to protect against meningococcal strains (Parikh et al., 2018). Endemic disease (caused by serogroups B and also serogroup C) due to heterogenous meningococcal clonal complexes, is of major concern in North and South America, Australia and Europe.

1.3.3 Disease caused by N. meningitidis serogroup C

Serogroup C disease has become relatively rare in countries where vaccination with a meningococcal conjugate vaccine preventing serogroup C has been introduced. For example, the United Kingdom, the first country to introduce serogroup C conjugate vaccination in 1999, routinely reports very low rates of serogroup C disease (Findlow et al., 2019). The United States adopted routine vaccination of adolescents with conjugate ACWY vaccines in 2006 and rates of C disease are now at historic lows (Cohn & MacNeil, 2015). Australia introduced conjugate meningococcal C vaccination in 2003; rates of disease caused by serogroup C are also low (Lawrence et al., 2016). However, as noted above, outbreaks occur in other regions, which have not implemented preventative meningococcal C vaccination campaigns, including countries of the African meningitis belt that have seen an increase in MenC outbreaks due to a novel clone (ST-10217) since 2013 (Brynildsrud et al., 2018). An outbreak of serogroup C disease, also due to ST-10217, was reported in 2017 in Liberia, which is located outside the meningitis belt and does not typically experience outbreaks (Patel et al., 2017). In the 2000s in China, another novel clone of serogroup C (ST-4821) caused outbreaks (Li J et al., 2018).

1.3.4 Disease caused by N. meningitidis serogroup W

Serogroup W was a relatively uncommon cause of invasive disease worldwide until outbreaks of serogroup W disease during the Hajj pilgrimage were reported in Saudi Arabia around the turn of the twenty-first century (Popovic et al., 2000; Taha et al., 2000; Taha et al., 2004). This outbreak was caused by a serogroup W clone from the ST-11 complex, and this clone was shown to spread from pilgrims to their contacts once they returned to their home countries (Wilder-Smith et al., 2003). Serogroup W isolates belonging to the ST-11 complex were also isolated from patients with meningococcal disease in 1994 in Mali (Kwara et al., 1998), in Cameroon in 1995 and Chad in 1996 (Guibourdenche et al., 1996), in the Gambia (Kwara et al., 1998) and in Rio Grande do Sul, southern Brazil in 2003 (Weidlich et al., 2008). In Burkina Faso in 2002, more than 10 000 cases were caused by serogroup W (Decosas & Koama, 2002). Serogroup W ST-11 has since emerged in in 2010 in Latin America and has spread

from South America to Europe (Abad et al., 2014). Evidence of global spread has been augmented by whole genome sequencing of serogroup W isolates; following emergence in 2000, cases have been documented in South America and elsewhere (Abad et al., 2014; Lucidarme J et al., 2015; Mustapha et al., 2016). The increase in serogroup W disease has led to several countries introducing conjugate vaccination with quadrivalent ACWY meningococcal vaccines (Ladhani et al., 2016; Knol et al., 2018).

1.3.5 Disease caused by N. meningitidis serogroup X

Meningococcal disease due to serogroup X is uncommon but outbreaks have been reported. For example, from January to June 2006 in Niger (Boisier et al., 2007), a total of 4185 cases of meningitis were reported, with 2905 cerebrospinal fluid samples tested. Serogroup X represented 51% of 1139 confirmed cases of meningococcal disease, but in southwestern Niger, it represented 90% of reported cases. In the agglomeration of Niamey, the reported cumulative incidence of confirmed serogroup X meningitis was 27.5 cases per 100 000 population (74.6 cases per 100 000 population in children aged 5–9 years). The serogroup X isolates had the same phenotype (X:NT:P1.5) and sequence type (ST-181) as the serogroup X isolates that were circulating in small outbreaks in Niamey in the 1990s (Campagne et al., 1999; Djibo et al., 2003). Small outbreaks of serogroup X disease were also reported in northern Ghana (Gagneux et al., 2002), Burkina Faso, Kenya, Togo and Uganda (Materu et al., 2007; Caugant et al., 2012; Xie et al., 2013). Also recently, meningococcal disease caused by serogroup X has been reported among migrants in Italy (Stefanelli et al., 2017).

1.3.6 Disease caused by N. meningitidis serogroup Y

Although asymptomatic carriage of serogroup Y is relatively common in many parts of the world, disease remains relatively rare. However, in the United States from 1996 to 1998, the number of cases involving serogroup Y increased so that one third of cases were due to this serogroup (Rosenstein et al., 2001). In the 1970s, serogroup Y was also recognized as a frequent cause of sporadic disease in certain populations in the United States (Galaid et al., 1980) and was also associated with several outbreaks among military personnel (Smilack, 1974). A moderate increase of serogroup Y disease has also been noted in Europe, in particular Scandinavian countries; of note, approximately 50% of cases were aged 45–88 years (Bröker et al.,2015).

1.4 Risk factors for meningococcal carriage

The meningococcus is only capable of colonizing the nasopharynx of humans and has no other known host or environmental niche. The prevalence of asymptomatic carriage varies by age and tends to be higher among adolescents and teenagers in Europe and North America (Christensen et al., 2010) and in school-aged children in the African meningitis belt (Cooper et al., 2019a). Other respiratory infections (Mueller et al., 2008; Cooper et al., 2019b), exposure to tobacco smoke (MacLennan et al., 2006), contact with a case of invasive meningococcal disease (Kristiansen et al., 1998), living in dense quarters, including in military barracks (Pether et al., 1988), being a college/university student or living in dormitories (Ala'aldeen et al., 2011) and intimate kissing (MacLennan et al., 2006) have all been associated with increased risk of meningococcal carriage, among other factors (Harrison et al., 2018).

1.5   Risk factors for meningococcal disease

The meningococcus is transmitted from person-to-person by aerosol droplets or by contact with respiratory secretions. Risk factors for meningococcal disease have been investigated in many settings and include: contact with a case of invasive meningococcal disease (de Wals et al., 1981); deficiencies in the complement pathway that can lead to repeated cases among the same individual (Nicholson & Lepow, 1979; Fijen et al., 1994; Lewis & Ram, 2014); use of eculizumab which is a complement inhibitor (McNamara et al., 2017); having been born pre-term (Tully et al., 2006); HIV positive status (Cohen et al., 2010; Miller et al., 2014; Simmons et al., 2015); being a college/university student or living in dormitories (Bruce et al., 2001; Nelson et al., 2001; Tully et al., 2006); exposure to smoke (Fischer et al., 1997; Coen et al., 2006); exposure to indoor firewood stoves (Hodgson et al., 2001); bar and club/disco patronage (Cookson et al., 1998; Honish et al., 2008); binge drinking (Finn et al., 2001) and concomitant or recent influenza or other respiratory infections (Moore et al., 1990; Cartwright et al., 1991; Harrison et al., 1991; Jacobs et al., 2014) among other factors (Harrison et al., 2018).

1.6   Clinical presentation

The classical presentation of meningococcal disease includes fever, rash and meningitis, with symptoms including abrupt onset of fever, headache, photophobia, myalgias, malaise and altered consciousness; however, these symptoms can be indistinguishable from other bacterial or viral illnesses (Steven & Wood, 1995; Thompson et al., 2006). In infants, there may be a more gradual onset of fever, with poor appetite and lethargy often reported, plus bulging fontanel indicating involvement of the central nervous system. Dissemination into the bloodstream results in rapid progression of severe septicaemia with petechial or purpuric rash and hypotension, and can lead to multiple organ failure. Meningococcal disease can also present as pneumonia, which in the absence of a rash may be difficult to recognize. Meningococcal disease caused by serogroup Y is more likely to cause pneumonia than disease caused by other serogroups (Koppes et al., 1977; Ladhani et al., 2012). Recent reports in the United Kingdom identified cases of serogroup W disease presenting with severe gastrointestinal symptoms (Campbell et al., 2016), underscoring the need to consider the possibility of meningococcal disease given patient presentation with a wide range of clinical symptoms, especially since meningococcal disease is characterized by rapid progression and high case fatality. In addition, a high proportion of those who recover from meningococcal disease experience permanent sequelae including loss of limbs (peripheral gangrene), hearing loss and neurological complications.

1.7   Diagnosis

The WHO has issued comprehensive guidelines for the laboratory confirmation of meningococcal disease, including methods for confirming cases, serogrouping isolates and determining antibiotic susceptibility (WHO laboratory manual, 2011). Diagnosis of meningococcal disease is traditionally made by culture of the meningococcus (a Gram-negative diplococcus) from a sterile site such as from blood or cerebrospinal fluid. Initial morphological identification of colonies should be followed by confirmatory testing, including using Kovac's oxidase test and carbohydrate utilization followed by serological tests to identify the serogroup. Increasingly polymerase chain reaction (PCR) and other molecular methods are used; these are often critical for further characterization (WHO laboratory manual, 2011).

1.8   Treatment

Due to the severity and high case fatality of meningococcal disease, cases require hospitalization and significant medical care (Nadel & Kroll, 2007). There are several antimicrobial agents available for the treatment of meningococcal disease; the WHO notes that a range of treatments including penicillin, ampicillin, chloramphenicol and ceftriaxone can be effective. Ceftriaxone is considered the drug of choice in many settings, including in resource-limited settings and during epidemics in Africa, and it can also be used to treat pregnant women and infants (WHO Health Emergencies Programme). Early initiation of antibiotic therapy and presentation to hospital has been associated with reduced mortality and morbidity (Public Health England, 2018; Jolly & Stewart, 2001). Rifampicin, ciprofloxacin, ceftriaxone, cefixime and azithromycin have been recommended for the prevention of secondary cases among close contacts of an index case in some settings (European Centre for Disease Prevention and Control, 2010). While routine antibiotic prophylaxis is not currently recommended for contacts of meningitis cases during outbreaks in the African meningitis belt, a recent clinical trial found that village-wide distribution of a single-dose oral ciprofloxacin within three days of identifying a case could reduce meningitis attack rates during an outbreak in Niger (Coldiron et al., 2018). Further evaluations of this approach are warranted.

2. Immunity to meningococci

Serum antibodies confer protection against meningococci by activating complement-mediated lysis and by enhancing opsonophagocytosis (Granoff, 2009). Immunity to meningococcal disease is known to develop with age. The classic studies of Goldschneider and colleagues (1969a), in the 1960s, provided indirect evidence by defining the characteristic curve (Figure 3) showing an inverse relationship between disease risk and acquisition of serum bactericidal antibodies (SBA) with age in the United States. Initially, transfer of maternal antibodies protects infants (Goldschneider et al., 1969a) and maternal antibodies are known to persist for several months after birth. After this, there is a rapid decline in SBA levels followed by a steady increase commensurate with age. In young children aged less than 2 years, low levels of bactericidal antibodies are observed, corresponding to the highest risk of infection in that age group compared to others. There is a gradual increase in the acquisition of SBA from two years onwards, coinciding with a decrease in disease incidence. The acquisition of protective SBA as a person ages, is thought to occur initially through the asymptomatic carriage of *N. lactamica* and then *N. meningitidis*. In studies in North America and Europe, carriage rates of *N. lactamica* are highest in 18 month-old infants and decline to a much lower rate in teenage children; conversely, low levels of meningococcal carriage are detected in infants during the first four years of life with increased carriage in adolescence (Gold et al., 1978; Cartwright et al., 1987; Bakir et al., 2001). The same patterns may not be observed elsewhere. Inoculating volunteers with *Neisseria lactamica* to induce nasopharyngeal colonization was shown to induce opsonophagocytosis but not SBA response to *Neisseria meningitidis* (Evans et al., 2011). It has also been hypothesized that carriage of other species with cross-reacting antigens (Robbins et al., 1972; Vann et al., 1976; Guirguis et al., 1985) can also contribute to the acquisition of protective SBA. However, the role of these organisms in inducing SBA activity to meningococci has been questioned (Trotter et al., 2007) and the same inverse relationship between SBA and disease incidence has not been observed in populations of the African meningitis belt (Trotter et al., 2013).

Figure 3: Age-related incidence of meningococcal disease in the USA and prevalence of serum bactericidal activity against three pathogenic strains of *N. meningitidis*

▲   Number of cases/100 000 age-specific population, 1965.
△   Number of cases/100 000 age-specific population, 1966.
---   Age distribution of 72 cases admitted to Los Angeles Children's Hospital 1944–1953.
●   Percent of sera in each age group having a bactericidal titre of 1:4 or greater against meningococcal strains A1, B11, and C11. Sera from 282 children (at least 20 in each age group) and 567 army recruits (ages 19 to 26 years) were tested in the presence of exogenous complement.

Source: Goldschneider et al., 1969a.

The direct evidence of the role of SBA in protective immunity to meningococcal disease was confirmed by studies performed by Goldschneider and colleagues in the 1960s (Goldschneider et al., 1969a). This study involved collecting blood samples from American (United States) army recruits at the start of their basic training, and related the occurrence of meningococcal disease due to capsular group C during basic training, to the presence or absence of SBA at recruitment. Disease occurred in only 1% of individuals who had detectable SBA at the start of training, but in 22% of those who had undetectable SBA. This was further confirmed by the population study, performed by the same authors, who demonstrated the inverse relationship between disease incidence and the presence of SBA (Goldschneider et al., 1969a) (Figure 3).

The activation of the complement cascade by antibody is one of the critical mechanisms of immunity to meningococci. Evidence of this is provided by studies of individuals who have a deficiency in the complement cascade and are more susceptible to meningococcal disease (Nicholson & Lepow, 1979). Individuals with late complement component deficiency (C5–C9) are at a greater risk of infection and also recurrent infection (Ross & Densen, 1984; D'Amelio et al., 1992). Patients receiving complement inhibitors, such as eculizumab, are also at increased risk of meningococcal disease (McNamara et al., 2017; Parikh et al., 2017). Infections in such individuals differ from those in immunocompetent individuals as they usually occur at an older age and may involve a rare capsular group or non-capsulated meningococcus (Petersen et al., 1979;

Ross & Densen, 1984; Fijen et al., 1989; D'Amelio et al., 1992). Those individuals with deficiency in the properdin or factor D, both components of the alternative complement pathway, have a much higher case-fatality rate (Ross & Densen, 1984; Densen, 1991) but there is rarely a recurrence of infection among survivors. Hence the alternative complement pathway also has a role to play in the immunity to meningococci.

In the study of military recruits (Goldschneider et al., 1969a), more than half of the recruits had undetectable SBA and were colonized with the circulating epidemic strain but did not develop disease. This suggests that other mechanisms can contribute to immunity to meningococci, such as opsonophagocytosis and antibody-dependent cellular cytotoxicity (Lowell et al., 1980; Halstensen et al., 1989).

Although meningococci colonize the nasopharynx, our understanding of mucosal immunity is still limited. The process of colonization involves a complex interaction between the meningococci and host factors (Bourdoulous & Nassif, 2006). This results in many different factors with the potential to be involved in host defense mechanisms. Secretory immunoglobin (IgA) and other antibodies are present in nasopharyngeal secretions (Brandtzaeg, 1992) and are likely to contribute to the prevention of carriage. Meningococcal-reactive T-cells have been identified in the mucosa, suggesting cellular immunity at this localized site (Davenport et al., 2003). Since carriage of meningococci is hypothesized to induce the development of natural immunity, the interaction at the mucosa will contribute to the generation of both localized and systemic immunity.

3. Immunological assays

3.1   Serum bactericidal antibody assay

Following the studies of Goldschneider and colleagues in the 1960s (Goldschneider et al., 1969a; Goldschneider et al., 1969b), the measurement of SBA in vitro became the gold standard assay for the assessment of immunity to meningococci. The SBA assay allows for the determination of antibody-mediated complement lysis of meningococcal cells, and is therefore a measurement of functional antibodies. The original SBA assays used human complement lacking anti-meningococcal antibodies as the source of exogenous complement. Obtaining suitable human complement involves screening many donors or sources, and is quite often not suitable for universal use against a panel of diverse meningococcal strains. It is also difficult to standardize, and therefore is a factor to be considered when comparing data generated from different laboratories.

In an effort to standardize the assay, a recommended protocol using baby rabbit complement as the exogenous source was published (Maslanka et al., 1997) and was adopted by the WHO as the recommended assay for the assessment of SBA titres following immunization with meningococcal polysaccharide vaccines (WHO, 1976). Meningococci are known to be more susceptible to complement-mediated lysis in the presence of exogenous rabbit complement compared to human complement (Griffiss & Goroff, 1983; Zollinger & Mandrell, 1983). Studies have shown a positive correlation between titres following serogroup C conjugate vaccination obtained from an SBA assay using either human or baby rabbit complement (Borrow et al., 2001a; Trotter et al., 2003; Trotter et al., 2008). Serogroup C conjugate vaccines were licensed in the United Kingdom partly on the basis of immunogenicity data generated using an SBA assay with baby rabbit complement (Miller et al., 2001). For the assessment of future vaccines containing a serogroup C conjugate component or serogroup A conjugate vaccines, assessment of immunogenicity by SBA assay, using either human or baby rabbit complement, is recommended (WHO, 2004; WHO, 2006). This is now also the case for serogroups W and Y.

Human complement is still the preferred choice of exogenous complement for the determination of SBA against serogroup B because the use of baby rabbit complement has been associated with elevated SBA titres due to the presence of low-avidity anti-serogroup B capsular polysaccharide antibody in test sera (Zollinger & Mandrell, 1983; Mandrell et al., 1995). Efforts have been made to investigate the use of non-human complement sources for group B SBA assays but, to date, a viable alternative has not been found (Zollinger & Mandrell, 1983; Zollinger et al., 1997; Findlow et al., 2007b; Brookes et al., 2013). The difficulties of trying to standardize SBA assays for serogroup B have been highlighted (Borrow et al., 2005a; Borrow et al., 2006a).

It has become more apparent that the selection of target strain in the SBA assay is of critical importance. Strains for serogroups A (strain F8238) and C (strain C11) have been recommended for use in a standardized SBA assay (Maslanka et al., 1997), but for serogroups B, W and Y there is no consensus on target strains. Even for serogroup A, an alternative target strain, strain 3125, has been chosen by various researchers as it bears the lipooligosaccharide (LOS) immunotype L10 associated with invasive disease isolates as opposed to strain F8238 which habours L11, more commonly associated with carriage (Poolman et al., 2011; Trotter et al., 2013; Tall et al., 2015). It has been postulated that SBA activity measured against strain 3125 is a more specific measure of vaccine-induced immunity as it does not capture bactericidal action of antibodies directed against L11 resulting from natural exposure during carriage, while it is equally sensitive to antibody induced by vaccination with serogroup A polysaccharide-containing vaccines (Poolman et al., 2011).

For serogroup B, the diverse epidemiology of prevalent strains and the fact that the antigens inducing protective antibodies are subcapsular, make it necessary to analyse multiple strains to evaluate vaccine candidates. Two approaches have been taken here for evaluation of the new generation broad coverage protein-based vaccines (including 4CMenB and Bivalent rLP2086). Firstly, the use of target strains that are matched for one vaccine antigen but mismatched for the other vaccine antigens allows researchers to quantify the response to the matched antigen (Findlow et al., 2010; Snape et al., 2010). The second approach is to perform antigenic characterization of disease-causing strains from a global collection following selection of the primary test strains and taking into account specific selection criteria to ensure that test strains appropriately represent the antigenic diversity of strains globally. Such criteria include: firstly, expression of fHbp variants that differed from the vaccine antigens; secondly, expression of fHbp variants prevalent in contemporary strains from various countries; thirdly, representative in vitro surface expression levels of the fHBP vaccine antigens across all strains; lastly, demonstration of low baseline bactericidal hSBA titres with the selected strains (Donald et al., 2017). In outbreak situations, it has been informative to utilize the outbreak strain isolated from a case as the reference strain when conducting hSBA with vaccinees' sera, to gauge the potential effectiveness of the vaccine strain coverage (Basta et al., 2016; Lujan et al., 2017).

The choice of target strain regardless of serogroup is important, particularly for studies of natural immunity, because the subcapsular makeup, in addition to the serogroup, are representative of the circulating strains. This was illustrated by a study in Niger where the proportion of individuals protected against the outbreak of serogroup W strain bearing a PorA subtype P1.5,2, increased from 26% to 42% within 10 months, whereas against a reference strain (M.01, 0240070) with a PorA subtype P1.18-1,3, the proportion of individuals protected did not increase significantly (34% to 37%) (Boisier et al., 2006).

Studies have highlighted that strains considered to be phenotypically or genotypically similar can result in variable SBA titres from the same serum samples (Vermont et al., 2003; Findlow et al., 2006; Martin et al., 2006; Findlow et al., 2007a). Differences in SBA titres have been observed in different laboratories using the same serogroup B strain (Borrow et al., 2005a). This was attributed to the different methods used to prepare stocks of the strain for use in the SBA assay that resulted in different expression of minor outer membrane proteins.

3.2　Measurement of serogroup-specific immunoglobulin

The determination of serogroup-specific immunoglobulin (Ig) provides a measurement of antibody that recognizes the individual capsular groups but does not necessarily reflect the level of functional (protective) antibody. Original assays were performed as radioimmunoassay or precipitation assays and tended to measure total Ig. The only correlate of protection suggested to date that is based on an antibody-binding assay comes from the Finnish efficacy trials of a meningococcal polysaccharide serogroup A vaccine and was determined to be 2 µg/mL Ig by radioimmunoassay (Makela et al., 1975; Peltola et al., 1977). Serological evaluation of vaccines normally includes measurement of serogroup-specific IgG. A standardized enzyme-linked immunosorbent assay (ELISA) for the determination of serogroups A and C-specific IgG was recommended and used by most laboratories (Carlone et al., 1992; Gheesling et al., 1994). Protocols for measuring serogroup W and Y-specific IgG have been developed, although there is no consensus on a standardized assay (Elie et al., 2002; Giardina et al., 2003; Joseph et al., 2004; Giardina et al., 2005). Multiplex immunoassays for the measurement of IgG to serogroups A, C, W and Y using bead-based assays have been developed that have the advantage of using very small volumes of sera, usually less than 5 µL, to determine the concentrations of IgG to four serogroups in one assay and are also more sensitive than a traditional ELISA due to their greater dynamic range (Lal et al., 2004; Martins et al., 2009; Bårnes et al., 2015). The measurement of serogroup-specific IgG subclasses has also been described and used in evaluating response to vaccination (Giardina et al., 2003; Holme et al., 2015). The correlation between serogroup-specific IgG and SBA titres is not sufficiently strong to allow measurement only of IgG when evaluating immune response to vaccines (Granoff et al., 1998b).

3.3　Opsonophagocytic assays

Phagocytosis of meningococci has been demonstrated (Roberts, 1970; Halstensen et al., 1989; Plested et al., 2001; Jack et al., 2005) and it is thought that this contributes to protection. The original method of measuring opsonophagocytosis (OPA) was by fluorescence microscopy and visual inspection; however, this was very labour-intensive and alternative methods have been developed. Chemiluminescence (Sjursen et al., 1992) and flow cytometry (Halstensen et al., 1989; Aase et al., 1995; Aase et al., 1998; Humphries et al., 2015) protocols have been developed with various end-points using cell lines or freshly isolated peripheral blood mononuclear cells. Different targets can be used in these assays with killed meningococci (Aase et al., 1995; Findlow et al., 2006; Humphries et al., 2015), viable meningococci (Aase et al., 1998), or latex particles coated with capsular polysaccharide or outer membrane proteins (Lehmann et al., 1999). A multiplex flow cytometric assay has been developed that allows determination of the OPA activity to groups A, C, W and Y (Martinez et al., 2002). Cell surface labelling assays have also been developed and may be an alternative to the OPA assays (Findlow et al., 2006; Humphries et al., 2015).

The importance of this mechanism of immunity to protection against meningococcal infection is still unclear. The production of SBA is established as the correlate of protection for serogroup C and is likely to have a similar role for serogroups A, W and Y where the capsular polysaccharide is immunogenic. However, for serogroup B, OPA has been suggested to contribute to protection, and consequently has been used in the assessment of immune responses to candidate serogroup B vaccines (Lehmann et al., 1997; Naess et al., 1999; Findlow et al., 2006; Wedege et al., 2007). There is currently no standardized protocol for OPA assays.

3.4   Other assays

Several other immunological assays have been utilized in the assessment of immunological responses to meningococcal infection or vaccination. The whole-blood assay analyses the bactericidal killing observed in an individual's whole blood rather than just the antibody-mediated killing in serum (Ison et al., 1999). This assay has been used in the study of outer membrane vesicle (OMV) vaccine responses (Morley et al., 2001) and is reported to be more sensitive than the SBA assay (Ison et al., 1999; Morley et al., 2001); however, due to the labour-intensive nature of the assay, the requirement for fresh blood to be analysed and the difficulty in standardizing such an assay, it is more suitable for vaccine development purposes or small-scale studies, not evaluation of candidate vaccines.

Animal models for the study of meningococcal pathogenesis have been developed and used in the assessment of protection against meningococci. However, as humans are the only natural hosts for *N. meningitidis*, the results obtained using animal models may not be entirely relevant to human disease. Models using mice have been developed (Miller, 1933) and widely used to analyse active immunization or the role of various host factors in pathogenesis, but tend to be sensitive to the level of challenge bacteria and require iron supplementation (Holbein, 1980; Gray-Owen & Schryvers, 1996). Investigators have used transgenic mice expressing various human molecules such as human carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) ((Johswich et al., 2013), human factor H (Johnson et al., 2012; Lujan et al., 2015) and human transferrin (Zarantonelli et al., 2007), but these are purely research tools. Infant rat models have been developed (Saukkonen, 1988) which allow the demonstration of passive protection and can be used to evaluate human sera for protective immunity to serogroup B meningococci (Toropainen et al., 1999). Other assays, such as immunoblots and T-cell assays, are useful research tools but are not suitable for large-scale studies evaluating meningococcal vaccines.

4. Surrogates of protection

Laboratory markers of immunity are often referred to as correlates or surrogates of protection, although there has been some disagreement and inconsistency in the use and definitions of these terms. Regardless of semantics, such laboratory markers of immunity are particularly useful for meningococci because they can be used to infer the protection provided by vaccines without the need to perform large-scale efficacy trials. For meningococcal vaccines, the low incidence of meningococcal disease in most settings would require tens of thousands of participants to establish vaccine efficacy against invasive disease.

The accepted biomarker of protection for meningococci is SBA activity (Frasch et al., 2009). Protection against disease is not necessarily only mediated by such antibodies, so this may be considered a surrogate (that is, indirect measure) rather than an absolute correlate of protection. The surrogates of protection for meningococci have been extensively reviewed (Balmer & Borrow, 2004a; Borrow et al., 2005b; Borrow & Miller, 2006; Findlow & Borrow, 2017) where more complete details can be found.

The surrogate of protection for serogroup C meningococci was established in the studies of Goldschneider and colleagues (Goldschneider et al., 1969a). These studies demonstrated that the presence or absence of naturally-occurring SBA (a titre of ≥4 using human complement) to serogroup C in military recruits, predicted the risk of subsequent serogroup C disease in an individual. Confirmation that the SBA was mediating the protection was demonstrated by removal of serogroup C-specific SBA from sera that resulted in a loss of bactericidal activity in vitro (Goldschneider et al., 1969b). As discussed in section 3.1, this surrogate was established using human complement in the SBA assay. Studies have been performed to establish an equivalent surrogate of protection using rabbit complement in the SBA (Borrow et al., 2001a; Andrews et al., 2003). Assessment of the level of natural immunity in the United Kingdom prior to the introduction of the serogroup C conjugate vaccine, aimed to repeat the observation of Goldschneider and colleagues and showed a modest correlation between age-specific risk of disease and a rabbit complement SBA (rSBA) titre ≥ 8 (Trotter et al., 2003).

An hSBA titre ≥ 4 is an individual-based surrogate of protection, but establishing this for an rSBA titre ≥ 8 required a large cohort to be analysed pre- and post-vaccination and then followed up prospectively for occurrence of disease, as in the original Goldschneider study (Goldschneider et al., 1969a). Post-licensure surveillance following the introduction of the serogroup C conjugate vaccine in the United Kingdom allowed age-specific efficacy estimates to be calculated. An rSBA titre ≥ 8 was observed to correlate with the vaccine efficacy estimate for young children in the United Kingdom (Andrews et al., 2003).

Both an hSBA titre ≥ 4 and an rSBA titre ≥ 8 are surrogates of short-term protection. It has been shown in the British experience that rSBA titres wane rapidly in young children, following three vaccine doses in infancy, regardless of maufacturer (Richmond et al., 1999; MacLennan et al., 2000; Borrow et al., 2002). The assumption was that immunological memory may be a predictor of long-term protection (Richmond et al., 1999; Borrow et al., 2002), but data have now indicated that this may not be the case and that persistence of SBA is critical (Trotter et al., 2004; Auckland et al., 2006).

The laboratory correlate for the induction of immunological memory following meningococcal serogroup C conjugate (MCC) vaccination used to be an SBA titre greater than or equal to that of the primary response one month following a 10 µg dose of plain polysaccharide administered at least six months after the primary series of immunization (WHO, 2004). However, as depletion of immunological memory and antibody hyporesponsiveness have been observed after a dose of plain polysaccharide meningococcal serogroup C vaccine, particularly in young children, this is no longer recommended (Gold et al., 1979; MacLennan et al., 2000; WHO, 2006). Recommendations for assessing immunological memory now include demonstration of an anamnestic response to a booster dose of conjugate vaccine when administered at least six months after completion of the primary series or changes in the avidity (Goldblatt, 1997) of serogroup-specific IgG from pre- to post-primary series, and before and after a booster dose of conjugate vaccine (WHO, 2006). However, as indicated above, for young children demonstration of memory responses alone may be insufficient.

For serogroups A, B, W and Y there is no established surrogate of protection although there is evidence indicating that SBA is a relevant laboratory marker. In the studies of Goldschneider and colleagues (Goldschneider et al., 1969a), an hSBA titre ≥ 4 to serogroups A and B was observed to predict protection against serogroup C disease. These data suggest that the protection observed in this study incorporated both capsular polysaccharide and subcapsular antigen-specific SBA activity. However, other studies have indicated that carriage of serogroup A meningococci induces hSBA activity to both capsular and subcapsular antigens, but in the absence of carriage of serogroup A, any hSBA activity observed naturally is directed to subcapsular antigens (Amir et al., 2005). These data suggest that an hSBA titre ≥ 4 could be a generic surrogate of protection against meningococcal disease (Borrow et al., 2006). For serogroup B, hSBA activity has been correlated to clinical efficacy observed with OMV vaccines (Sierra et al., 1991; Holst et al., 2003; Milagres et al., 1994) and has been recommended as a suitable surrogate of protection for predicting the effectiveness of a meningococcal serogroup B vaccine (Borrow et al., 2006a).

Determination of capsular polysaccharide-specific IgG for serogroups A, C, Y and W, or antibodies specific to OMV preparations or proteins for group B, are often performed in conjunction with SBA titre measurement. The correlation between non-functional (SBA was not measured) antibody levels and protection was described in Finnish efficacy studies of a group A polysaccharide vaccine where a level of 2 µg/mL of total Ig determined by radioimmunoassay was the mean level in unimmunized adults (Makela et al., 1975; Peltola et al., 1977). There are no established correlates of protection associated with non-functional antibody levels for the other groups. However, the measurement of specific antibodies (for capsular polysaccharide, OMV or proteins) can be useful in assessing immune responses to immunization for new candidate vaccines.

The lack of an established surrogate for serogroups other than C has not prohibited the licensure of new vaccines that have been licensed based on safety and immunogenicity alone. For serogroup A monovalent and ACWY quadrivalent conjugate vaccines, the key criterion was the demonstration of non-inferiority over existing plain polysaccharide vaccines. Studies of naturally-acquired immunity to serogroup A in Burkina Faso failed to demonstrate a Goldschneider-like inverse relationship between age-specific disease incidence and rSBA titres (Trotter et al., 2013), suggesting that it may be challenging to define an absolute surrogate of protection for serogroup A in this setting. The choice of target strain within the SBA may also be influential (Poolman et al., 2011), as noted in section 3.1.

For multicomponent protein vaccines designed to offer protection against serogroup B disease, alternative approaches were required to identify suitable biomarkers that could not only assess immunogenicity (and therefore likely effectiveness) but also the breadth of coverage against highly variable serogroup B strains. This resulted in the development of the Meningococcal Antigen Typing System (MATS) to predict 4CMenB strain coverage by analysing isolates recovered from disease cases (Donnelly et al, 2010). Early indications from post-licensure surveillance in the United Kingdom, which show good agreement between actual and predicted effectiveness and strain coverage, provide further support that SBA immunogenicity data are a suitable surrogate of protection (Parikh et al., 2016; Findlow & Borrow, 2017).

5. Available vaccines

Licensed vaccines against meningococcal disease have been available for more than 50 years. Over time, there have been major improvements in strain coverage and vaccine availability, but to date no universal vaccine against meningococcal disease exists.

The first plain polysaccharide vaccines were developed in the 1960s, with a serogroup C polysaccharide vaccine licensed in the United States in 1974. A bivalent A/C polysaccharide vaccine followed in 1978, with quadrivalent A, C, W, Y vaccines arriving in 1981 (Immunization Action Coalition). In the 1990s following the success of *Haemophilus influenzae* type b (Hib) conjugate vaccines, meningococcal polysaccharide-protein conjugate vaccines were developed. Meningococcal serogroup C conjugate (MCC) vaccines were first introduced in the United Kingdom in 1999. These conjugate vaccines were shown to overcome many of the problems associated with the plain polysaccharides; they were immunogenic in infants, could generate memory responses, overcame hyporesponsiveness and, perhaps most crucially, were able to reduce carriage and transmission leading to herd protection (Borrow & Miller, 2006). Quadrivalent meningococcal conjugate vaccines followed but at a cost out of the reach of many countries. The Meningitis Vaccine Project, a partnership between WHO and PATH established in 2001, successfully developed an affordable vaccine against *N. meningitidis* serogroup A that has been rolled out across the meningitis belt in preventive mass campaigns since 2010 (Okwo-Bele et al., 2015).

The development of effective vaccines against serogroup B disease has been more challenging. The meningococcal serogroup B capsular polysaccharide is a homolinear polymer of $\alpha(2{\to}8)$ N-acetyl neuraminic acid (polysialic acid), an autoantigen (Finne et al., 1987). The polysaccharide is expressed in a number of human tissues and is poorly immunogenic. Approaches to serogroup B vaccine development have thus focused on surface-exposed subcapsular antigens. In the 1980s, OMV vaccines were developed to protect against particular strains causing hyperendemic disease (first used in Cuba and Norway and later in New Zealand) (Holst et al., 2013). The OMV vaccines did not provide broad protection against a range of group B strains and the first MenB vaccine with broad coverage to be licensed was a combination of an OMV and recombinant proteins (4CMenB). A vaccine composed of two factor H binding protein variants recombinantly expressed in Escherichia coli as native lipoproteins (bivalent rLP2086) is licensed for use in individuals aged 10 years and older.

The plain polysaccharide, polysaccharide-conjugate, OMV and protein-based vaccines available have been implemented in various strategies globally in response to outbreaks or epidemics, or introduced into the routine immunization schedules of selected countries.

Details on the licensed vaccines, and vaccines nearing licensure, including composition and recommendations for use, are given in Tables 1 and 2. Conjugate vaccines have now largely replaced polysaccharide vaccines in high-income countries, but the latter still form an important part of the response to epidemics in the meningitis belt (refer to section 1.3.1 and WHO, 2000).

Table 1: Currently licensed meningococcal polysaccharide and conjugate vaccines, including those in clinical trial

Manufacturer	Vaccine	Active constituents per dose	Adjuvant	Other excipients	Presentation	Recommendations
Polysaccharide vaccines						
Sanofi Pasteur	Mengivac™	50 µg each of serogroup A, C polysaccharide	None	Lactose (2 mg)		Manufacturing ceased but remaining product licensed until 2019
Sanofi Pasteur	Menomune™	50 µg each of serogroup A, C, W, Y polysaccharide	None	Lactose (2.5–5.0 mg); Sodium chloride (4.25–4.75 mg)	1 or 10 dose/ vials	Manufacturing ceased but remaining product licensed until 2019
GSK Biologicals	ACWY Vax™	50 µg each of serogroup A, C, W, Y polysaccharide	None	Lactose (12.6 mg)		
Bio Manguinhos / Finlay Institute		50 µg each of serogroup A, C, W polysaccharide	None		10 dose vials	WHO stockpiled for use in epidemic situation in Meningitis Belt
Lanzhou Institute; Bejing IBP; Shanghai IBP; Wuhan IBP		50 µg of serogroup A polysaccharide	None		Freeze dried, 1, 2, 5 or 10 dose/ vials	China: Two doses at 6–18 months with 3 months interval; 2 further doses at 3 and 6 years, respectively
Lanzhou Institute	Meng Ling Kang®	50 µg each of serogroup A, C polysaccharide	None		Freeze dried, 1 dose/vial	China: Used for 2 doses at 3 and 6 years in selected provinces
Chongqing Zhifei Biological Products Co., Ltd.	Menwayc®	50 µg each of serogroups A, C, W, Y polysaccharide	None	Lactose (3.5 mg)	Lyophilized	China: high-risk groups more than 2 years of age

Manufacturer	Vaccine	Active constituents per dose	Adjuvant	Other excipients	Presentation	Recommendations
Conjugate vaccines						
GlaxoSmithKline	Menjugate™ and Menjugate™ Kit	10 µg O-acetylated serogroup C oligosaccharide conjugated to 12.5 to 25.0 mg CRM_{197}	$Al(OH)_3$	Mannitol, sodium phosphate buffer	Single dose, freeze dried, vial reconstituted with diluent	2 doses in infancy 2 months apart, booster in second year of life or 1 dose at ≥12 months Infants < 12 months, 3 doses from 2 months onwards, interval of at least 1 month Children ≥ 12 months, adolescents and adults, 1 dose
Pfizer	NeisVac-C™	10 µg de-O-acetylated serogroup C oligosaccharide conjugated to 10–20 µg tetanus toxoid	$Al(OH)_3$	Sodium chloride	Single dose, liquid suspension vial	
Serum Institute of India	MenAfriVac™	10 µg serogroup A polysaccharide conjugate to 10–33 µg tetanus toxoid	$AlPO_4$	Thiomersal	Ten dose, freeze dried, vial reconstituted with diluent	Sub-Saharan Africa: Single dose 1–29 years of age
Serum Institute of India	EPI formulation of MenAfriVac™	5 µg serogroup A polysaccharide conjugate to 10–20 µg tetanus toxoid	$AlPO_4$	Thiomersal	Ten dose, freeze dried, vial reconstituted with diluent	Sub-Saharan Africa: Single dose between 9 and 18 months
Chongqing Zhifei Biological Products Co., Ltd.	MeningACon®	Serogroups A and C polysaccharide conjugated to tetanus toxoid			Liquid	China only. For children with 3–24 months age 3 doses and a booster; above 2 years of age single dose
Yunnan Walvax	Wo Er Kang	Serogroups A and C polysaccharide conjugated to tetanus toxoid			One dose , freeze dried, vial reconstitured with diluentl	China
Xiangrui (also known as Beijing Sanroad)	Nao Man Ning	Serogroups A and C polysaccharide conjugated to tetanus toxoid				China

Manufacturer	Vaccine	Active constituents per dose	Adjuvant	Other excipients	Presentation	Recommendations
GlaxoSmithKline	Menitorix®	5 µg Hib polysaccharide and 5 µg group C polysaccharide each conjugated to ~ 17.5 µg of tetanus toxoid	None	Trometamol, Sucrose, Sodium chloride	Single dose, freeze-dried vial reconstituted with prefilled syringe	UK and Australia routine: single dose at 12 months
Sanofi Pasteur	Menactra®	4 µg each of serogroups A, C, Y and W polysaccharide conjugated to ~ 48 µg of diphtheria toxoid	None	Sodium chloride	Single dose, prefilled syringe	USA routine: adolescents 11–12 yrs, 1 dose, booster at 16 yrs At-risk groups: 2 months–55 yrs Canada routine: not recommended (unless epidemiology warrants use in 11–24 yrs) At-risk: 2–55 yrs, 1 dose; ≥ 56 yrs 1 dose of Menactra™
Sanofi Pasteur	MenQuadfi™	10 µg of each serogroup A, C, Y, and W and approximately 55 µg of tetanus toxoid	None	Sodium acetate buffered saline	Liquid single-dose vial	USA indication: 2 years and older (single dose) Phase III toddler trial in progress
GlaxoSmithKline	Menveo™	5 µg each of serogroups C, Y and W oligosaccharide and 10 µg of serogroup A oligosaccharide conjugated to 33–64 µg CRM$_{197}$	None	Sucrose, potassium dihydrogen phosphate, sodium dihydrogen phosphate monohydrate, disodium mmm phosphate dehydrate, sodium chloride	Single-dose vial with lyophilized serogroup A component; single-dose vial with the 3 other components in liquid form	Licensed from 2 months of age. Infant schedule 2, 4, 6 and 12 months of age In children 7–23 months, 2 doses with second dose in second year of life and at least 3 months after the first. Single dose from 2 years of age USA routine: adolescents 11–12 yrs, 1 dose, booster at 16 yrs At-risk groups: 2 months–55 yrs Canada routine: not recommended (unless epidemiology warrants use in 11–24 yrs) At-risk: 2–55 yrs, 1 dose; ≥ 56 yrs 1 dose

Manufacturer	Vaccine	Active constituents per dose	Adjuvant	Other excipients	Presentation	Recommendations
	Single-dose vial with lyophilized serogroup A component; single-dose vial with the 3 other components in liquid form	Licensed from 2 months of age. Infant schedule 2, 4, 6 and 12 months of age	None	Sucrose, trometamol and sodium chloride	Single dose, freeze-dried vial reconstituted with prefilled syringe	Infants from 6–12 weeks of age, series consists of 3 doses, first dose from 6 weeks of age and an interval of 2 months to second dose; third (booster) dose at 12 months of age
Pfizer	Nimenrix™	5 each of serogroups A, C, Y and W polysaccharide conjugated to 44 µg of tetanus toxoid	None	Sucrose, trometamol and sodium chloride	Single dose, freeze-dried vial reconstituted with prefilled syringe	Infants from 6–12 weeks of age, series consists of 3 doses, first dose from 6 weeks of age and an interval of 2 months to second dose; third (booster) dose at 12 months of age
Protein-based vaccines						
GlaxoSmithKline	Bexsero®	Recombinant GNA2091-fHbp fusion protein ID 1*; recombinant NHBA-GNA130 fusion protein; recombinant NadA; OMV (strain NZ98/254 PorA P1.4)	$Al(OH)_3$	Sucrose, histidine, and sodium chloride	Liquid single dose	USA: 10 through 25 years of age, 2 doses 1 month apart

UK: Routine: 2, 4 and 12 months of age |
| Pfizer | Trumenba® | Recombinant fHbp protein ID 45 and ID 55* | $AlPO_4$ | Polysorbate-80 (E433), histidine-buffered saline and sodium chloride | Liquid 1, 5, and 10 prefilled syringes | EU: 10 years and older, either 2 doses at a 6 month interval or 3 doses; 2 doses at least 1 month apart, followed by a third dose at least 4 months after the second dose

USA: Same as EU except from 10–55 years of age only |
| Finlay Institute | VA-MENGOC-BC | OMV (B:4:P1.19,15) and 50 µg of serogroup C polysaccharide | $Al(OH)_3$ | Thimerosal, disodium hydrogen phosphate, dehydrated sodium dihydrogen phosphate, sodium chloride | Liquid 1, 10 and 20 dose vials | Cuba: 2 doses at 3 and 5 months of age |

* fHbp peptide ID by (http://pubmlst.org/Neisseria/fHbp/).

Table 2: Meningococcal vaccines in clinical trials

Manufacturer	Vaccine	Active constituents per dose	Adjuvant	Other excipients	Presentation	Recommendations
Serum Institute of India	Pentavalent	5 µg each of serogroups A, C, W, Y and X. Serogroups C, W and Y conjugated to CRM_{197}; serogroups A and X conjugated to tetanus toxoid	$AlPO_4$	Sodium chloride	Lyophilized 1 and 5 dose vials	Phase I trial complete
GlaxoSmithKline	ACWYX conjugate	Those found in Bexsero and Menveo	Data not in public domain	Data not in public domain	Data not in public domain	Phase II trials

6. Response to immunization

6.1 Meningococcal polysaccharide vaccines

Polysaccharide vaccines are T-cell independent antigens and elicit SBA responses in the absence of T-cell involvement, hence these vaccines tend to be immunogenic in older children and adults, but fail to be as immunogenic in young children. This age-related response is likely to reflect intrinsic B-cell maturation, possibly due to natural priming as the antibodies elicited in adults are isotype-switched that is normally representative of a secondary antibody response (Barington et al., 1996; Baxendale et al. 2000; Zhou et al., 2002). Immunization of infants with polysaccharide vaccine can induce anticapsular antibody, but often this is not bactericidal (Lieberman et al., 1996; Campagne et al., 2000) and SBA titres elicited by polysaccharide immunization in older children and adults tend to be greater than those observed in young children (Maslanka et al., 1998; Campagne et al., 2000; Harris et al., 2003). Age-dependent responses to immunization are seen with polysaccharide vaccines (Jokhdar et al., 2004; Al-Mazrou et al., 2005; Khalil et al., 2005) and with a quadrivalent ACYW polysaccharide vaccine were observed in children and adults in Saudi Arabia (Lepow et al., 1977; Makela et al., 1977; Kayhty et al., 1980; Jokhdar et al., 2004; Khalil et al., 2005; Al-Mazrou et al., 2005). This age-dependent increase in antibody responses is shown clearly in the studies of the quadrivalent A, C, W, Y polysaccharide vaccine in Saudi Arabia (Figure 4). Children aged ≤ 2 years received two doses two months apart and children aged ≥ 3 years received one dose, with a significant increase in the proportions with an rSBA titre ≥8 for each serogroup pre- to post-immunization only observed in those aged ≥ 3 years).

Figure 4: Age-dependent response to meningococcal serogroups A, C, W and Y polysaccharide vaccine in children and adolescents in Saudi Arabia
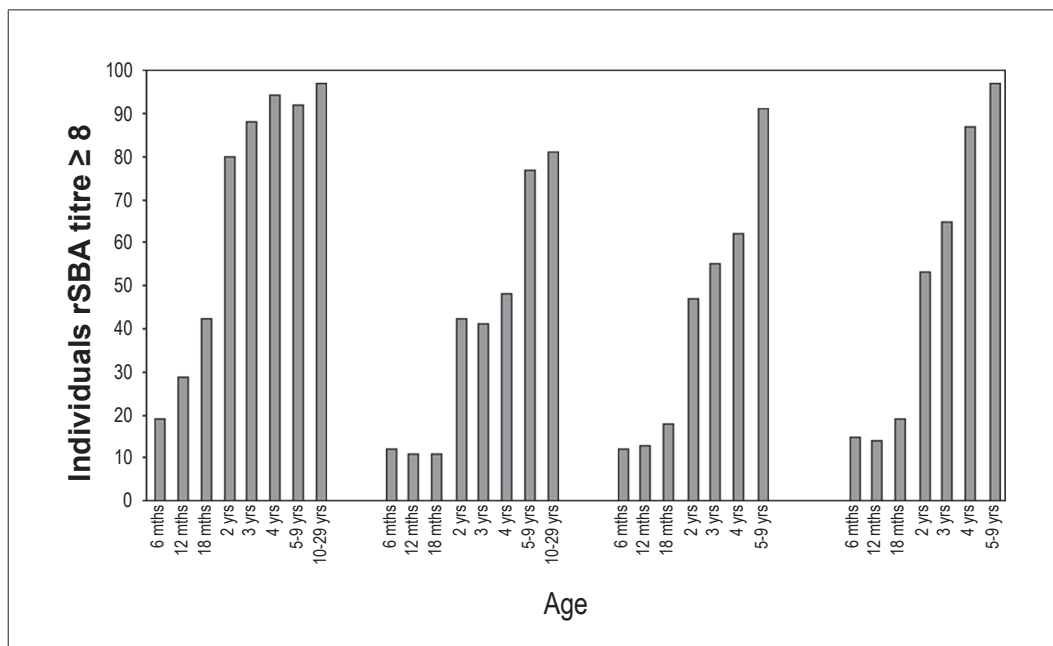
Source: Borrow & Balmer, 2010 (original data from Jokhdar et al., 2004; Khalil et al., 2005; Al-Mazrou et al., 2005).

The antibody response following polysaccharide immunization is usually present after 10 days and is traditionally assessed by four weeks post-immunization (Zangwill et al., 1994; Borrow et al., 2001b). In adults, the SBA declines over the next two years, but remains above baseline for approximately 10 years (Zangwill et al., 1994). The decline is more rapid in children with serogroup C SBA titres, returning to baseline by one year in 18 month to 5 year-olds (Espin Rios et al., 2000). Gambian children given two doses at 3 and 6 months had SBA titres similar to an unimmunized cohort at 18–23 months of age and also three years later following a further dose at 18–23 months (Leach et al., 1997; MacLennan et al., 1999).

Response to re-immunization with meningococcal polysaccharide vaccines is dependent upon the individual polysaccharides. An initial dose of serogroup A polysaccharide primes for a booster response to a second dose of serogroup A polysaccharide, even in young children (Gold et al., 1979; Leach et al., 1997; Jokhdar et al., 2004). However, serogroup A polysaccharide does seem to be different to serogroup C, W and Y polysaccharides in that it is not strictly acting in the traditional T-cell independent manner associated with polysaccharide antigens. There are extensive data published on antibody hyporesponsiveness to serogroup C polysaccharide immunization in all age groups (Gold et al., 1975; Leach et al., 1997; MacDonald et al., 1998; Granoff et al., 1998a; Richmond et al., 2000; Borrow et al., 2000b; Jokhdar et al., 2004). Hyporesponsiveness is when the immune response is of lower magnitude following a second or more dose of vaccine as opposed to the initial dose. As mentioned above, one dose of serogroup C polysaccharide vaccine is immunogenic in older children and adults, but it has been demonstrated that it can also impair the subsequent immune response to a dose of conjugate vaccine (Southern et al., 2004; Keyserling et al., 2005; Vu et al., 2006a). The disparity in the responses to repeated doses of the individual polysaccharides reflects potential differences in the respective mechanism(s) of immunogenicity that currently

remain poorly understood. The clinical relevance of antibody hyporesponsiveness is unknown, as polysaccharide vaccines have been extensively used with no reported increase in risk of acquiring meningococcal disease (Jackson et al., 1995; Rosenstein et al., 1998; De Wals et al., 2001). In many countries, polysaccharide vaccines have been replaced by conjugate vaccines.

6.2   Meningococcal conjugate vaccines

To overcome the problem of the T-cell independent nature of meningococcal polysaccharide vaccines, and the lack of immunogenicity in infants and young children, the successful approach was taken of conjugating the polysaccharide to a protein carrier applied to Hib vaccines. These conjugate vaccines stimulate T-cells to provide the necessary co-stimulation for B-cells, improving the immunogenicity of the polysaccharide even in infants who are unresponsive to unconjugated polysaccharide. Conjugate vaccines also stimulate the induction of immunologic memory through the generation of long-lasting memory B-cells (Goldblatt, 1998; Joseph et al., 2001; Richmond et al., 2001a; Kelly et al., 2005; Kelly et al., 2006) which, upon challenge with a low dose of meningococcal polysaccharide, produce a rapid antibody response at a greater magnitude than that of the primary response and the antibody tends to be of increased avidity. Commonly-used carrier proteins include tetanus toxoid, non-toxigenic natural variant of diphtheria toxin (CRM197) and diphtheria toxoid.

6.2.1 Monovalent serogroup C conjugate vaccines

In 1999, the United Kingdom became the first country to introduce MCC vaccine into the national childhood immunization schedule, together with a catch-up campaign up to 18, then 24 years of age (Miller et al., 2001). Extensive pre-licensure studies had demonstrated the safety and immunogenicity of these vaccines in infants (Richmond et al., 1999; MacLennan et al., 2000; Richmond et al., 2001a) and toddlers (Richmond et al., 2001b). No large-scale efficacy trials were performed; the vaccines were granted licensure by the demonstration of immunogenicity relative to the accepted surrogate of protection (Goldschneider et al., 1969a; Goldschneider et al., 1969b) and the known efficacy of the polysaccharide vaccine in children aged > 2 years.

The MCC vaccines were observed to be highly immunogenic in infants, stimulating high rSBA titres after two doses, as was shown in Figure 4. The proportion of infants with rSBA titres ≥ 8 was ≥ 98% after two doses, irrespective of the vaccine formulation (Fairley et al., 1996; Richmond et al., 1999; Borrow et al., 2000a; Richmond et al., 2001a). The SBA geometric mean titres (GMTs) observed in infants were similar to those observed in adults receiving one dose of polysaccharide vaccine (Richmond et al., 2000). Toddlers receiving one dose of MCC had high rSBA titres following vaccination, with ≥ 91% achieving an rSBA titre ≥ 8 (Richmond et al., 2001b). Immunization of pre-school children (3.5–6 years) and school leavers (13–18 years) in the United Kingdom, with one dose of serogroup C conjugate vaccine, resulted in high GMTs and virtually all subjects achieved protective rSBA titres ≥ 8 (Burrage et al., 2002). Serogroup C conjugate vaccines are highly immunogenic in adults, with significant increases in GMT and fourfold increases observed before, and one month following vaccination (Richmond et al., 2000; Borrow et al., 2001b; Goldblatt et al., 2002). The high immunogenicity of MCC vaccines allowed studies of a single primary dose in infancy to be performed and then implemented, for two of the three MCC vaccines in the United Kingdom primary infant immunization schedule. This study demonstrated

one dose of MCC-TT (NeisVac-C®) or MCC-CRM197 (Menjugate®) at 3 months gave comparable responses (SBA titres ≥ 8) to two doses, both post-primary vaccination and post-booster Hib/MCC-TT (Menitorix®) at 12 months (Findlow et al., 2012). However, the magnitude of the SBA GMT was higher in the MCC-TT primed post-booster.

Infants immunized at 2, 3 and 4 months have high SBA titres one month after the third dose, but this declines during the first year of life (Richmond et al., 1999) with between 47% and 70% of infants still having protective rSBA titres ≥ 8 at 12–13 months of age (Richmond et al., 2001a; Borrow et al., 2003). In children aged 3 to 4 years of age who had received three doses of MCC in infancy, 61% had hSBA titres ≥ 4 (Vu et al., 2006b) and 12% had rSBA titres ≥ 8 respectively (Borrow et al., 2002). Analysis of longer-term persistence of rSBA, up to 4–5 years, in children immunized at 2, 3 and 4 months, has revealed a rapid decline during the first 12 months but the rate of decline is not as great over the next three to four years with approximately 33% of children with rSBA titres ≥ 8.

A decline in SBA titres has been observed in toddlers following a single dose of MCC vaccine, with 75% and 37% protected (rSBA titres ≥ 8) at 6 months and 1.2–2.7 years post-vaccination, respectively (Richmond et al., 2001b; Snape et al., 2005). Twenty-five percent of children either 1.6–3 years, following one dose of MCC vaccine, had hSBA titres ≥ 4 (Vu et al., 2006b). The antibody persistence following a 12 months of age booster dose of MCC/Hib-TT, was investigated in young children who had been primed with each of the three MCC vaccines at 2, 3 or 2, 4 months of age (Borrow et al., 2010). The rSBA geometric mean titre was higher for those subjects primed with the MCC vaccine conjugated to tetanus toxoid (NeisVac-C) than for those primed with one of two MCC vaccines conjugated to CRM197 (Menjugate or Meningitec) up to one year following boosting. Two years after boosting, the percentages of subjects with SBA titres of ≥ 8 for children primed with NeisVac-C™, Menjugate™ and Meningitec™ were 43%, 22% and 23%, respectively (Borrow et al., 2010) (Figure 5).

Figure 5: Percentages of subjects with rSBA titres ≥ 8 before, 1, 12 and 24 months following administration of MCC/Hib-TT booster by priming MCC vaccine
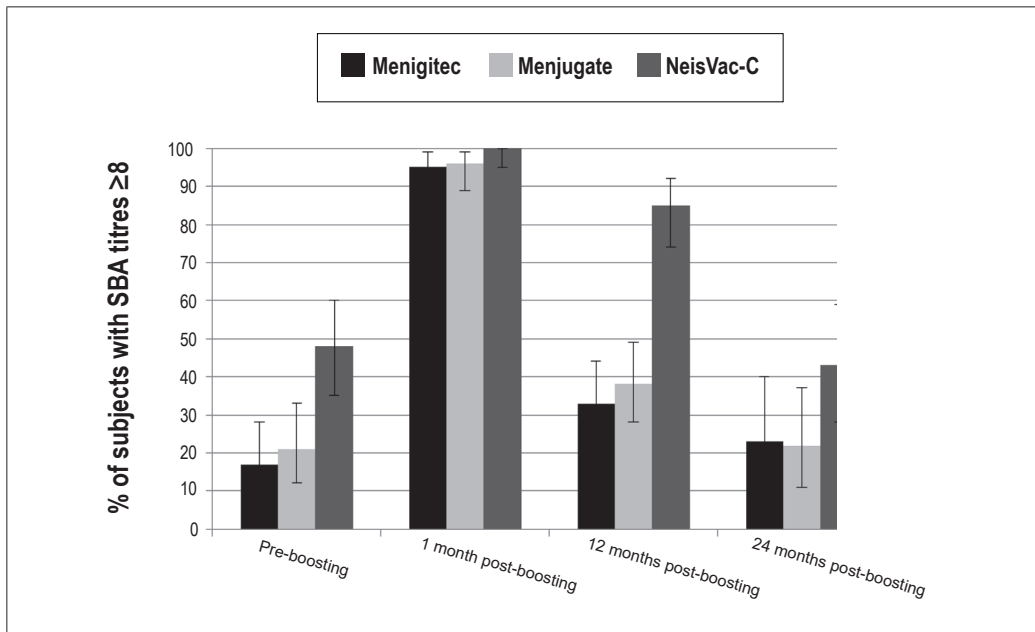
Source: Borrow et al., 2010.

Following MCC vaccination in adolescents, there is only a slight decline in SBA GMT during the initial 12-month period following a single dose of MCC vaccine (Choo et al., 2000). Ninety-six percent of adolescents vaccinated at 11–15 years with one dose of MCC vaccine have rSBA titres ≥ 8 at one to two years post-immunization (Borrow et al., 2007). In a study of healthy adolescents aged 11–20 years, previously immunized with MCC vaccine five years previously at age 6–15 years, 84.1% (95% CI: 81.6–86.3%) of 987 participants had a rSBA of ≥ 8. The rSBA GMTs were significantly lower in 11–13 year olds, 147 (95% CI: 115–188) as opposed to 14–16 year olds, 300 (95% CI: 237–380) and 17–20 year olds, 360 (95% CI: 252–515) (Snape et al., 2008a). Therefore, SBA GMTs were higher in those immunized at aged 10 years or above, as opposed to those immunized before the age of 10 years. Also, persistence of antibody appears to be age-dependent and is critical for the long-term persistence of SBA effectiveness of the group C conjugate vaccines (refer to section 7.2.1 on serogroup C conjugate vaccine efficacy).

6.2.2 Quadrivalent meningococcal polysaccharide-protein conjugate vaccines

As of April 2020, four quadrivalent meningococcal A, C, W, Y conjugate vaccines (MCV4) with different carrier protein are licensed in numerous countries.

6.2.2.1 MCV4-DT

MCV4-DT (Menactra®) contains 4 µg of each of the capsular polysaccharides conjugated to a total of approximately 48 µg of diphtheria toxoid protein. MCV4-DT has been shown to be highly immunogenic in adolescents and adults and non-inferior to immunization with the quadrivalent polysaccharide vaccine (Campbell et al., 2002; Bilukha & Rosenstein, 2005; Keyserling et al., 2005; National Advisory Committee on Immunization (NACI), 2007). In a study in infants, MCV4-DT was administered at 2, 4 and 6 months of age with between 54% and 92% achieving an rSBA titre ≥ 8 depending on the serogroup and amount of polysaccharide in the vaccine (Rennels et al., 2004). On this basis, MCV4-DT was not considered suitable in infants. In a similar study in toddlers aged 12–22 months, 78–100% achieved an rSBA titre ≥ 8 to each of the four serogroups following two doses 6–12 weeks apart (Rennels et al., 2002). One dose of MCV4-DT in children aged 2–10 years was observed to induce greater rSBA titres for all four serogroups compared to those children receiving one dose of quadrivalent polysaccharide vaccine (Pichichero et al., 2005). The number of subjects with a ≥ 4-fold rise in baseline rSBA titres (from < 8) was also greater in children receiving one dose of MCV4-DT vaccine. In a study of children aged 2–10 years of age in Chile, MCV4-DT was found to be non-inferior to one dose of quadrivalent polysaccharide vaccine with between 66% (serogroup Y) and 92% (serogroup W) of children, receiving either vaccine, achieving a ≥ 4-fold rise in rSBA one month following vaccination (Lagos et al., 2005). SBA persists in children aged 2–10 years of age 6 months after one dose of MCV4-DT, at a greater level than those who had received one dose of quadrivalent polysaccharide (Pichichero et al., 2005). However, waning of SBA titres at six months following vaccination was evident in both groups. Higher rSBA titres have been observed in children (24–36 months of age in the initial study) two years following a dose of MCV4-DT, compared to age-matched vaccine-naive children. Persistence of antibody in 11–17 year-olds three years after initial vaccination was reported to be greater in those receiving MCV4-DT compared to a quadrivalent polysaccharide vaccine (Keyserling et al., 2005).

Immunological interference has been demonstrated when MCV4-DT was given concomitantly with pneumococcal 7-valent conjugate vaccine (PCV7) and also when MCV4-DT was given 30 days after DTaP (Sanofi Pasteur, 2018). In one study where MCV4-DT was given alone at nine months of age and a second dose with PCV7 at 12 months, lower pneumococcal serotype GMTs were demonstrated for serotypes 4, 6B and 18C. No data are published on the coadministration of MCV4-DT and the currently used PCV13. A second study in children aged 4–6 years where DTaP was given 30 days before MCV4-DT and lower antibodies were recorded for all four serogroups. This was not observed when MCV4-DT was given concomitantly with DTaP.

6.2.2.2 MCV4-CRM

MCV4-CRM (Menveo™) contains 5 µg of each serogroups C, W and Y and 10 µg of serogroup A conjugated to 33–64 µg of CRM197. A study in British and Canadian infants, who received either MCV4-CRM or MCC at 2 and 4 months of age, demonstrated that over 80% of quadrivalent conjugate vaccine recipients had hSBA titres ≥ 4 following vaccination for serogroups C, Y and W and over 60% for serogroup A (Snape et al., 2008b). In a randomized study of a single dose of MCV4-CRM or MCV4-DT in children 2–10 years of age, hSBA GMTs were similar for serogroups A and C but ~2-fold higher in the MCV4-CRM group for serogroups Y and W (Halperin et al., 2010). In a study of MCV4-CRM or MCV4-DT in 11–18 year olds, higher hSBA titres were seen for the MCV4-CRM group for serogroups A, W and Y, while for serogroup C the GMTs were comparable (Figure 6) (Jackson et al., 2009).

Figure 6: Comparison of hSBA GMTs 1 month after vaccination with MCV4-CRM or MCV4-DT in 11–18 year old children
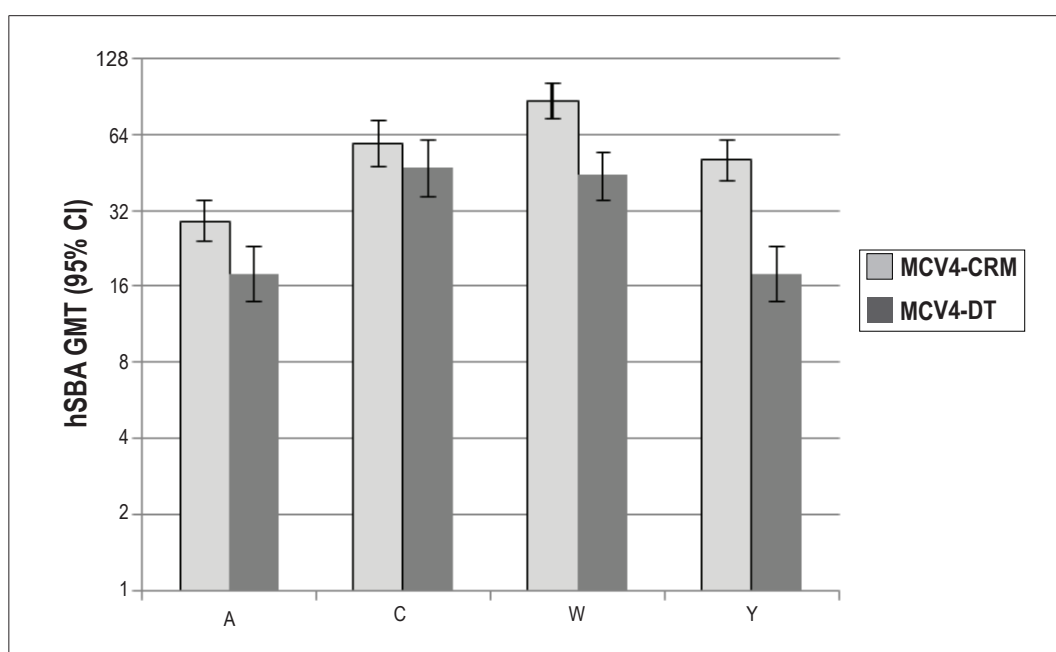
Source: Jackson et al., 2009.

6.2.2.3 MCV4rix-TT

MCV4rix-TT (Nimenrix™) contains 5 µg of each capsular polysaccharide conjugated directly to tetanus toxoid (W + Y) or via a spacer (A + C). MCV4rix-TT is licensed in Europe for individuals aged ≥ 6 weeks against invasive disease caused by meningococcal serogroups A, C, W and Y. Numerous Phase II-IIIb clinical studies showed that MCV4rix-TT administered as primary or booster vaccination was highly immunogenic for all four vaccine serogroups and had an acceptable reactogenicity profile in individuals aged 6 weeks to ≥ 56 years. MCV4rix-TT is as immunogenic and safe as other previously-licensed monovalent serogroup C or quadrivalent serogroup A, C, W and Y vaccines and can be coadministered with other routine vaccines without adversely affecting the immunogenicity or safety profiles of either vaccine (Figure 7) (Nimenrix, SPC; Dhillon & Pace, 2017).

Figure 7: Non-inferiority of MCV4rix-TT serogroup C component to MCC-CRM or MCC-TT
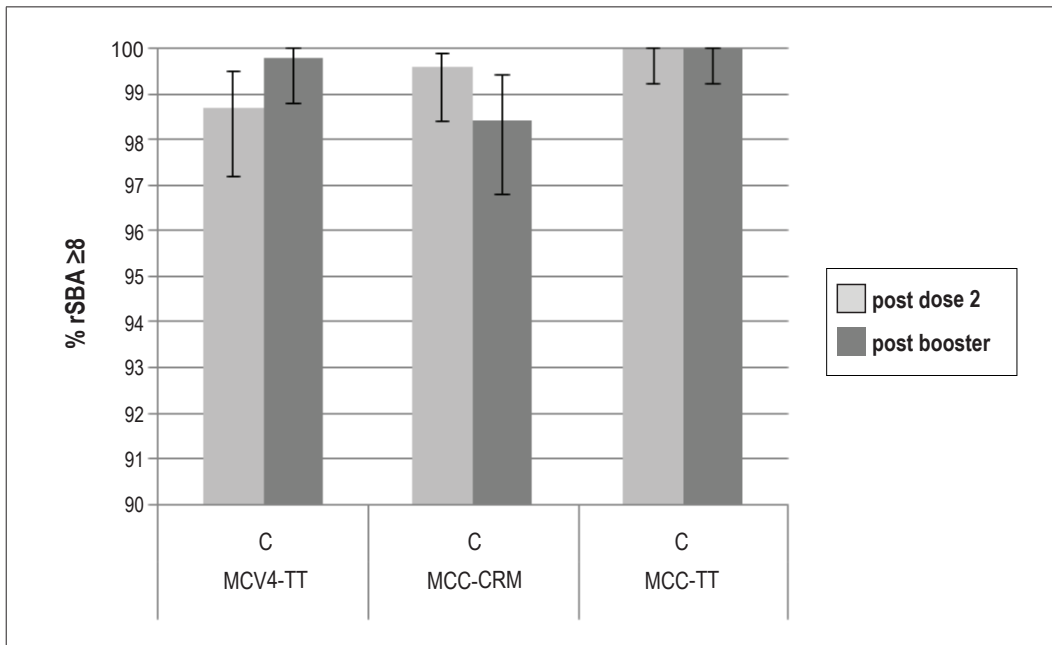
Source: Nimenrix, SPC.

First dose given at 6–12 weeks, second dose after an interval of two months, booster dose at 12 months of age.

One study compared MCV4rix-TT with MCV4-DT showing that vaccine responses ranging from 51.0% to 82.5% for the four serogroups after MCV4rix-TT and 39.0–76.3% for MCV4-DT where a vaccine response was defined as a hSBA titre of ≥ 8 in subjects with pre-vaccination hSBA titres of < 4 or for those subjects with pre-vaccination titres of ≥ 4, a ≥ 4-fold rise pre- to post-vaccination (Halperin et al., 2014).

Studies of MCV4rix-TT and MCV4-CRM have been reported in toddlers, adolescents and young adults (Ishola et al., 2015; Pellegrino et al., 2015; Bona et al., 2016). In toddlers aged 12–15 months, receiving either one dose of MCV4rix-TT or MCV4-CRM, immunogenicity was comparable between the two vaccines with the exception of serogroup A where higher rSBA GMTs were seen for MCV4-CRM, reflecting the higher quantity of serogroup A oligosaccharide in MCV4rix-CRM (Figure 8) (Bona et al., 2016).

Figure 8: rSBA GMTs (95% CI) against serogroups A, C, W and Y at baseline, one and six months following vaccination of toddlers with MCV4rix-TT or MCV4-CRM
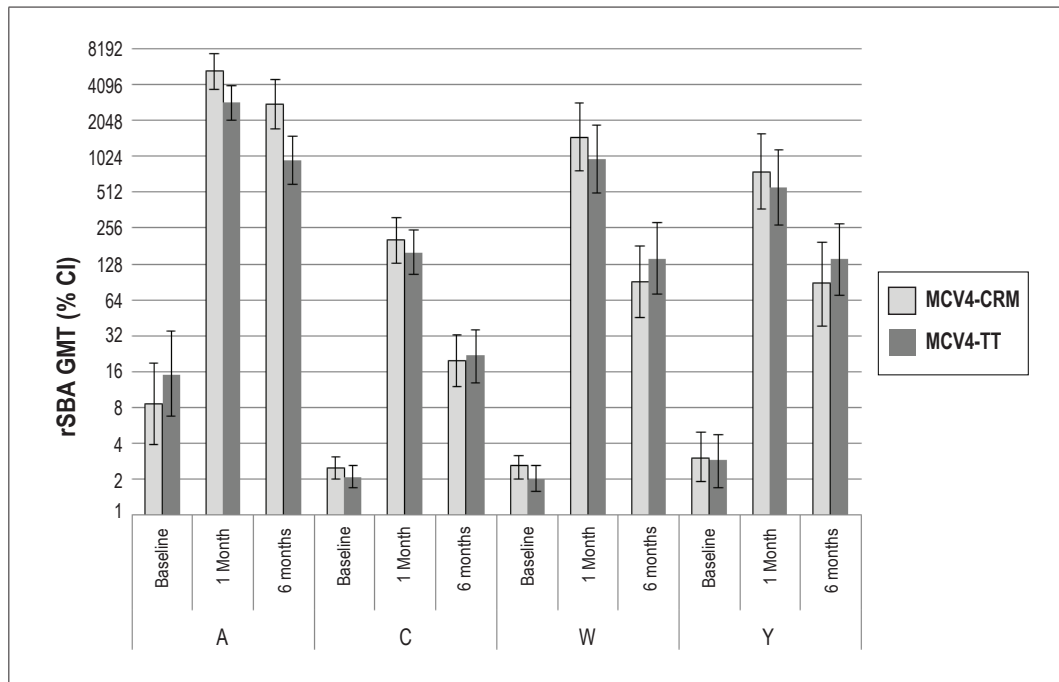
Source: Bona et al., 2016.

A randomized study compared MCV4rix-TT and MCV4-CRM in adolescents who had been primed in childhood with one of the three MCC vaccines (Ishola et al., 2015). Both MCV4 vaccines were highly immunogenic giving rSBA titres ≥ 8 in ≥ 98% of subjects. The highest serogroup C rSBA titres were seen in those MCC–TT-primed and MCV4rix-TT boosted, rSBA GMT ~ 22 000 followed by those boosted with MCV4-CRM irrespective of priming, rSBA GMT ~ 12 000.

6.2.2.4 MCV4fi-TT

MCV4fi-TT (MenQuadfi™) contains 10 µg of each serogroup A, C, Y, and W and approximately 55 µg of tetanus toxoid protein carrier per 0.5 mL dose. MCV4fi-TT is licensed for use in the United States from 2 years of age. MCV4fi-TT has been shown to be non-inferior to MCV-CRM in healthy adolescents in the United States (Chang et al., 2020). MCV4fi-TT has also been demonstrated to be immunogenic and safe in adults aged ≥ 56 years (Kirstein et al., 2020). Although awaiting confirmation in a Phase III study, an exploratory Phase II study of a single dose of MCV4fi-TT, as compared to MCV4rix-TT, has demonstrated the possibility of the use of a single dose of MCV4fi-TT in toddlers (Vesikari et al., 2020).

6.2.3 Monovalent serogroup A conjugate vaccines

In 2001, a 10-year grant was awarded to WHO and PATH from the Bill and Melinda Gates Foundation to support the Meningitis Vaccine Project (MVP) with the goal of eliminating meningococcal epidemics in sub-Saharan Africa through vaccination. The candidate vaccine had to meet a defined profile: induce long-lasting immunity after one dose; interrupt transmission (herd protection); be produced in accordance with the highest standards for quality control, production and rigorous licensure process; be available as quickly as possible, and have enough capacity for approximately 25 million doses per year over 10 years at a cost that would facilitate its widespread use in Africa. To fit this profile, a monovalent serogroup A conjugate (MenAfriVac, PsA-TT), manufactured at a cost agreeable to African countries, was agreed upon. The Serum Institute of India, Pune, was selected to manufacture the vaccine (which contains 10 μg of serogroup A polysaccharide conjugated to 10–20 μg tetanus toxoid and aluminium phosphate as adjuvant. A Phase I study to assess safety, immunogenicity and antibody persistence in adults was performed in India (Kshirsagar et al., 2007). The vaccine was observed to be immunogenic with a ≥ 4-fold increase in rSBA titres in 83% of individuals compared to 72% of the control group who received one dose of meningococcal polysaccharide vaccine A + C. Significantly higher geometric mean concentrations of serogroup A-specific IgG were observed after PsA-TT immunization, as compared to bivalent A + C polysaccharide vaccine. After one year, rSBA titres were significantly higher in those receiving PsA-TT vaccine in comparison to the control group (Figure 9).

**Figure 9: Serogroup A rSBA persistence at weeks 24 and 48
post-vaccination with PsA-TT vaccine in adults**
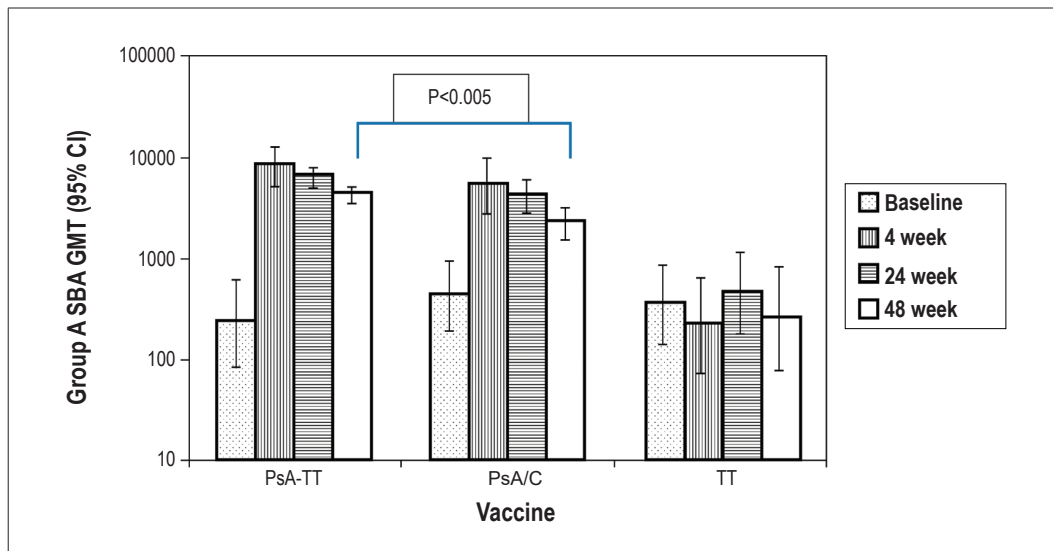
Source: Kshirsagar et al., 2007.

Following the encouraging results of the Phase I trial, a Phase II trial was performed to assess the responses in African toddlers aged 12–23 months. A total of 601 children, 12–23 months of age, were randomly assigned to receive PsA-TT, a quadrivalent polysaccharide reference vaccine (PsACWY), or a control vaccine (Hib-TT). Ten months later, these children underwent a further round of randomization within each group to receive a full dose of PsA-TT, a one-fifth dose of PsACWY, or a full dose of Hib-TT (Sow et al., 2011). A total of 96.0% of the subjects in the PsA-TT group and 63.7% of those in the

PsACWY group had rSBA titres that were ≥ 4 times as high as those at baseline. The rSBA GMT in the PsA-TT group was greater by a factor of 16 than the rSBA GMT in the PsACWY group. At week 40, the PsA-TT group had higher rSBA GMTs than the PsACWY group and demonstrated immunological memory after receiving a polysaccharide challenge. These children were then followed up for evaluation of antibody persistence up to five years after primary vaccination (Tapia et al., 2015a). The rSBA titres were shown to decline in the year following vaccination, but plateaued at levels significantly above baseline for up to five years following primary vaccination.

The next study was performed in 900 African subjects between 2 and 29 years of age who were randomly assigned to receive PsA-TT or PsACWY (Sow et al., 2011). In total, 78.2% of subjects in the PsA-TT group and 46.2% of those in the PsACWY group had rSBA titres that were ≥ 4 times as high as those at baseline. These subjects were followed up for four years; substantial rSBA decay was observed at six months post-vaccination in both vaccine groups and this was more marked in the PsACWY group (Diallo et al., 2015). The rSBA titres were significantly higher in the PsA-TT group than the PsACWY group for all time-points and the majority (over 93%) of subjects in the PsA-TT group, regardless of age, maintained rSBA titres ≥ 128 up to 4 years post-vaccination (Diallo et al., 2015). Seroprevalence studies following the introduction of PsA-TT one year following the campaign from Burkina Faso, and two years following the campaign in Mali (Basta et al., 2015; Tall et al., 2015). Both studies showed high levels of protection of the population targeted for vaccination.

6.2.4 Pentavalent ACWYX vaccines

Due to a number of outbreaks of serogroup X in the Meningitis belt (Campagne et al., 1999; Gagneux et al., 2002; Djibo et al., 2003; Boisier et al., 2007; Caugant et al., 2012), a pentavalent meningococcal conjugate vaccine targeting serogroups A, C, W, Y and X (MCV5) was trialled in a single-centre, double-blind, randomized controlled Phase I trial. Participants were healthy adults aged 18–45 years and randomized to a single, 0·5 mL, intramuscular injection of aluminium-phosphate adjuvanted MCV5, non-adjuvanted NmCV-5, or control (the quadrivalent meningococcal conjugate vaccine MCV4-DT). Serum was collected before vaccination, and 28 days after vaccination, for immunological assessment with an rSBA assay (Chen et al., 2018). Both adjuvanted and non-adjuvanted MCV5 elicited high rSBA titres against all five meningococcal serogroups. The pre-vaccination GMTs ranged from 3.36 to 53.80 for the control, from 6.28 to 187.00 for the adjuvanted vaccine and from 4.3 to 350 for the non-adjuvanted vaccine, and the post-vaccination GMT ranged from 3.1 to 3214 for the control, from 1351 to 8192 for the adjuvanted vaccine and from 1607 to 11,191 for the non-adjuvanted vaccine. This Phase I trial allowed progression to Phase II trials in young children.

6.2.5 Combination vaccines

Combination vaccines provide a useful way to deliver a wide range of vaccines in a single injection. One meningococcal serogroup C and Hib tetanus toxoid conjugate vaccine was licensed in the United Kingdom in December 2005 (Electronic Medicines Compendium, 2005). This combination, administered as a single dose, is mainly utilized to boost immunity to meningococcal serogroup C and Hib in toddlers that have previously completed a primary immunization series with other meningococcal group C or Hib conjugate vaccines, such as in the United Kingdom childhood immunization programme (Department of Health, 2006). Coadministration of the combined meningococcal serogroup C and Hib conjugate vaccine with the measles, mumps and rubella (MMR) vaccine does not interfere with the immune response and is safe and well tolerated (Carmona et al., 2010). Limited data are published on the immunogenicity of the combined meningococcal serogroup C and Hib conjugate vaccine as a booster in the second year of life, although large increases in SBA indicating successful priming with induction of immune memory are demonstrated. Whether infants are primed with either a meningococcal CRM197-based or TT-based conjugate, the proportion of infants putatively protected with SBA titres ≥ 8 is similar at 98–100% (Electronic Medicines Compendium, 2005). However, if a TT-based conjugate is used to prime in infancy, SBA GMTs and SBA titres ≥ 128 are higher, as opposed to those if primed with a CRM197-based conjugate (Electronic Medicines Compendium, 2005). Hib responses are also enhanced when the priming and/or boosting serogroup C conjugate is conjugated to tetanus toxoid (TT), whether as a combined meningococcal serogroup C and Hib conjugate vaccine or as an MCC vaccine (Electronic Medicines Compendium, 2005; Kitchin et al., 2007). The combined meningococcal serogroup C and Hib conjugate vaccine, coadministered with DTaP3-HBV-IPV has been demonstrated in a randomized pre-licensure study to induce a higher SBA GMT than an MCC-CRM197 vaccine, coadministered with DTaP-HBV-IPV/Hib at 2, 4 and 6 months of age (Tejedor et al., 2007). However, a similar study, but using a 2, 3 and 4-month schedule, demonstrated lower SBA GMTs for the combined meningococcal serogroup C and Hib conjugate vaccine than for a MCC-CRM197 vaccine (Schmitt et al., 2007).

6.3 Meningococcal protein vaccines

6.3.1 Outer membrane vesicle (OMV) vaccines

Serogroup B meningococci are a major cause of invasive meningococcal disease in the Americas and in many European countries, and over the last 30 years there have been epidemics in Brazil (Sacchi et al., 1992), Chile (Cruz et al., 1990), Cuba (Sierra et al., 1991), New Zealand (Martin et al., 1998) and Norway (Bjune et al., 1991). Most cases during a serogroup B epidemic are clonal and share the same PorA subtype. Therefore, for the development of a vaccine against a single group B strain, the PorA outer membrane protein (OMP) is considered as the most important protein with regard to protection, although in addition, SBA responses to other OMPs and antigens are also induced (Rosenqvist et al., 1995). This was clearly demonstrated in a randomized controlled trial in Chile where the Finlay Institute OMV vaccine (PorA P1.15) and Norwegian vaccine (PorA P1.7,16) were used, and sera were assayed by hSBA against both vaccine strains. Responders were defined as a subject with a $\geq$ 4-fold rise pre- to one-month post third dose of OMV vaccine. Good responses were seen in those vaccinated with the Finlay vaccine against the corresponding vaccine strain but not against the Norwegian strain, and also in those vaccinated with the Norwegian vaccine against the Norwegian strain, but not the Finlay strain (Tappero et al., 1999) (Figure 10).

OMV vaccines can be tailor-made for the control of a particular epidemic and are usually based on a clinical isolate from the actual epidemic (Holst et al., 2005). Immunization with an OMV vaccine induces SBA activity that correlates with protection (Holst et al., 2003), and the licensure of serogroup B vaccine will be on the basis of SBA activity together with safety data, without large-scale efficacy studies (Borrow et al., 2006a).

Figure 10: Percentage of hSBA responders by target strain, vaccine group and age group one month following three doses of vaccine
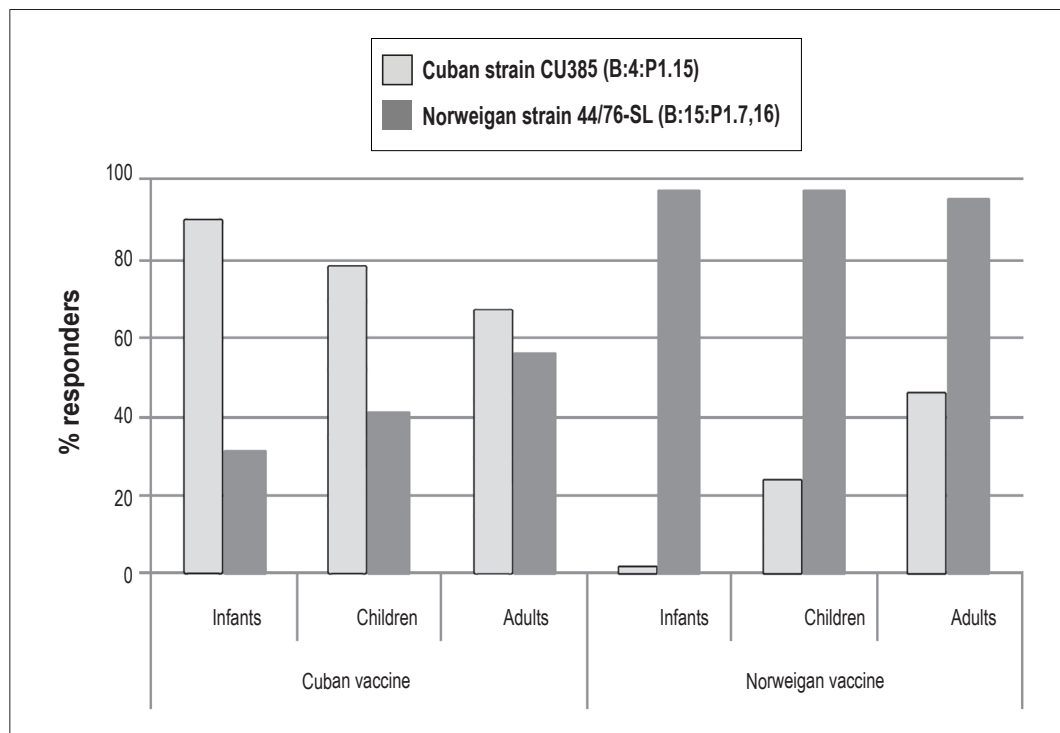
Source: Tappero et al., 1999.

In order to broaden further the coverage provided by OMV vaccines, a multivalent PorA vaccine was developed in the Netherlands. The vaccine, containing six different PorA OMPs, was based on two strains, each expressing three different PorA OMPs (P1.7,16; P1.5-1,2-2; P1.19,15-1; P1.5-2,10; P1.12-1,13; P1.7-2,4) (van der Ley et al., 1995; Claassen et al., 1996). It was found to be safe, well tolerated and immunogenic in infants (Cartwright et al., 1999) and in toddlers and schoolchildren (de Kleijn et al., 2000). To expand coverage further, a nonavalent OMV vaccine was next developed adding a third trivalent vesicle (containing PorAs P1.7-2,4; P1.22,14; P1.7-1,1 and P1.18-1,3,6) (Van den Dobbelsteen et al., 2007). This nonavalent PorA OMV vaccine is yet to undergo clinical evaluation. Numerous approaches have been taken in modifying meningococcal OMV vaccines, by either using native as opposed to detergent extracted OMVs and/or down regulation of unwanted antigens and/or upregulation of immunogenic antigens, and some have entered clinical evaluation (Zollinger et al., 2012; Marsay et al., 2015). An OMV vaccine has also been prepared from a strain of *N. lactamica* (Gorringe, 2005). It has been hypothesized that the development of natural immunity to meningococci in young children may be due to cross-protection induced by carriage of the commensal *N. lactamica* that has many common surface structures with *N. meningitidis* but not PorA or capsular polysaccharide. Thus, immunization with an OMV vaccine that lacks PorA may, theoretically, shift the antibody responses to other

antigens that are poorly immunogenic in the presence of PorA but capable of eliciting protective antibodies in its absence. A Phase I study analysing the immunogenicity of three doses of an *N. lactamica* OMV vaccine has been completed and the vaccine was shown to elicit increases in SBA responses similar to those seen with a meningococcal OMV vaccine against PorA heterologous strains (Gorringe et al., 2009).

6.3.2 4CMenB

Developments in the meningococcal genomics and proteomics have provided additional approaches to identification of novel vaccine candidate antigens (Pizza et al., 2000; Sun et al., 2000) with the term "reverse vaccinology" being adopted for antigens first identified by computer analysis of the genome (Rappuoli, 2000; Kurz et al., 2003; Capecchi et al., 2004; Mora et al., 2006). Using reverse vaccinology, a large number of novel meningococcal antigens were identified, five of which were taken forward and expressed in a form suitable for large-scale manufacturing. The antigens included were Neisseria Heparin Binding Antigen (NHBA) (GNA2132) (Welsh et al., 2003), ubiquinone-8 binding protein (GNA1030) (Pizza et al., 2000; Donnarumma et al., 2015), a lipoprotein (LP) (GNA2091) (Pizza et al., 2000), factor H binding protein (fHbp) (GNA1870) (LP 2086) (Masignani et al., 2003; Welsch et al., 2004; Giuliani et al., 2005; Hou et al., 2005; Cantini et al., 2006; Madico et al., 2006) and NadA (Comanducci et al., 2002; Capecchi et al., 2005). To increase the immunogenicity and stability, fHbp is fused with GNA2091 and NHBA with GNA1030 (Pizza et al., 2000). These two fusion proteins were formulated with NadA to produce a novel recombinant MenB vaccine (rMenB). The formulation consisting of five different recombinant antigens was at that time called Five Component Vaccine against Meningococcus B (5CVMB) (Jacobsson et al., 2009). To investigate ways of increasing immunogenicity, rMenB was then formulated with OMVs derived from either the Norwegian strain 44/76-SL, B:15:P1.7,16 (rMenB+OMVnw) or New Zealand strain NZ98/254, B:4:P1.7-2.4 (rMenB+OMVnz) (Toneatto et al., 2011). The final vaccine formulation, which progressed through clinical trials (Toneatto et al., 2011) and was submitted in December 2010 to the European Medicines Agency for a marketing authorization, is rMenB+OMVnz and has been assigned the trade name of Bexsero® and is also termed four component meningococcal serogroup B vaccine (4CMenB).

Following the Phase I study, the first Phase II was performed in infants with a 2, 4, 6 and 12-month schedule (Findlow et al., 2010). Serum was collected at five time-points, pre-vaccination, one month post 2 doses, one month post 3 doses and pre- and one month-post booster. The percentage of infants with hSBA titres ≥ 4 and hSBA GMTs are depicted, respectively, in Figure 11 and Figure 12. Good responses were seen both in terms of hSBA titres ≥ 4 and hSBA GMTs one month following the second dose at 4 months of age. These data, together with cost-effectiveness data, were used in formulating the United Kingdom 4CMenB national infant immunization schedule which is 2, 4 and 12 months of age (Ladhani et al., 2016). Following the third dose, antibody levels declined to 12 months of age, rapidly for the PorA antigen with only 34% of infants having hSBA titres ≥ 4 pre-booster. Following the booster, 93–100% of infants had hSBA titres ≥ 4 (Findlow et al., 2010). The antibody persistence and response to a booster was studied in a subset of these children at 40–44 months of age (Snape et al., 2013). Although antibody levels declined over the 28–32 months following the 12-month booster, 41–76% of infants had hSBA titres ≥ 4 depending on the antigen. One month following a booster of 4CMenB given at 40–44 months of age, hSBA titres ≥ 4 was 89–100% depending on the antigen.

Figure 11: Percentage of infants with hSBA ≥4 (95% CIs) one month after 2 and 3 doses of 4CMenB at 2, 4, 6 months of age and before, and one month after a booster dose at 12 months of age and at 40–44 months of age
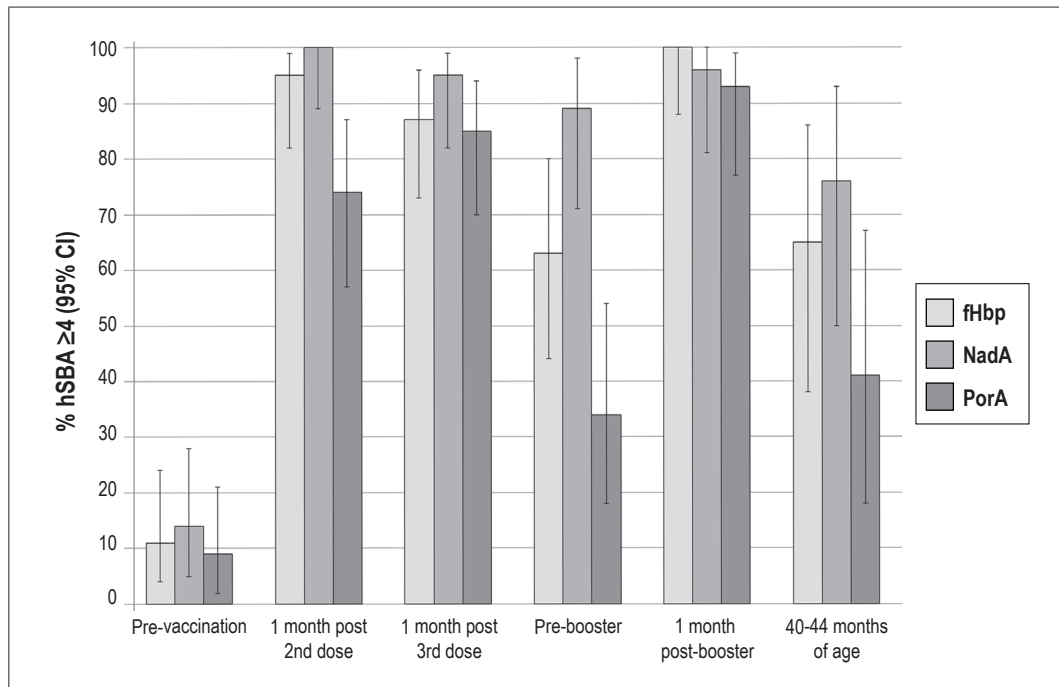
Source: Findlow et al., 2010 & Snape et al., 2013.

Figure 12: hSBA GMTs (95% CIs) one month after 2 and 3 doses of 4CMenB at 2, 4, 6 months of age and before, and one month after a booster dose at 12 months of age and at 40–44 months of age
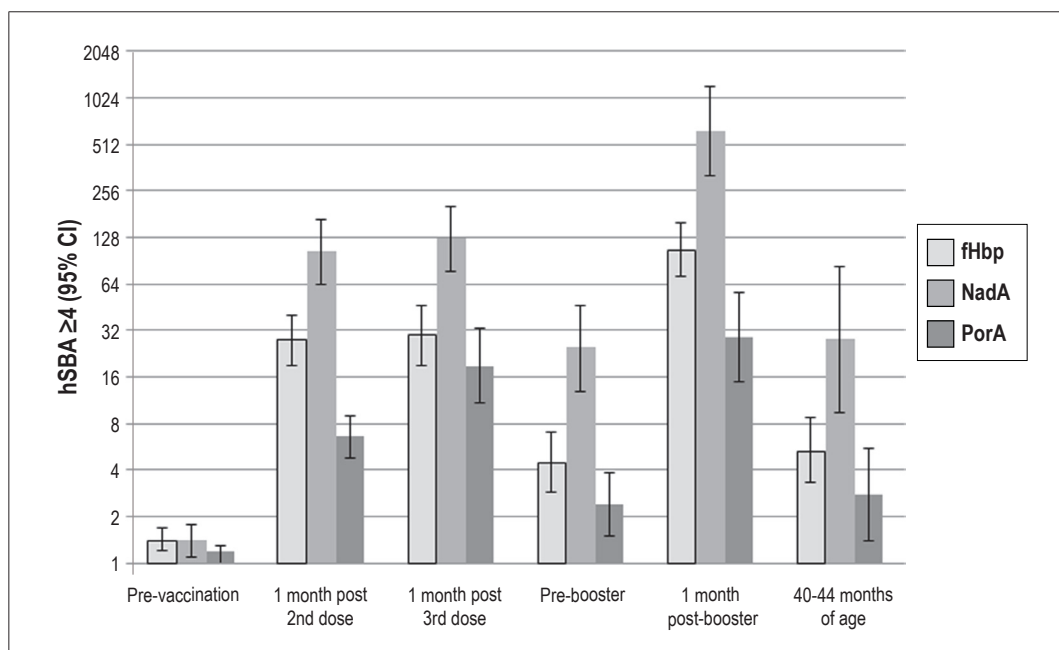
Source: Findlow et al., 2010 & Snape et al., 2013.

A Phase IIIb study in infants compared three different 4CMenB schedules, 2 + 1 schedule at 3.5, 5, 11 months or 6, 8, 11 months of age or a 3 + 1 schedule at ages 2.5, 3.5, 5, 11 months (Martinón-Torres et al., 2017). No major differences were noted one month following the booster in terms of hSBA ≥4 or GMTs between 3.5, 5, 11 months or 2.5, 3.5, 5, 11 schedules. These children were followed out to 24–36 months post-booster and antibody persistence was also similar for both schedules (Martinón-Torres et al., 2018).

Adolescents aged 11–17 years received one, two, or three doses of 4CMenB at one month, two months, or six-month intervals in a key randomized study in Chile (Santolaya et al., 2012; Santolaya et al., 2013). High baseline levels of hSBA ≥4 were noted ranging from 21–42% depending on vaccine group and target antigen. For those receiving a single dose of 4CMenB, 93% of subjects had hSBA titres ≥ 4 one month post-vaccination, declining to 62–73% at 18–24 months post-vaccination, depending on the target antigen. For each of the different 2- and 3-dose schedules, no major differences in % hSBA ≥ 4 ranging from 98–100% (Figure 13). These were the main data for the licensure of a 2-dose schedule, not less than one month apart for those over 11 years of age (Bexsero, SPC). The hSBA GMTs are shown in Figure 14 with, as for the percentage of subjects with hSBA ≥4, the 1-dose schedule performing poorly (Santolaya et al., 2013). For the fHbp antigen, no major differences were seen between the different two and 3-dose schedule, but for NadA and PorA the 3-dose schedules, in particular, 0,1,6 and 0,2,6, gave higher hSBA GMTs with better antibody persistence.

**Figure 13: Percentage of adolescents with hSBA titres ≥ 4
at baseline one month after last dose and at
18–24 months after last dose according to vaccine schedule**
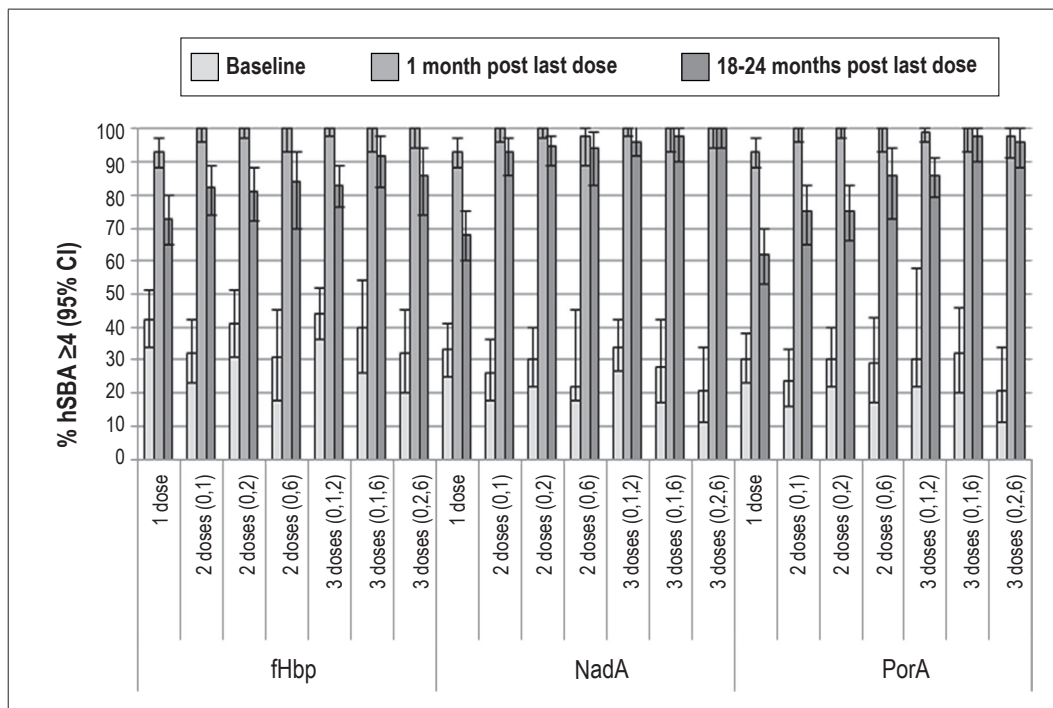
Source: Santolaya et al., 2013.

**Figure 14: hSBA GMTs (95% CI) of adolescents at baseline
one month after last dose and at 18–24 months after last dose
according to vaccine schedule**
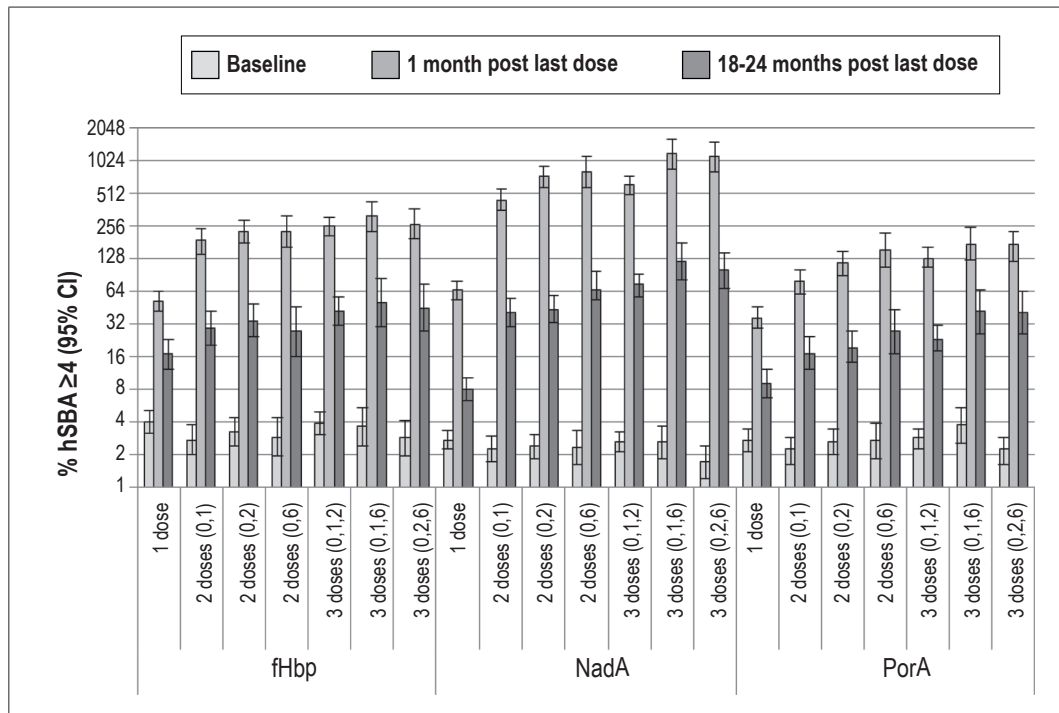
Source: Santolaya et al., 2013.

6.3.3 Bivalent rLP2086

Bivalent rLP2086 (Trumenba®) is composed of two recombinant fHbp proteins. fHbp was identified as a potential vaccine target due to its ability to stimulate a strong antibody response capable of killing diverse serogroup B strains (Fletcher et al., 2004). fHbp can be immunologically categorized into two distinct protein subfamilies, A and B, with 83–99% sequence identity within subfamilies but only 60–75% sequence identity between subfamilies (Murphy et al., 2009). Preclinical studies and data from early clinical studies confirmed that antibodies directed to fHbp are predominantly subfamily-specific and therefore supported a vaccine formulation composed of a protein from each fHbp subfamily (Fletcher et al., 2004; Jiang et al., 2010; Marshall et al., 2013). Two Phase III studies assessed the immunogenicity of the vaccine against diverse strains of group B meningococcus (Ostergaard et al., 2017). A total of 3596 adolescents (10–18 years of age) were randomized to receive bivalent rLP2086 or hepatitis A virus vaccine and saline, and 3304 young adults (18–25 years of age) to receive bivalent rLP2086 or saline at baseline, at two months and six months. The percentage of adolescents who had a ≥ 4-fold rise in the hSBA titre against each of four primary target strains ranged from 56.0% to 85.3% after dose 2 and from 78.8% to 90.2% after dose 3. The percentages of young adults ranged from 54.6% to 85.6% and 78.9% to 89.7% after doses 2 and 3, respectively. Bivalent rLP2086 is licensed from 10 years of age, either as a 2-dose 0, 6 month schedule or a 3-dose 0, 1–2, 6-month schedule (Trumenba, SPC).

6.4 Clinical risk groups

6.4.1 Asplenia

Asplenic individuals are known to be at increased risk of infection with encapsulated bacteria such as *N. meningitidis* (Eraklis et al., 1967; Krivit, 1977). The immune response of 103 asplenic individuals in the United Kingdom has been investigated following MCC vaccine (Balmer et al., 2004b). Asplenic individuals had significantly lower SBA GMTs when compared to an age-matched control group. However, 80% of asplenic individuals achieved the putative protective SBA titre ≥ 8. A significant reduction in SBA GMT, or the number of subjects with a SBA titre ≥ 8, was observed if the reason for splenectomy was a medical cause, or if vaccination occurred < 10 years after splenectomy. The United States recommendations are for vaccination with an age- and formulation-appropriate MCV4 vaccine from two months of age and serogroup B vaccine from 10 years of age (CDC MMWR, 2014; CDC MMWR, 2017). The United Kingdom guidance is similar; however, serogroup B vaccine (4CMenB) is recommended from two months of age (Department of Health, 2016).

6.4.2 Pre-term infants

Pre-term infants are at greater risk of infection than those born at full term due to the relative immaturity of their immune system. A follow-up of meningococcal group C disease in the United Kingdom, following the introduction of the MCC vaccine, found that, of 21 subjects with vaccine failure vaccinated at less than one year of age, two (10%) had a history of prematurity (Auckland et al., 2006). This proportion is similar to that found in a study of Hib conjugate vaccine failures, in which 12% of those vaccinated at less than one year were premature (Heath et al., 2000). Pre-term infants have been shown to generate adequate responses and equivalent protective antibody titres to term infants following administration of routine infant vaccines (Bernbaum et al., 1985; D'Angio et al., 1995; Ramsay et al., 1995; Kristensen et al., 1996). This led to recommendations that pre-term infants should receive the routine infant immunization schedule in accordance with their chronological age; for example, in Australia (The Australian Immunization Handbook, 2017), the United Kingdom (Department of Health, 2016) and the United States (Saari et al., 2003), provided they are well and there are no contraindications to immunization.

There are, however, several studies of premature infants that report decreased antibody responses to a number of vaccine antigens including, diphtheria, pertussis, tetanus toxoid and Hib (Conway et al., 1993; Kirmani et al., 2002; Heath et al., 2003). In the United Kingdom, the immune response of premature infants has been shown to elicit comparable protective SBA titres to term infants following immunization with an MCC conjugate vaccine in the two, three, four-month schedule when coadministered with either whole-cell pertussis (Collins et al., 2005) or acellular pertussis vaccines (Slack et al., 2001; Slack et al., 2005). An Italian study of a three, five and 11-month booster dose of MCC conjugate vaccine also showed comparable protective SBA titres between pre-term and term infants (Esposito et al., 2007).

6.4.3 Human immunodeficiency virus (HIV)

Meningococcal infection, although rare in individuals living with human immunodeficiency virus (HIV), has been observed (Nitta et al., 1993; Couldwell, 2001; Pearson et al., 2001; Simmons et al., 2015; Harris et al., 2016), with reports of disseminated meningococcal that may present with a variety of clinical manifestations, such as pneumonia or arthritis (Nitta et al., 1993). A data linkage of national datasets in England between 2011 and 2013 demonstrated the incidence among persons diagnosed with HIV was 6.6 per 100 000 compared to 1.5 per 100 000 among HIV-negative individuals, with a relative risk of 4.5 (95% CI: 2.7–7.5) (Simmons et al., 2015).

Limited data are available for immune responses following meningococcal vaccination in HIV-infected children. A United Kingdom study in 51 children (median age 7.3 years, range 1.2–15.7 years), of whom 74% were on antiviral therapy, reported only 49% of the children having protective SBA titres ≥ 8 following a single dose of MCC vaccine (Ruggeberg et al., 2002). Data were available in 11 of the non-responders who received a booster dose, of whom 63% had SBA titres ≥ 8; hence, the immunogenicity of MCC vaccines is compromised in this patient group. A study in Brazil showed high seroconversion following a booster dose of MCC in 2–18 years old HIV-infected subjects who had been previously primed 12–18 months previously with MCC (Frota et al., 2017).

MCV4-DT has now been trialled in HIV-infected individuals aged 11–24 years in the United States (Lujan-Zilbermann et al., 2012). In subjects infected with HIV with a CD4% ≥ 15, a second dose of MCV4-DT given six months after the initial dose significantly improves response rates. Subjects with CD4% < 15 at entry had lower response rates despite two doses of MCV4-DT. MCV4-DT was also studied in a trial in HIV-infected children aged 2–10 years with CD4 ≥ 25% (Siberry et al., 2012). Two doses of MCV4-DT were given at entry and at week 24; rSBA responses were high after one dose for serogroups A (92%) and W (98%) but the second dose of MCV4-DT improved responses to serogroup C (43–80%) and serogroup Y (76–84%).

6.4.4 Complement deficiency

Persons with terminal complement defects and properdin deficiency, including those on eculizumab therapy, are at highest risk, with reported invasive meningococcal disease incidences up to ten thousand-times higher than in the general population (Hellenbrand et al., 2015). Repeat episodes are relatively common in this patient group (Platonov et al., 2003). The meningococcal strains that cause disease in complement-deficient persons are usually those associated with carriage; hence, these are more likely to be either non-encapsulated or uncommon serogroups (McNamara et al., 2017; Rosain et al., 2017). In a study in 45 Russian patients with late complement component deficiency (LCCD) who had experienced between one and five episodes of meningococcal infection, 31 were immunized with a meningococcal ACWY polysaccharide vaccine and were followed for 3–8 years (Platonov et al., 2003). Total and Ig class-specific concentration of antibodies to meningococcal polysaccharides in sera increased significantly one month following vaccination and remained elevated for three years. Revaccination of LCCD patients with ACWY polysaccharide vaccine three years after the first dose restored the total Ig concentrations to those observed one year after the first vaccination. Six new episodes of meningococcal infection developed in four patients in the group of 31 vaccinees; six episodes in six patients developed in the same period in the group of 14 non-vaccinated LCCD persons, demonstrating that the risk of contracting meningococcal disease decreased significantly for those vaccinated as opposed to not vaccinated.

Eculizumab is indicated for therapy of patients with symptomatic paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uraemic syndrome (aHUS). Owing to inhibition of terminal complement cascade, patients on eculizumab are susceptible to meningococcal infections. The two main means to reduce the risk of infection are vaccination and antibiotic prophylaxis. In an evaluation of 23 PNH patients, immunogenicity of meningococcal vaccination, either MCV4-DT (n = 17), MCC-CRM197 (n = 1), or meningococcal polysaccharide vaccine, either ACWY or AC (n = 4) was analysed by measuring rSBA titres against serogroups A, C, W, and Y (Alashkar et al., 2017). Protection was defined by an rSBA titre ≥ 8. Forty-three percent had been vaccinated more than once. Overall serological responses for the meningococcal serogroups were serogroup A 78%, C 87%, W 48% and Y 70%. This is difficult to interpret as a mixture of conjugate and polysaccharide vaccine; also due to differences in valency of the vaccine, that is, all patients received serogroup C but not all the other serogroups. No meningococcal infections were observed.

6.4.5 Standard and intensive chemotherapy

After treatment of patients with acute leukaemia, there is a decrease in vaccine-specific antibody and an increased susceptibility to certain vaccine-preventable diseases. In a United Kingdom study of 59 children, median age 5.4 years (range 1.1–15.9) with acute lymphoblastic leukaemia (ALL) or acute myeloid leukemia (AML), 96% had rSBA titres ≥ 8 following a single dose of MCC vaccine administered ≥ 6 months following standard chemotherapy (Patel et al., 2007a). Before revaccination, only 12% had rSBA titres ≥ 8; therefore, protection can be achieved following revaccination of children after completion of standard chemotherapy for acute leukaemia.

Another United Kingdom study demonstrated that all 38 children after haematopoietic stem cell transplant (HSCT) had rSBA titres ≥ 8 following revaccination with MCC at a median age of 13 years of age (range 3.7–18.8) (Patel et al., 2007b). Only 11% had rSBA titres ≥ 8 before revaccination; hence, revaccination of paediatric HSCT recipients provides good levels of protection.

6.4.6 Malaria, malaria chemoprophylaxis and sickle-cell trait

The immune response to capsular polysaccharide antigens, including meningococcal polysaccharide, is suppressed by malaria (Williamson & Greenwood, 1978). Antibody levels are better maintained in children who are receiving chemoprophylaxis for malaria, as opposed to those who are not, as malaria increases the γ-globulin turnover (Cohen et al., 1961). Two years following vaccination, in Gambian children aged 1–3 years, with a bivalent meningococcal A/C polysaccharide vaccine, the mean serogroup A-specific IgG concentrations were significantly higher in 26 children who had received chemoprophylaxis; Maloprim (pyrimethamine/dapsone) once every 14 days during the rainy season, as opposed to 27 children who received placebo (Ceesay et al., 1993). Similar findings have also been found in Nigerian children 1–2 years of age following meningococcal bivalent A and C polysaccharide vaccine, where the malaria chemoprophylaxis used was chloroquine, with control children receiving vitamin C (Bradley-Moore et al., 1985). Subjects with the haemoglobin genotype AS (sickle-cell trait), have been reported to have higher antibody responses (Greenwood et al., 1980a) and better antibody persistence (Greenwood et al., 1980c) to serogroup C polysaccharide vaccine, compared to those with the genotype AA.

7. Effectiveness

7.1   Polysaccharide vaccines

7.1.1 Serogroup C

In 1969 and 1970, two large-scale field trials of serogroup C polysaccharide vaccine were performed among American military recruits (Artenstein et al., 1970; Gold & Artenstein, 1971). A total of 28 245 recruits from both trials received group C polysaccharide vaccination, with 114 481 men included as unimmunized controls. The route of vaccination was either needle or jet gun. During the eight-week follow-up, 73 culture-confirmed cases of serogroup C occurred among the controls (an attack rate of 0.64 per 1000) as compared to two cases among the vaccinated (excluding one case that occurred nine days after vaccination); an attack rate of 0.07/1000. Vaccine efficacy (VE) from the combined dataset was 89% (95% CI: 55–97%). The protection induced by the serogroup C polysaccharide vaccine was group-specific. In the first trial, there was no reduction in disease due to serogroup B in the vaccinated group, while in the second trial there were no cases of serogroup B disease in the vaccinated or control groups.

The first evaluation of efficacy of serogroup C polysaccharide vaccination in young children was conducted as a prospective field trial in 1974 during a large serogroup C epidemic in São Paulo, Brazil (Taunay et al., 1974; Taunay et al., 1978). Approximately 67 000 children aged 6–36 months were randomized 1:1 to receive either a dose of group C polysaccharide vaccine (via jet injector) or, as a control, diphtheria-tetanus toxoid. During the 17-month follow-up, there were 32 culture- or serologically-confirmed cases among the vaccinated group and 45 cases among the controls (VE 31%, 95% CI: 11–58%). For children aged 6–23 months, vaccine efficacy was 12% (95% CI: –55–62%); however, for children 24–36 months, vaccine efficacy was 55% (95% CI: 4–72%).

In Quebec, Canada, approximately 1.6 million doses of meningococcal polysaccharide vaccine were administered to persons aged six months to 20 years in 1992–1993 in response to an increase in the incidence of meningococcal serogroup C disease. This provided an opportunity to evaluate the effect of a large so-called real-world programme to assess duration of protection and examine vaccine effectiveness by age (De Wals et al., 2001). Overall, there was evidence of vaccine protection from serogroup C disease in the first two years following vaccination (VE, 65%; 95% CI: 20–84%), but not in the subsequent three years (VE, 0%; 95% CI, –5–65%). Age at vaccination was also an important determinant of vaccine effectiveness: 83% (95% CI: 39–96%) for 15–20 year olds, 75% (95% CI: –17–93%) for 10–14 year olds and 41% (95% CI: –106–79%) for those aged 2–9 years. There was no evidence of protection in children younger than two years.

Vaccine effectiveness of serogroup C polysaccharide has also been evaluated in an epidemic setting using a case-control design (Rondy et al., 2016). In 2015 in Niger, in reaction to a large outbreak of serogroup C disease, 2–15 year olds were targeted with two different C-containing polysaccharide vaccines. Vaccine effectiveness at more than 10 days following vaccination was 84% (95% CI: 75–89%) and 97% (95% CI: 94–99%) for the tri- and quadrivalent vaccines, respectively.

7.1.2 Serogroup A

In the 1970s, there were seven controlled field trials measuring the efficacy of meningococcal serogroup A polysaccharide vaccines in Eygpt (Wahdan et al., 1973; Wahdan et al., 1977), Finland (Makela et al., 1975; Peltola et al., 1977), Sudan (Erwa et al., 1973) and Upper Volta and Mali (Saliou et al., 1978). Interpretation of these trial data is hampered by the small number of cases and also the short duration of observation. Even so, high VE levels were reported in all studies, in all age groups, including infants.

The effectiveness of the serogroup A polysaccharide vaccine has also been reported from observational studies performed during mass immunization campaigns in epidemic conditions. In 1979, Nigeria suffered a serogroup A epidemic for the third year in succession. Due to limited vaccine supplies, immunization was only carried out in children over one year of age from villages who had at least two cases of meningitis. A population of 10 000 was immunized with a serogroup A and C polysaccharide vaccine, and subsequently there were 10 cases of meningococcal disease. Of these 10 cases, two occurred in vaccinated individuals, but were not vaccine failures as their symptoms commenced on the day of vaccination (Greenwood & Wali, 1980b). Almost two-thirds of the estimated 671 000 population of Bamako were vaccinated with a single dose of bivalent serogroup A and C polysaccharide between January and April 1981 in response to a group A epidemic (Binkin & Band, 1982). Those aged 1–30 years were targeted. The vaccine was effective in limiting further spread of the epidemic, and the attack rate among those who received vaccine was lower than that in the unvaccinated (0.7/10 000 versus 4.7/10 000).

Vaccine effectiveness was also studied in a serogroup A epidemic in Auckland, New Zealand, between 1985 and 1986 (Lennon et al., 1992). The age group targeted for vaccination were those aged three months to 13 years, with special emphasis on reaching populations at highest risk (Maori and Pacific Island Polynesian children). Two doses of monovalent serogroup A polysaccharide vaccine were administered to children aged 3–23 months, with those aged 2–13 years receiving a single dose. Although coverage was approximately 90% for a single dose, only 26% of children less than two years of age received their second dose. There were no cases of serogroup A disease (100% efficacy) observed among children following a single dose of vaccine at 18 months of age or older. In contrast there was no evidence of significant protection in children vaccinated between 3–18 months, with efficacy during the first year of follow-up at 52% (95% CI: -330–95%), then 16% (95% CI: -538–90%) after one year. Of those children who received their second dose, none developed disease.

Evidence on the duration of protection is limited but suggests that protection wanes rapidly. One of the controlled field trials in Egypt followed children aged 6–15 years for two years following immunization (Wahdan et al., 1977). There was high efficacy for the first year but no efficacy between one and two years. However, these data must be interpreted with caution as a sub-optimal, low molecular weight polysaccharide was used in the study. Efficacy was also shown to wane over time in a retrospective study in Ouagadougou, Burkina Faso, where approximately 103 000 infants and children aged three months to 16 years were vaccinated in response to a group A epidemic (Reingold et al., 1985). The results of case-control studies conducted one, two and three years after vaccination indicated overall efficacy of 87% (95% CI not given) for year one, 70% for year two and 54% for year three. This also indicated age differences in the duration of protection by age. In the first year after vaccination, age had no effect on the observed efficacy and, although efficacy remained relatively high in children four years of age, it dropped progressively in those < 4 years of age at the time of vaccination, such that three years following vaccination there was no evidence of protection in children less than four years of age (VE 8%; 95% CI: -102–58%), compared to 67% (95% CI: 40–82%) for children aged four to 16 years of age.

A Cochrane review concluded that serogroup A polysaccharide vaccines are strongly protective for the first year in children over five and adults, but its efficacy beyond the first year could not be determined with precision. Children aged 1–5 years in low-income countries were also protected but the efficacy in this age group could not be determined (Patel & Lee, 2005).

7.1.3 Serogroups Y and W

The licensure of the quadrivalent meningococcal polysaccharide vaccines was obtained through immunogenicity data based on ≥ 4-fold rises in rSBA responses (WHO, 1980) and from this the efficacy of the serogroup Y and W components was inferred. There are no data on the efficacy of serogroups Y and W polysaccharides.

7.2 Conjugate vaccines

7.2.1 Serogroup C (MCC)

Meningococcal serogroup C conjugate vaccines were licensed on the basis of safety and immunogenicity data; a Phase II efficacy trial was not carried out, hence, post-licensure surveillance data, particularly from the United Kingdom, which was the first country to use MCC vaccines in a national immunization programme, was crucial for determining effectiveness. Within 12–18 months of vaccine introduction, there was a marked decline observed in the number of cases and deaths caused by serogroup C disease in the age groups targeted for immunization (Miller et al., 2001; Gray et al., 2006). Formal estimates of age-specific VE in England up to September 2001 were approximately 90% or above for all vaccinated age groups (Miller et al., 2001; Ramsay et al., 2001). When effectiveness was measured again more than one year after vaccination, there was a significant decline in effectiveness for infants vaccinated in the routine infant immunization programme (Trotter et al., 2004). The effectiveness in infants vaccinated at two, three and four months of age significantly declined from the first year 88% (95% CI: 58–93%) to up to June 2006 where there was no demonstrable efficacy 7% (95% CI: -3733–85%). For those infants aged 5–11 months in the catch up who received two doses of MCC vaccine,

effectiveness remained high 91% (95% CI: 8–100%) within the first year and 84% (95% CI: 31–97%) after more than one year. In toddlers, the youngest group to receive a single dose, efficacy was 71% (95% CI: 40–93%) compared to 89% (95% CI: 64–98%) in the first year. The confidence intervals for both the infant and toddler effectiveness data are wide, and so the true extent of protection is uncertain. For those 3–18 years of age, efficacy remained high at 92% (95% CI: 85–96%) more than one year on following vaccination.

In Spain, infants vaccinated in the routine two, four and six-month schedule, also received high levels of protection, although declines in effectiveness over time were also noted. Vaccine effectiveness in infants fell from 98% (95% CI: 96–99%) within one year from vaccination, to 78% (95% CI: 3–95%) one year following vaccination (Larrauri et al., 2005). In Canada, mass immunization campaigns with MCC vaccine were undertaken in 2001 with the schedules followed varying by age and location. Similar to the United Kingdom, declines in the burden of disease were rapidly observed. After seven years of follow-up, VE was measured to be 87% (95% CI: 75–94%) overall with lower and waning protection in children vaccinated at < 2 years of age (De Wals et al, 2011).

In the Netherlands, MCC was introduced into the routine immunization programme in September 2002 in a one-dose schedule at 14 months of age. In addition, a catch-up campaign was conducted from June to November 2002 targeting nearly three million children up to 19 years of age. The reasons for commencing at 14 months of age, and not immunizing infants, were based partially on the evidence of herd protection as demonstrated in the United Kingdom, as well as a low incidence of serogroup C disease in the under one year olds. Up to February 2007, no vaccine failures have been reported and the number of serogroup C cases fell from 276 in 2001 to four in 2006 (de Greeff et al., 2006; De Greeff et al., 2007). Both the Flanders and Wallonie regions in Belgium also adopted a single-dose strategy from 12 months of age (ECDC). Australia also introduced a single dose early in 2003 at 12 months of age, with a catch up to 20 years; however, impact was more difficult to assess due to disease incidence already falling before vaccine introduction in New South Wales. Nevertheless, there was over 75% reduction in disease from 213 cases in 2002, to 50 in 2005 (Booy et al., 2007).

In Brazil, routine infant immunization with MCC vaccines began in November 2010, scheduled at three and five months plus a booster at 12–15 months of age. Although vaccine effectiveness was not estimated, an interrupted time-series analysis for 2008–2014 showed that incidence of serogroup C disease was reduced by 67% (95% CI: 43–91%) for infants < 12 months of age, 92% (95% CI: 77–106%) for children aged 12–23 months and 65% (95% CI: 25–105%) for children aged 2–4 years (Andrade et al., 2017). Effectiveness of MCC vaccines has not yet been assessed in an African outbreak setting, although 800 000 doses were deployed in northern Nigeria, in 2017, in response to a serogroup C epidemic.

7.2.2 Serogroup A

As with MCC vaccines, there was no Phase III efficacy trial for a monovalent serogroup A conjugate vaccine produced specifically for use in African populations (PsA-TT). The vaccine was first used in a national campaign in Burkina Faso in 2010. After vaccine introduction, there was a 71% decline in risk of meningitis (hazard ratio 0·29; 95% CI: 0·28–0·30, p<0·0001) and a 64% decline in risk of fatal

meningitis (0·36; 0·33–0·40: p<0·0001) (Novak et al., 2012). There were no cases of confirmed serogroup A disease in vaccinated individuals, although a few cases were reported in 2010 before vaccination commenced. Compelling evidence of vaccine impact comes from a study in Chad that was experiencing an ongoing serogroup A epidemic at the time of vaccine introduction (Daugla et al., 2014). Approximately 1·8 million individuals aged 1–29 years received one dose of PsA-TT during a vaccination campaign in three regions in and around N'Djamena during December of 2011. Here, the incidence of meningitis in the following dry season was 2·5 per 100 000, whereas in the unvaccinated, incidence was 43·8 per 100 000, that is, a 94% difference in crude incidence (p<0·0001) and an incidence rate ratio of 0·096 (95% CI: 0·046–0·198). No cases of confirmed serogroup A meningococcal meningitis were reported in the three vaccinated regions despite enhanced surveillance. Incidence of serogroup A disease subsequently declined across Chad after PsA-TT was rolled out nationally (Gamougam et al., 2015). Vaccine impact has subsequently been evaluated in nine countries of the meningitis belt with consistent surveillance (Trotter et al, 2017). The incidence of suspected meningitis cases was 57% (95% CI: 55–59%) lower in vaccinated populations and there was a > 99% decline in the incidence of confirmed serogroup A disease. In addition, a 59% (95% CI: 44–69%) decline in the risk of a district reaching or exceeding the epidemic threshold of 10 cases per 100 000, per week, was observed in vaccinated populations.

7.2.3 Quadrivalent ACWY

There is more limited evidence on the effectiveness of MCV4 vaccines. These vaccines have been recommended for adolescents aged 11–18 years and others at increased risk (including college freshmen) in the United States since 2007, with effectiveness estimated specifically for the main vaccine in use, that is, ACWY polysaccharide conjugated to diphtheria toxin. An early assessment of breakthrough cases in the United States estimated that the observed number of cases was consistent with effectiveness of 80–85% (McNeil et al., 2011). Subsequently, a case-control study was used to estimate VE and duration of protection (Cohn et al., 2017). The overall VE estimate 0–8 years post-vaccination was 69% (95% CI: 51–80%); VE was 79% (95% CI: 49–91%) at < 1 year, 69% (95% CI: 44–83%) at 1 to < 3 years and 61% (95% CI: 25–79%) at 3 to < 8 years. In terms of effectiveness against different serogroups, VE was 77% (95% CI: 57–88%) against serogroup C and 51% (95% CI: 1–76%) against serogroup Y.

7.3   Protein vaccines

7.3.1 Outer membrane vesicle (OMV) vaccines

OMV vaccines have been tailor-made in response to hyper-endemic disease incidence due to particular group B clones. In Norway, an epidemic of a ST32 clonal complex serogroup B meningococci (phenotype B:15:P1.7,16) commenced in the late 1980s. A placebo-controlled double-blind efficacy trial was conducted in Norwegian secondary schools, with randomization at the school level. Vaccine effectiveness of 57% (lower 95% interval of 27.7%) was reported (Bjune et al., 1991).

A Cuban vaccine based on a phenotype B:4:P1.15 strain, belonging to the ST32 clonal complex, also includes serogroup C polysaccharide and alum (Sierra et al., 1991). Following two doses of this OMV vaccine in 10–14 year olds, the efficacy was found to be 83% (95% CI: 42–95%) (Sierra et al., 1991). The same vaccine was evaluated in São Paolo, Brazil, again as a 2-dose schedule, and the efficacy was found to vary with the age group studied (de Moraes et al., 1992). Efficacy was 37% (95% CI: < -100–73%) in 3–23 month olds, 47% (95% CI: -72–84%) in 24–47 month olds and 74% (95% CI: 16–92%) in the 4–7 year olds. In Rio de Janeiro, Brazil, the same OMV vaccine showed efficacy of 41% (95% CI: -96–82%) in 6–23 month olds and 14% (95% CI: -165–72%) in 24–47 month olds (Noronha et al., 1995).

In New Zealand, vaccination of 0–20 year olds with an OMV vaccine commenced in July 2004 in response to a B:4:P1.7–2,4, ST-41/44 clonal complex epidemic (Dyet & Martin, 2005). Vaccine effectiveness was estimated, using an observational cohort study and a two-year follow-up period, as 80% (95% CI: 53–92%) for children aged six months to < 5 years and 85% (95% CI: 59–94%) for those aged six months to < 3 years (Galloway et al., 2009). Vaccine effectiveness in everyone aged under 20 years was estimated with a Poisson regression model in the years 2001–2008, including adjustments for year, season, age, ethnicity, region and socioeconomic status. This estimated VE to be 77% (95% CI: 62–85%) after three doses, given a mean follow-up time of 3.2 years (Arnold et al, 2011).

7.3.2 4CMenB vaccine

The United Kingdom was the first country to introduce a new vaccine offering broad protection against serogroup B meningococcal disease, in September 2015, incorporating the vaccine into the routine immunization schedule at two, four and 12 months. For cases diagnosed between 1 September 2015 and 30 June 30 2016, VE was assessed using the screening method (Parikh et al., 2016). Two-dose VE was 83% (95% CI: 24–95%) against all serogroup B cases, equivalent to VE of 94·2% against the highest predicted serogroup B strain coverage of 88%. The effectiveness was then evaluated for the first three years of the programme (Ladhani et al., 2020). Vaccine effectiveness against meningococcal group B disease was 52.7% (95% CI: -33.5–83.2%) with a 2-dose priming schedule for infants and 59.1% (95% CI: -31.1–87.2%) with a 2-dose priming schedule, plus a booster at one year. Significantly, over the three-year period there were 169 cases of meningococcal group B disease in the vaccine-eligible cohorts and an estimated 277 cases (95% CI: 236–323%) that were prevented. The 4CMenB programme was associated with continued positive effect against meningococcal group B disease in children in England over the first three years of the programme.

8. Safety

8.1 Polysaccharide vaccines

Since the 1970s, until the development of conjugate vaccines, meningococcal polysaccharide vaccines were administered to millions of individuals, including: those enlisted in the military; in certain at-risk groups; international travellers and, as part of mass vaccination campaigns to prevent or control outbreaks (WHO, 2011; Vipond et al., 2012). The widespread use of polysaccharide vaccines became more limited with the introduction of conjugate vaccines in the early 2000s. However, polysaccharide vaccines are still used to control outbreaks in many endemic and resource-limited regions (Greenwood, 1999; WHO, 2011). Until recently, they were the only licensed vaccines for those aged over 55 years in the United States, but now production has ended and recommendations have been updated to include the use of conjugate vaccines in this age group (Cohn et al., 2013).

Overall, meningococcal polysaccharide vaccines have been demonstrated to be safe and well-tolerated. The most common adverse events include minor pain and redness at the site of injection that tends to last between one and two days. Less than 5% of vaccinees report low-grade fever, although it occurs in infants more commonly than other age groups; high-grade fevers are even more rare (<1%) (Gold et al., 1975; Peltola et al., 1978). Severe adverse events are uncommon (Gold et al., 1975; Peltola et al., 1976; Makela et al., 1977; Peltola et al., 1978; Hankins et al., 1982; Ambrosch et al., 1983; Lepow et al., 1986; Roberts & Bryett, 1988; Scheifele et al., 1994; Yergeau et al., 1996; Aseffa et al., 2007; Bentsi-Enchill et al., 2007) although wheezing or urticaria is estimated to occur in one per 1 million doses administered and anaphylaxis in <1 per 1 million doses administered (CDC MMWR, 2000). In 2014, the United States Institute of Medicine (IOM) assessed the epidemiologic and mechanistic evidence to assess whether a causal relationship exists between meningococcal vaccination and anaphylaxis, and found that the clinical evidence presented by Yergeau et al. (1996) based on their study of meningococcal AC and meningococcal ACWY polysaccharide vaccines, indicated strong clinical evidence to support a causal link (Stratton et al., 2014). Studies of vaccination during pregnancy have not reported an increase in adverse events among either newborns or pregnant women (de Andrade Carvalho et al., 1977; McCormick et al., 1980; Leston et al., 1998); hence, there are no special considerations regarding meningococcal polysaccharide vaccination during pregnancy (WHO, 2011).

8.2 Conjugate vaccines

Overall, conjugate meningococcal vaccines of various formulations have also been found to be safe and well-tolerated. They have been associated with few adverse events, both when assessed during clinical trials and following licensure.

8.2.1 Meningococcal C conjugate vaccines

During the United Kingdom MCC vaccine campaign, three manufacturers' vaccines were utilized, each of which had been evaluated for safety in a comprehensive series of pre-licensure studies (Richmond et al., 1999; MacLennan et al., 2000; Richmond et al., 2001a; Richmond et al., 2001b; Southern et al., 2006). The most commonly observed adverse event in the first three days following vaccination was transient headache of mild to moderate severity (among an estimated 12% of participants in these pre-licensure studies). As with polysaccharide vaccines, reports of local reactions of mild to moderate severity at the injection site were reported, and consisted of temporary pain, tenderness and occasional redness. Following licensure, safety continued to be monitored rigorously through passive surveillance of adverse events reported to the United Kingdom's Committee on Safety of Medicines (formerly Medicines Control Agency) that indicated a frequency of one adverse event per 2875 doses of MCC vaccine distributed in the first 10 months of the campaign (Medicines Control Agency et al., 2000). The majority of the adverse events reported consisted of headache, local reactions, fever, or dizziness. Anaphylaxis was reported at a frequency of one per 500 000 doses administered. Though post-licensure monitoring identified some additional adverse events (such as headache, nausea, vomiting, abdominal pain and malaise, in all age groups), the benefits of preventing meningococcal disease were judged to outweigh the risks (Snape & Pollard, 2005).

During enhanced post-licensure surveillance, health professionals were requested to report any suspected adverse events following MCC vaccination, regardless of severity, to the United Kingdom licensing authorities. Based on this passive surveillance, concerns were raised about a possible association between MCC vaccination and convulsions and purpura. To investigate this further, all hospital admissions among children in the South East of England due to convulsions (n=1715) and purpura (n=363), between November 1999 and September 2003, were identified and linked to vaccination records for MCC vaccine and other childhood vaccines. The analysis found no evidence of an increased relative incidence of convulsions two weeks after, or pupura four weeks after MCC vaccination (Andrews et al., 2007).

No association between vaccination and relapse of nephrotic syndrome was identified during a follow-up study (Taylor et al., 2007) to a previous study published in 2003 (Abeyagunawardena et al., 2003) that had initially suggested that the relapse rate of nephrotic syndrome had increased after the MCC mass-vaccination campaign. In the follow-up study, researchers used an active population-based surveillance system and also undertook ecological analyses to compare outcomes pre- and post-MCC vaccination in various age groups to assess the potential association; no evidence of an increased risk was found in either analysis (Taylor et al., 2007). Five cases of Guillain-Barré syndrome (GBS) were reported following administration of millions of doses of MCC vaccine during the United Kingdom catch-up campaign. The frequency of these

reports was considered by the United Kingdom Department of Health to be lower than the expected background rate of GBS. Subsequently, a study among 1.9 million vaccinees aged two months to 20 years, in Canada, found no link between MCC and GBS (de Wals et al., 2008). Furthermore, United States IOM assessed the epidemiologic and mechanistic evidence to assess whether a causal relationship could be established between MCC vaccination and GBS; they concluded that the evidence is not sufficient to establish a causal link (Stratton et al., 2014).

Currently, the most commonly reported adverse events associated with MCC (occurring in more than one in 10 vaccinees) include injection-site reactions such as temporary redness, swelling and tenderness/pain (all ages), vomiting (infants), irritability, drowsiness, difficulty sleeping, loss of appetite and diarrhoea (infants/toddlers), headache (schoolchildren), malaise (older children and adults) and muscle/joint pains/nausea (adults) (Menjugate package leaflet; Menjugate SPC).

8.2.2 Meningococcal A conjugate vaccines

Both before and after the introduction of meningococcal A conjugate vaccine mass-vaccination campaigns in the African meningitis belt, beginning in 2010, numerous studies assessed MenAfriVac™ (PsA-TT) vaccine safety. Of note, the meningococcal A conjugate vaccine trials conducted in multiple countries of sub-Saharan Africa, and in India, reported extensively on the vaccine's safety profile (Kshirsagar et al., 2007; Sow et al., 2011; Tapia et al., 2015b; Hirve et al., 2012). Briefly, in a Phase I study in Indian adults, the most frequent local and systemic solicited reactions within seven days after vaccination were pain, redness, swelling, headache, fatigue, malaise and arthralgia; no differences were observed compared to adverse events reported following licensed meningococcal bivalent polysaccharide or tetanus toxoid (TT) vaccines administered to those in the comparison groups. In addition, no serious adverse events (SAEs) were reported during the one-year safety follow-up period (Kshirsagar et al., 2007). In a Phase II study in the Gambia and Mali where 200 toddlers received the PsA-TT, the five SAEs reported were unrelated to the study vaccines (Sow et al., 2011). More extensive evaluation during Phase III trials enrolling infants found mild, transient local reactions, including pain and tenderness at the injection site, to be the most common adverse event observed (Sow et al., 2011; Enwere et al. 2015; Tapia et al., 2015b; WHO, 2015b). In addition, lessons learned from monitoring safety during and following multiple PsA-TT mass-vaccination campaigns in low-resource settings have been reported (Diomandé et al., 2015; Enwere et al. 2015; Vannice et al., 2015; Ateudjieu et al., 2016;), highlighting the need for robust surveillance efforts to assess post-introduction safety.

Of note, an assessment of meningococcal A vaccination during pregnancy found an acceptable safety profile and no concern about adverse birth outcomes (Wak et al., 2015; WHO, 2015b).

8.2.3 Meningococcal quadrivalent ACWY conjugate vaccines

Meningococcal quadrivalent ACWY vaccines conjugated to diphtheria toxin (MenACWY-D) were introduced in the United States in 2005 and meningococcal quadrivalent ACWY vaccines conjugated to CRM (MenACWY-CRM) were licensed in 2010.

Prior to introduction of MenACWY-D vaccines, they had been administered to thousands of individuals during pre-licensure studies and found to be safe and well-tolerated (Campbell et al., 2002; Keyserling et al., 2005; Lagos et al., 2005; Pichichero et al., 2005). In randomized studies of both polysaccharide and conjugate quadrivalent vaccines among 11–18 year olds in the United States, local reactions were more common in the adolescent conjugate vaccine recipients (72.3%) than in the adolescent polysaccharide vaccine recipients (34.7%) (Keyserling et al., 2005). A study enrolling 2–10 year old children in Chile and the United States, found similar frequencies of reported adverse events among conjugate vaccine recipients compared to polysaccharide vaccine recipients (Lagos et al., 2005; Pichichero et al., 2005). The overall frequency of systemic reactions among adolescents and children was similar for both conjugate and polysaccharide vaccine recipients (Keyserling et al., 2005; Pichichero et al., 2005). Serious systemic reactions, including high fevers or headache, fatigue, malaise, chills or arthralgias requiring bed rest, anorexia (missing three or more meals), three or more episodes of vomiting, or five or more episodes of diarrhoea, or the presence of rash or seizures, occurred in less than 5% of conjugate or polysaccharide vaccine recipients in these studies.

Between March 2005 and April 2007, multiple confirmed cases of GBS with onset within six weeks of quadrivalent polysaccharide-diphtheria conjugate vaccination were reported to the Vaccine Adverse Event Reporting System (VAERS) (CDC MMWR, 2006; WHO, 2007a). An increased rate of GBS has not been observed after vaccination with meningococcal quadrivalent polysaccharide or diphtheria toxoids, the two principal components of quadrivalent polysaccharide-diphtheria conjugate vaccine. The suggestion of a small increased risk of GBS after the administration of quadrivalent polysaccharide-diphtheria conjugate vaccine via a passive surveillance system like VAERS, given the inherent limitations of passive surveillance and the uncertainty regarding background incidence rates for GBS, must be viewed with caution and investigated further. Using health plan and claims data, Velentgas and colleagues (2012) conducted a follow-up study in a large retrospective cohort of 12.6 million adolescents aged 11–21 years between 2005 and 2008. While no confirmed cases of GBS were documented within six weeks of vaccination, the analysis, including approximately 1.4 million MenACWY-D vaccinations, estimated that the attributable risk for GBS ranged from zero to 1.5 additional cases of GBS per 1 million vaccines within the six-week period following vaccination (Velentgas et al., 2012). Further follow-up through the Vaccine Safety Datalink from January 2005 to March 2010 did not identify any cases of GBS in the 1–42 days following vaccination after 889 684 vaccine doses of MenACWY-D were administered (Cohn et al., 2013). Based on this evidence, the United States Advisory Committee on Immunization Practices (ACIP) "determined that the potential small increased risk for GBS post-MenACWY-D vaccination was outweighed by the protection that the vaccine offers against meningococcal disease" and removed the precaution for individuals with a history of GBS (Cho et al., 2010; Cohn et al., 2013).

8.3   Meningococcal B vaccines

While the meningococcal B multi-component protein-based vaccines have been licensed relatively recently compared to other meningococcal vaccines, several clinical trials and studies have evaluated the safety profile of both 4CMenB (Vesikari et al., 2013; Findlow et al., 2015) and MenB-fHbp (Richmond et al., 2012; Vesikari et al. 2016; Fiorito et al., 2018) meningococcal B vaccines.

Based on data from seven clinical trials evaluating MenB-fHbp vaccine safety among more than 4000 participants, a review by the ACIP found no significant increase in the risk for SAEs among adolescents aged 10–25 years (ACIP, 2014; FDA, 2014; MacNeil et al., 2015; Patton et al., 2017). However, common adverse events following MenB-fHbp vaccination included pain at the injection site, fatigue, headache, myalgia and chills that were reported among a high proportion of participants (Patton et al., 2017 FDA, 2014; Vesikari et al., 2016).

A recent systematic review of 10 clinical trials and eight additional studies of 4CMenB vaccine found that the most commonly reported mild-to-moderate adverse events included a significant increase in fever, pain at the injection site and any local or systemic reaction when compared with other vaccines (Flacco et al., 2018). In addition, the authors noted that cases of SAEs, including febrile convulsions, arthritis and Kawasaki disease, were reported, although further investigation would be needed to assess the potential causal relationship and to quantify the impact of 4CMenB vaccination on the incidence of these outcomes (Flacco et al., 2018). A mass-vaccination campaign implemented in Canada identified only two SAEs (bronchospasms) following vaccine administration to more than 43 000 vaccinees, although nearly all recipients experienced pain at the injection site (de Serres et al., 2014).

Since 4CMenB introduction in the infant vaccination schedule in the United Kingdom in 2015, there has been an increase in medically attended fever (Kapur et al., 2017; Ladhani & Riordan, 2017; Murdoch et al., 2017; Nainani et al. 2017; Harcourt et al., 2018). An estimated 50–60% of infants experience a fever following administration of 4CMenB along with other routine vaccinations, and the United Kingdom recommended concomitant administration of paracetamol prophylactically, that has been shown to significantly reduce the occurrence of fever among infants receiving 4CMenB (Martin & Snape, 2013). However, no major safety concerns have been identified by the Medicine and Healthcare Products Regulatory Agency among those receiving the first 3 million doses administered after roll-out (Ladhani et al., 2018). Through a comprehensive, prospective assessment of outcomes among the 1.29 million infants immunized through the United Kingdom immunization programme, from its start in 2015 until mid-2017, researchers used an extensive passive surveillance system to determine whether any safety concerns warranted additional follow-up. Reassuringly, no significant concerns were identified (Bettinger et al., 2018; Bryan et al., 2018). Additional post-licensure surveillance will be needed to continue to monitor the safety and efficacy of meningococcal B vaccines now that they are being recommended for routine use in several countries.

8.4   Combination vaccines

Combination vaccines that have been developed to deliver protection against multiple antigens in a single injection, undergo the same level of rigorous testing in clinical trials and evaluation in post-licensure studies, to assess their safety, as all new vaccine formulations. Studies have been undertaken to evaluate the safety profile of both the combined Hib/MenC TT conjugate vaccine (Hib-MenC-TT) and the combined Hib/MenCY TT conjugate vaccine (Hib-MenCY-TT). Clinical trials and more recent follow-up studies have not raised any significant safety concerns for either vaccine (Schmitt et al., 2007; Tejedor et al., 2007; Habermehl et al., 2010; Marchant et al., 2010; Nolan et al., 2011). For example, from pre-licensure studies with vaccination at two, three and four months (Schmitt et al., 2007) or at two, four and six months (Tejedor et al., 2007), administered concomitantly with DTaP-HBV-IPV, redness at the injection site and drowsiness/irritability were the most commonly-reported local and general solicited adverse events, with no differences in reports compared to the MCC conjugate vaccine group. There were no SAEs deemed to result from the combined Hib-MenC-TT vaccine; evaluation of the Hib-MenCY-TT vaccine found an acceptable safety profile compared to Hib-TT (Nolan et al., 2011).

9. Concomitant use

The success of conjugate vaccines has led to the introduction of meningococcal conjugate vaccines into the immunization schedules of numerous countries. In addition, the recent development of meningococcal B multi-component protein vaccines has also led to their inclusion in both infant and adolescent schedules in various countries.

Incorporating new vaccines into an existing recommended schedule of vaccinations raises questions about whether the concomitant administration of multiple antigens and vaccine formulations might interfere with robust immune responses, and whether coadministration may lead to enhanced immune responses, or whether there will be no difference. In addition, questions about whether additional safety concerns might be raised when vaccines are coadministered at various ages must also be addressed. Research into these questions must take into consideration, in particular, the age at vaccination and the number and type of vaccines that are coadministered with a given meningococcal vaccine. To address any potential concerns, studies must be undertaken to compare the safety and immunogenicity of each meningococcal vaccine formulation administered concomitantly with other infant, adolescent or adult vaccines, compared to each meningococcal vaccine formulation administered alone.

Overall, evidence suggests that concomitant administration of meningococcal vaccines with a wide range of other vaccines is feasible, safe and effective. Different sites of administration should be used for each vaccine, and specific guidance issued by manufacturers should be consulted for further information prior to administration (WHO, 2011).

This is an area of active inquiry, as new vaccine formulations are tested in combination with routinely administered existing vaccines and new combination vaccinations are developed. For some vaccine formulations, such as MCV4 vaccines, more evidence is available relative to other vaccines given the longer history of their use. For example, a recent review of 10 Phase III and post-licensure Phase IV studies did not find evidence of reduced immune responses to MCV4-CRM197 vaccines after coadministration with multiple other routinely administered vaccines among infants, adolescents, or adults (Gaspirini et al., 2016). Less evidence is available for the recently licensed MenB vaccines, but interest in these questions persists as recommendations for routine vaccination using these vaccines are implemented. Below, a subset of the growing body of evidence aimed at addressing these questions is summarized.

9.1　Coadministration in infants, toddlers and young children

Meningococcal C conjugate vaccines, conjugated to either TT or to CRM197, have been evaluated extensively to understand whether coadministration with routinely administered infant vaccines may alter their immunogenicity. For instance, the utilization of whole-cell pertussis (wP) versus acellular pertussis (aP) vaccine has been shown to affect the magnitude of the rSBA response following vaccination with MCC-TT (Kitchin et al., 2007). In this randomized study, infants received either a wP or aP vaccine, and each group was further randomized to receive either an MCC-CRM197 or MCC-TT vaccine. There were no differences in the proportion of subjects with rSBA titres ≥ 8 following the accelerated two, three and four-month schedule, but the rSBA GMT was significantly lower for the MCC-TT conjugate group when administered with aP versus wP vaccine. No effect on the MCC-CRM197 conjugate vaccine response was demonstrated, regardless of whether aP or wP vaccines were coadministered. A randomized study of pre-school (3.5–6 year old) children administered one of three MCC vaccines either concomitantly with, before, or after vaccination with diphtheria-tetanus (DT) or tetanus diphtheria toxoid (Td) booster vaccines, showed all three MCC vaccines were highly immunogenic in any combination with DT or Td vaccines (Burrage et al., 2002). The rSBA GMT among the MCC-TT vaccinees was lower when DT or Td was administered before the conjugate vaccine, although levels remained high among all groups.

Coadministration of the combined DTaP-IPV-HB-PRP-T hexavalent vaccine at two, three and four months, with MCC-TT vaccine at two and four months, among infants aged 46–74 days did not provide evidence of an altered immune response to MenC (with 100% of participants demonstrating an rSBA titre ≥ 8 one month after the second dose) or raise any safety concerns (Vesikari et al., 2017). Coadministration of MCC vaccine with routine administration of DTaP-IPV-Hib vaccine plus RotaTeq® vaccine (administered as a 3-dose oral vaccine) to infants aged 6–7 weeks old, produced comparable immune responses compared with sequential administration of MenC and RotaTeq vaccines (Vesikari et al., 2011). However, the authors did note that "concomitant administration of the first doses of MCC, diphtheria and tetanus toxoids and acellular pertussis vaccine, inactivated poliovirus vaccine, and *Haemophilus influenzae* type b conjugate vaccine (DTaP-IPV-Hib) and RotaTeq was associated with a higher rate of vomiting and diarrhoea than concomitant administration of MCC and DTaP-IPV-Hib, but that was not observed after the second concomitant administration" (Vesikari et al., 2011).

Questions surrounding the possible interaction of meningococcal vaccines with other routinely administered vaccines have been extended to investigate whether combination vaccines containing MCC can be coadministered along with other vaccines offered in infant vaccination programmes. For example, a study of MCC-Hib combination vaccine administered along with PCV7 and MMR vaccine, compared with administering MCC-Hib separately, was undertaken among 12 month olds; the researchers found few notable differences in safety and immunogenicity, although there was a tendency towards higher immunogenicity and lower post-vaccination fever with coadministration (Miller et al., 2011).

Other studies have investigated the response to MCC vaccines administered with PCV13 compared to PCV7 (Diez-Domingo et al., 2013) and administered with or without MMRV vaccines (Durando et al., 2016) and found no concerns respecting the robustness of the immune response.

Similarly, studies that have investigated the concomitant use of MCV4 vaccines with other routine and recently-introduced vaccines, did not report any clinically meaningful differences in meningococcal antibody responses among infants when MCV4-CRM was administered with routine vaccinations (Abdelnour et al., 2014; Nolan et al., 2014; Tregnaghi et al., 2014) or among toddlers when MCV4-CRM was administered with MMRV (Klein et al., 2012).

With the recent development of meningococcal B vaccines, efforts to protect infants against as many strains of meningococci capable of causing invasive disease as possible, have led to studies of the effect of coadministration of MCC vaccine alongside MenB vaccines. A study of MCC-CRM and 4CMenB found non-inferior MCC responses and sufficient MenB responses (against fHbp, NadA, PorA) among infants aged 83–104 days compared to administration of MCC-CRM alone, though mild and moderate adverse events were reported more frequently with concomitant administration (Safadi et al., 2017).

A number of studies have investigated the concomitant administration of MenB vaccines with routine infant vaccinations, given the introduction of 4CMenB into the routine infant vaccination schedule in the United Kingdom, and its consideration elsewhere. In general, studies have found that 4CMenB is immunogenic against vaccine reference strains when administered in different dosing schedules alongside routine infant vaccines, but that reactogenicity is increased with concomitant administration (Gossger et al., 2012; Vesikari et al., 2013; Chiu et al., 2018). To address concerns about increased adverse events, primarily fevers, following coadministration with MenB vaccines, studies have investigated the potential benefits of giving infants paracetamol prior to vaccination. By comparing infants randomized to receive four doses of 4CMenB along with DTaP-HBV-IPV/Hib and PCV7, with or without prophylactic paracetamol, to one another and to a group receiving only MenC vaccine, researchers found that immune responses to 4CMenB were not decreased by the use of paracetamol prophylaxis and there were no clinically relevant effects on immune responses to routine vaccines. In addition, occurrence of fever was higher in infants coadministered with 4CMenB compared with those given MCC vaccine, but was significantly decreased by prophylactic paracetamol, as were other solicited reactions to vaccination, both local and systemic (Prymula et al., 2014).

9.2   Coadministration in adolescents

Overall, evidence suggests that coadministration of MCV4 vaccines or MenB vaccines with human papillomavirus (HPV), DTap, Tdap, or with each other, elicited similar immune responses as measured by SBA titres, though the specific reference strain used and the definition of non-inferiority differed between studies, as described below. As noted above, administration of DT or Td prior to MCC-TT, resulted in lower rSBA GMTs among 13–18 year olds in a randomized trial, although levels remained higher than the threshold for putative protection (Burrage et al., 2002). There is significant interest in coadministration of adolescent vaccines because of the potential to increase vaccine uptake and sustain high vaccination coverage by delivering multiple vaccines during a single health-care encounter.

Among adolescents aged 11–18 years who received one dose of bivalent rLP2086 (recombinant meningococcal B vaccine) concurrently with DTaP/IPV (diphtheria, tetanus and acellular pertussis and inactivated poliovirus vaccine) followed by two more MenB vaccine doses, 55–100% of vaccinees exhibited an hSBA response over the pre-specified thresholds when the hSBA assays were quantified for four MenB reference strains expressing fHbp proteins different from the antigens used to develop the vaccine (Vesikari et al., 2016). These responses were evaluated one month after the second and third doses (Vesikari et al., 2016); however, this trial did not include a bivalent rLP2086-only group for comparison.

In a study of adolescents aged 11–15 years, participants who received three doses of 9vHPV (9-valent human papillomavirus) vaccine administered concomitantly (both doses on day one) with either MCV4 or Tdap, were compared with those who received their MCV4 and Tdap doses at month one (non-concomitantly). The researchers reported that the proportion of participants with a fourfold rise, or greater, in the rSBA titres for each of the MenA, C, W and Y serogroups in the concomitant administration group, were non-inferior to those who received MCV4 and Tdap one month after starting the HPV9 series, when evaluated one month after MCV4 receipt. However, local reactions, primarily injection-site swelling, were more common in the group that received the vaccines concomitantly (Schilling et al., 2015).

Among adolescents aged 11–17 years who received three doses of bivalent rLP2086 coadministered with three doses of HPV-4 vaccine, the non-inferiority of the hSBA response against two MenB strains well matched to the vaccine, evaluated one month after the third dose, was demonstrated (Senders et al., 2016).

Among adolescent girls aged 11–18 years who received three doses of HPV-2 (human papillomavirus-16/18 AS04-adjuvanted) vaccine coadministered with MCV4 at month 0 or HPV vaccine coadministered with both MCV and Tdap at month 0 compared to MCV administered alone, non-inferiority of rSBA-MenA, rSBA-MenC, rSBA-MenY and rSBA-MenW geometric mean antibody titres (GMTs), evaluated one month after the MCV dose, was demonstrated (Wheeler et al., 2011).

Efforts to provide broad protection against as many disease-causing strains of *N. meningitis* as possible, as early in adolescence as possible, would require administration of both MCV4 vaccines and MenB vaccines. In a Phase II trial among 10–13 year olds, researchers investigated concomitant administration of bivalent rLP2086 and MCV4 and Tdap vaccines and found that "bivalent rLP2086 given concomitantly with MCV4 + Tdap met all non-inferiority immunogenicity criteria without a clinically meaningful increase in reactogenicity" (Muse et al., 2016).

9.3 Coadministration in Adults

Coadministration of meningococcal vaccines among adults primarily takes place in the context of vaccines administered prior to travel, given that some countries recommend meningococcal vaccination for travellers of all ages to areas of increased risk of meningococcal disease. Recent studies have investigated administration of MenACWY-CRM conjugate vaccines alongside other common travel vaccines, including typhoid Vi polysaccharide, live attenuated yellow-fever (YF) vaccine, adjuvanted Japanese encephalitis (JE) vaccine, a purified chick embryo cell-culture rabies vaccine, hepatitis A and hepatitis B vaccine, among adults aged 18–60 (Alberer et al., 2014; Alberer et al., 2015a; Alberer et al., 2015b). The researchers reported that coadministration with any of these vaccines did not compromise the immunogenicity of meningococcal vaccine when evaluated in the month following vaccination using hSBA assays; coadministration also did not raise any safety concerns (Alberer et al., 2014; Alberer et al., 2015a; Alberer et al., 2015b).

10. Effect of vaccines against carriage

10.1 Polysaccharide vaccines

A systematic review identified twenty-five studies that examined the effect of meningococcal polysaccharide vaccines on meningococcal carriage (Dellicour & Greenwood, 2007). While it was noted that many studies had methodological weaknesses, there was evidence that in high-risk groups in industrialized countries, such as military recruits, meningococcal polysaccharide vaccines reduced carriage prevalence at least in the short term. The results were less clear for civilian populations, with only one of five studies in Africa showing a significant reduction in carriage. Substantial herd protection has not been observed following widespread polysaccharide vaccination, suggesting that effects on carriage are very limited.

10.2 Conjugate vaccines

In general, the effect of conjugate vaccines on meningococcal carriage has been measured using observational studies rather than randomized controlled clinical trials. These before-and-after vaccine studies for monovalent conjugate vaccines, against serogroups C and A, have demonstrated a marked reduction in the prevalence of carriage in vaccinated compared with unvaccinated populations.

In the United Kingdom, extensive carriage studies in teenagers were conducted between 1999 and 2001 immediately before the introduction of MCC vaccines; then at one and two years after vaccination (Maiden et al., 2008). Across all three years, over 48 000 participants were swabbed and 8599 meningococci were isolated. Although carriage of group C was relatively rare, there was a significant reduction in prevalence of meningococci that expressed serogroup C capsule, and also in carriage of meningococci that contained the siaDC gene responsible for C capsule production (rate ratio, 0.19 and 0.46, respectively; $P < .001$ for both). Vaccine effectiveness against serogroup C carriage was estimated to be 75% (95% CI: 23–92%). There was no evidence of replacement with other virulent meningococci in either carriage (Maiden et al., 2008) or disease (Trotter et al, 2006).

The findings from MCC vaccines and the generation of substantial herd protection that resulted from declines in carriage prevalence, particularly by targeting teenagers in whom carriage prevalence is highest (Trotter & Maiden, 2009) were influential in the design of vaccine strategies for serogroup A conjugate vaccines in Africa. It was important to demonstrate that the anticipated herd effects would also be observed against serogroup A in the African meningitis belt, and so carriage studies across the meningitis belt were established before PsA-TT introduction (Kristiansen et al., 2011; MenAfriCar Consortium, 2013). In Burkina Faso, cross-sectional meningococcal

carriage studies in 1–29 year olds were performed in three districts before and up to 13 months after vaccination. Compared with a baseline serogroup A carriage prevalence of 0.39%, no serogroup A meningococci were identified after vaccination (Kristiansen et al., 2013). In Chad, 32 serogroup A carriers were identified in 4278 age-stratified individuals (0·75% prevalence) living in a rural area near the capital 2–4 months before vaccination, whereas only one serogroup A meningococcus was isolated from 5001 people living in the same community 4–6 months after vaccination (adjusted odds ratio 0·019, 95% CI: 0·002–0·138; p<0·0001) (Daugla et al., 2014). In Burkina Faso, carriage of serogroup A meningococci remained rare two years after MenAfriVac™ introduction, with only one carrier identified out of 4964 individuals swabbed (Kristiansen et al., 2014).

The effect of quadrivalent meningococcal conjugate vaccines on carriage was measured in a randomized controlled trial in England (Read et al., 2014). Significantly lower carriage rates were observed in the MenACWY-CRM group compared with controls. There was a 39% (95% CI: 17–55%) carriage reduction for serogroup Y and 36% (95% CI: 15–52%) carriage reduction for serogroup CWY. An uncontrolled observational study of University students in Nottingham, United Kingdom, found that carriage prevalence of serogroup W meningococci increased between September (15%, n=786) and March (46%, n=288) despite vaccine coverage of 71% in this population (Oldfield et al., 2018).

10.3   Protein vaccines

Three randomized controlled trials of OMV vaccines did not show any impact on carriage with serogroup B meningococci (Dellicour & Greenwood, 2007). The 4CMenB vaccine was evaluated in a three arm randomized controlled trial among university students aged 18–24 years from ten sites in England. Individuals were allocated to receive two doses one month apart of JE vaccine (controls), 4CMenB, or one dose of MenACWY-CRM then placebo. No specific effect on carriage of group B meningococci was observed (Read et al., 2014). From three months after dose two, there was a significant reduction in carriage of any meningococcal strain (18%, 95% CI: 3–31%) in the 4CMenB arm compared to controls. In South Australia, a cluster randomized study was used to assign, according to school, students in years 10–12 (aged 15–18 years) to receive 4CMenB vaccination either at baseline (intervention) or at 12 months (control) (Marshall et al., 2020). The primary outcome was oropharyngeal carriage of disease-causing meningococci (group A, B, C, W, X, or Y) in students in years 10 and 11, as identified by PCR assays for PorA and genogroups. A total of 24 269 students in years 10 and 11 and 10 220 students in year 12, were enrolled. At 12 months, there was no difference in the prevalence of carriage of disease-causing meningococci between the vaccination group (2.55%; 326 of 12 746) and the control group (2.52%; 291 of 11 523) (adjusted odds ratio, 1.02; 95% CI: 0.80–1.31; P = 0.85). Among Australian adolescents, 4CMenB had no discernible effect on the carriage of disease-causing meningococci, including group B. A further study of the effect of 4CMenB and MenB-fHbp on carriage is underway in United Kingdom teenagers.

10.4 Mechanism of action

Although the ability of conjugate vaccines to reduce the acquisition of carriage (certainly of serogroups A, C and Y) has been demonstrated, leading to remarkable herd protection, the mechanisms by which this is achieved have not been clearly elucidated. There are no established correlates of protection against meningococcal carriage, particularly as vaccine evaluation relies on measures of serum antibody, and not activity at the mucosal surfaces. A study in Ethiopia has shown that serogroup-specific IgG antibody levels in saliva increased significantly after vaccination with both monovalent A and quadrivalent ACWY vaccines, with the former also inducing increased salivary IgA antibodies. Serogroup-specific IgG concentrations in saliva and serum were found to correlate (Barnes et al., 2016).

11. Implications for immunization

A diverse range of meningococcal vaccination programmes designed to reduce the burden of meningococcal disease are now in place across the world. Given that the epidemiology of disease varies considerably by time, place and age group, there is no, so-called, one-size fits all policy. Mass campaigns targeting 1–29 year olds with PsA-TT were appropriate for the high-burden African meningitis belt, but in settings with a lower burden of disease, vaccines may be more suitably directed towards selected age groups or at-risk populations. Policy-makers should consider not only the burden of disease, but also the epidemiology of carriage, in their decisions about recommended vaccination strategies when considering vaccines that prevent or reduce carriage. Particularly for conjugate vaccines, the benefits of indirect (herd) protection, as a result of reductions in carriage and transmission, have been profound, and potentially have a greater impact on reducing disease than the benefits of direct protection against disease. Two large studies to date have shown no effect of 4CMenB on carriage of either genogroup B or all pathogenic genogroups (Read et al., 2014; Marshall et al., 2020). Further studies are underway to evaluate the effect of other multicomponent serogroup B vaccines on carriage. The future development of affordable multivalent meningococcal conjugate vaccines will strengthen our ability to prevent epidemics due to serogroups other than A, reducing the need for inefficient (though currently essential) reactive vaccination campaigns and vaccine stockpiles. High-quality post-licensure surveillance systems for meningococcal vaccines, licensed on the basis of limited safety and immunogenicity data, are essential to confirm vaccine safety, effectiveness, duration of protection and mode of action. Vaccine strategies and policies should adapt over time as more evidence is gathered and lessons are learned about the optimal use of meningococcal vaccines.

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